NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing
Ixekizumab for the treatment of moderate to severe plaque psoriasis (STA)

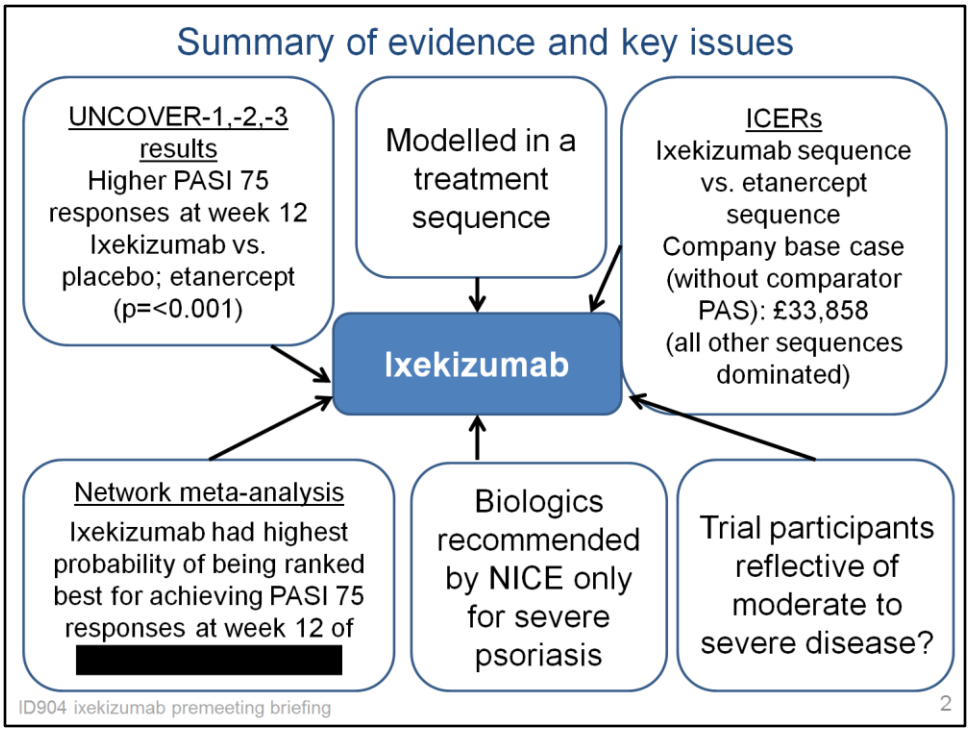
This slide set is the premeeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- 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 first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this presentation includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting


Summary of evidence and key issues
UNCOVER-1,-2,-3 results
Higher PASI 75 responses at week 12 Ixekizumab vs. placebo; etanercept (p=<0.001)
Modelled in a treatment sequence
ICERs
Ixekizumab sequence vs. etanercept sequence
Company base case (without comparator PAS): £33,858
(all other sequences dominated)
Ixekizumab
Network meta-analysis
Ixekizumab had highest probability of being ranked best for achieving PASI 75 responses at week 12 of
Biologics recommended by NICE only for severe psoriasis
Trial participants reflective of moderate to severe disease?
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Key issues for consideration

- How is moderate to severe disease defined?
- Are trial patients' baseline characteristics reflective of patients with moderate to severe disease?
- Where is ixekizumab in treatment pathway?
  - Would ixekizumab be used as 1st or 2nd biologic in a treatment sequence?
  - Do the treatment sequences reflect UK practice?
- Should the cost of adverse events be included in the model?
- Which populations should be used for treatment effectiveness and utility gains?
- When do people get the benefit of treatment (induction, maintenance)?

Psoriasis

- A common chronic inflammatory disease characterised by red, thick and scaly plaques on the skin
- Plaque psoriasis the most common form of the disease
- Typically follows a relapsing and remitting course
- Causes detrimental effects on patients' physical, psychological, social functioning
- 75% patients report burdensome symptoms (itching, redness, scaling, flaking)
- Associated with comorbidities such as obesity, hypertension, diabetes, hyperlipidaemia, depression, anxiety, cardiovascular disease
- Prevalence in England 1.75%; 2.55% of those eligible for biologic therapy

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Source: Company submission, Section 1 (page 17), 3.1 (page 36), 3.1.2 (page 37), 3.2 (page 38), 3.4 (page 45)

Ixekizumab (Taltz)

Eli Lilly

Mechanism of action	Antibody that inhibits IL-17A (interleukin-17A, a pro-inflammatory cytokine)
Marketing authorisation	"moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"
Administration & dose	Subcutaneous injection • Administered by 160mg at week 0, followed by 80mg every 2 weeks until week 12 (induction) • After week 12, 80mg every 4 weeks (maintenance)
Cost	List price £1,125 for 80mg PAS price £[redacted] for 80mg Average cost of a course of treatment • 1st year (18 injections) £[redacted] • 2nd year (13 injections) £[redacted]

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Source: Company submission, Sections 2.1, 2.2, 2.3 (pages 30-32)

Patient and professional feedback

- Psoriasis for some can be a debilitating disease that impacts all aspects of life, physically and psychologically
- Clearance of symptoms with low or manageable side effects is important to people with psoriasis.
- Access to treatments and a wide choice available in pathway if treatments fail
- Need for an alternative for those with failure of 1st biologic, or who lose response, are contraindicated or intolerant
- No additional resources required for ixekizumab
- Similar position in treatment pathway to secukinumab (after standard systemic therapies and/or phototherapy have failed)

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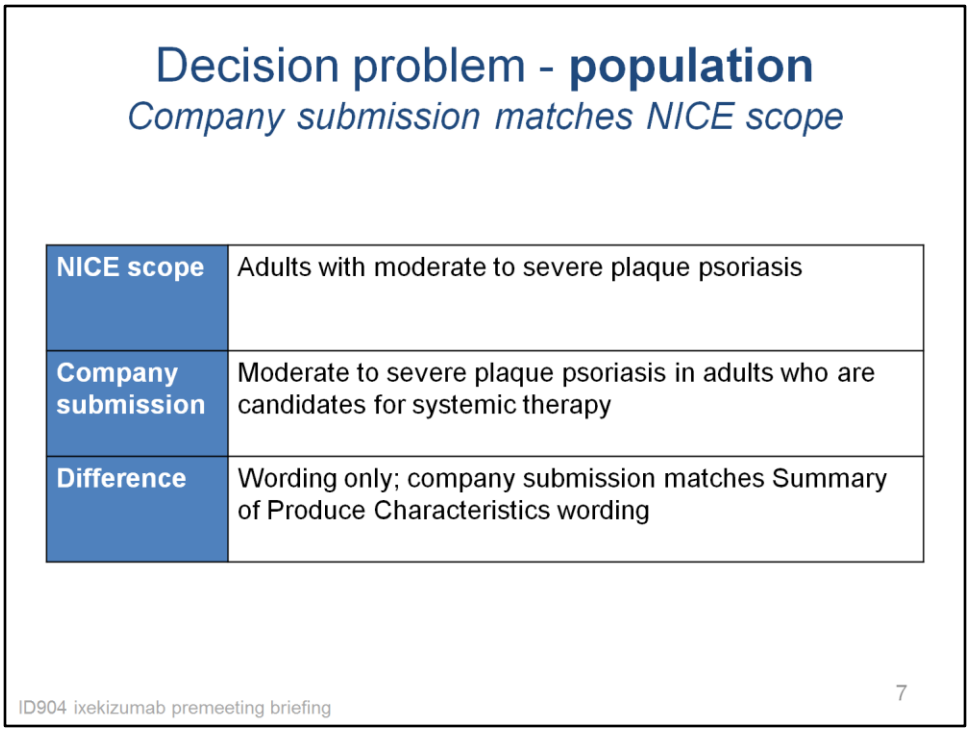
Source: Patient and professional submissions (British Association of Dermatologists, British Society for Rheumatology, Psoriasis and Psoriatic Arthritis Alliance, Royal College of Physicians)



Source: Company submission, Section 1.1, Table 1 (page 20)

Decision problem - **comparators**

Acitretin, fumaric acid esters, phototherapy missing from submission

NICE scope	Company submission
1) If non-biologic systemic treatment or phototherapy is suitable:	
• Systemic non-biological therapies (including acitretin, ciclosporin, fumaric acid esters, methotrexate) • Phototherapy with ultraviolet (UVB) radiation	• Systemic non-biological therapies (including ciclosporin and methotrexate)
2) For people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated:	
• TNF-α inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Best supportive care	• **TNF-α inhibitors (etanercept, infliximab, adalimumab)** • **Ustekinumab** • **Secukinumab** • **Best supportive care**
Company justification for difference	
• Insufficient data for fumaric acid, acitretin or phototherapy identified for analysis • Ixekizumab position in treatment pathway aligned to biologic therapies (population 2)	

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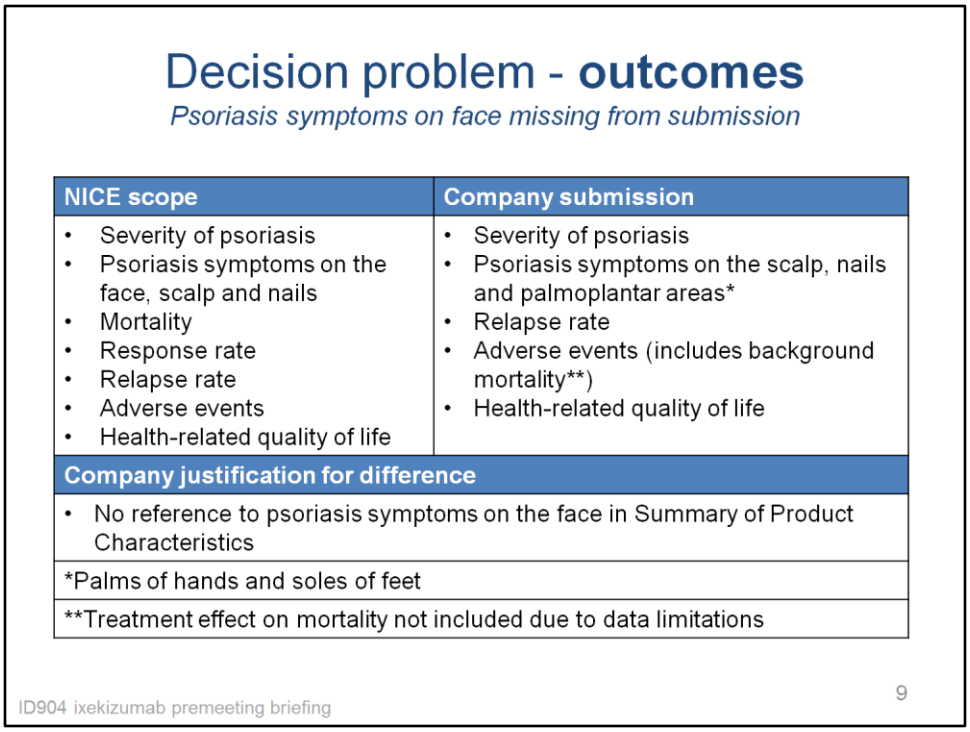
Source: Company submission, Section 1.1, Table 1 (page 20)

Only biologic comparators included in base case

Comparison with methotrexate and ciclosporin included in scenario analysis



Source: Company submission, Section 1.1, Table 1 (page 20)

Outcomes

Measures

Outcome	Measures
Severity of psoriasis	**Psoriasis Area and Severity Index (PASI)** Static Physician Global Assessment (sPGA)
Psoriasis symptoms on the scalp, nails and palmoplantar areas	Nail Psoriasis Severity Index (NAPSI) Psoriasis Scalp Severity Index (PSSI) Palmoplantar Psoriasis Severity Index (PPASI)
Relapse rate	Maintenance of response at week 60
Health-related quality of life	Dermatology Life Quality Index (DLQI)

PASI combines assessments of how much body surface area is covered and how severe the redness/thickness/scaling is in each area	
PASI score ranges from 0 (no psoriasis) to 72 (the most severe disease)	
≥75% improvement from baseline considered clinically meaningful	
PASI XX is the relative reduction in PASI score from baseline	**PASI 75** = 75% reduction from baseline

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Source: Company submission, Section 1.1, Table 1 (page 20), 4.3.6 (page 75), 5.4.5, Table 79 (page 247)

See also: ERG report, Section 4.2, Table 4.4 (page 45-6)

sPGA is a validated, standardised global score used in conjunction with PASI to assess efficacy (clear, nearly clear, mild, moderate, severe or very severe). Response rate measured by sPGA (0,1). sPGA 0 = clear, 1= nearly clear/minimal. (2 = mild, 3 = moderate, 4 = severe, 5 = very severe (Section 4.3.6, page 74)

DLQI = patient questionnaire (10 questions)

0 – 1 no effect at all on patient's life

2 – 5 small effect on patient's life

6 – 10 moderate effect on patient's life

11 – 20 very large effect on patient's life

21 – 30 extremely large effect on patient's life

(British Association of Dermatologists http://www.bad.org.uk/shared/get-file.ashx?id=1653&itemtype=document)

EMA recommends using 2 measures of efficacy – a validated, standardised global score as well as the PASI (Section 4.3.6, page 74)

ERG's clinical experts recommend using PASI and DLQI when describing disease severity in order to incorporate the patient's perspective.

Decision problem – ERG critique

Population	No consensus on definition of disease severity ('moderate to severe') using PASI thresholds: • Company: '**moderate to severe**'; PASI ≥10 and DLQI >10 • NICE (previous TAs): '**severe**'; PASI ≥10 and DLQI >10 *Has implications for generalisability of trial population and economic analysis*
Comparators	Inappropriate to exclude comparators in scope At clarification: company: UVB studies not searched in SLR; 'limited relevance' due to position in pathway. ERG: studies with UVB might be relevant for NWMA estimates
Outcomes	Symptoms on the face could have a psychological impact on patients Excluding this outcome makes it difficult to draw conclusions from clinical evidence for those with symptoms on face

Dermatology Life Quality Index (DLQI); Psoriasis Area and Severity Index (PASI); Systematic Literature Review (SLR); Network Meta-analysis (NWMA)

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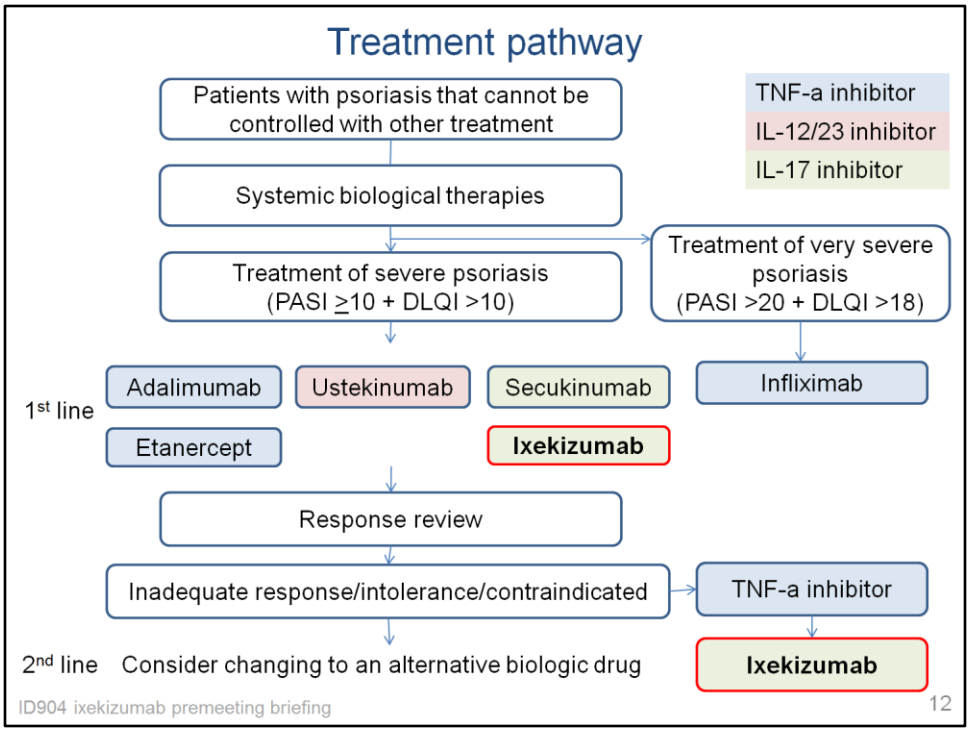
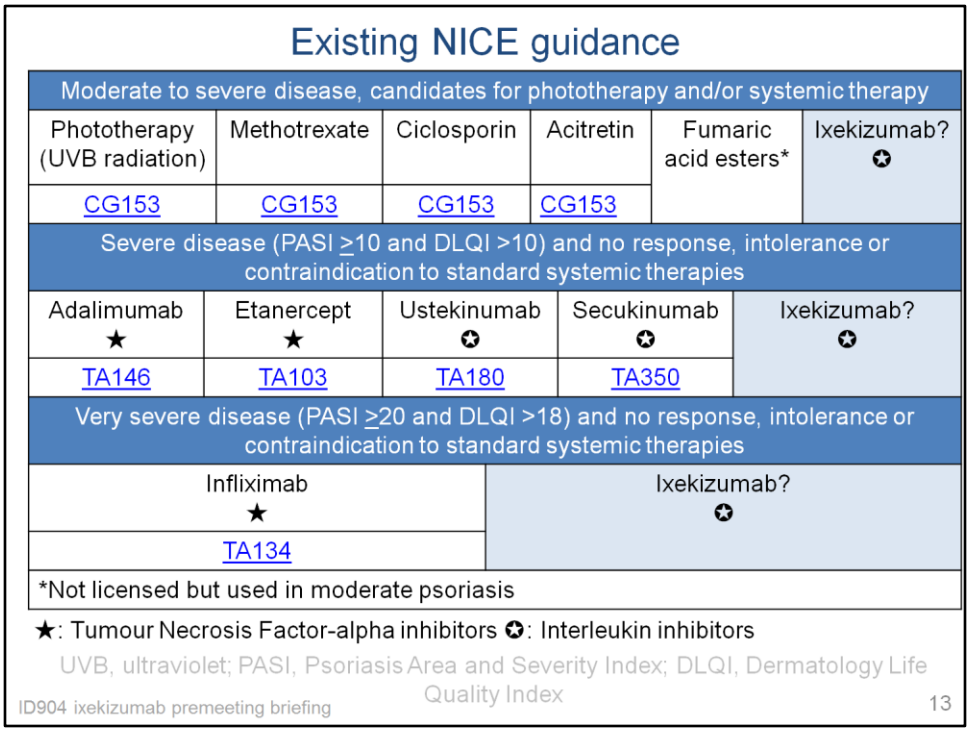
Source: ERG report, Sections 3.1, 3.3 (page 33), 3.4 (page 34), 4.2 (page 51)



Source: Adapted from Company submission, Section 3.3.2, Figure 5 (page 45)



Source: Company submission, Section 3.5 (page 46-7)

Ixekizumab is listed alongside the pre-biologic therapies because the MA wording suggests it could be used here (adults who are candidates for systemic therapy). However, NICE only recommends biologics after standard systemic therapies have failed, and the company align the position of ixekizumab with the other biologics.

NICE guidance refers to prior failure of PUVA (psoralen and long wave ultraviolet radiation). NICE guidance 153 recommends phototherapy (UVB radiation) and only to consider PUVA when treating palmoplantar pustulosis (because of increased risk of skin cancer).

Company's clinical evidence

3 key clinical trials

Trials	UNCOVER-1, UNCOVER-2, UNCOVER-3
Design	Phase III; multicentre; randomised; double-blind
Population	Adults with moderate to severe plaque psoriasis (who are candidates for phototherapy and/or systemic therapy) UNCOVER-1: 1,296; UNCOVER-2: 1,224; UNCOVER-3: 1,346
Intervention	Ixekizumab 160mg starting dose, 80mg Q2W or 80mg Q4W*
Comparator	UNCOVER-1 placebo UNCOVER-2 placebo; etanercept 50mg BIW UNCOVER-3 placebo; etanercept 50mg BIW
Primary Outcomes	• PASI 75 response rate at week 12 • sPGA (0,1) response rate at week 12 with at least 2-point improvement from baseline
Duration	5 years (including long-term safety and efficacy follow-up)
*Licensed dose: 160mg at week 0, 80mg Q2W until week 12 , then 80mg Q4W.	

Q2W, every 2 weeks; Q4W, every 4 weeks; BIW, twice weekly; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment

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Source: Company submission, Section 4.2, Table 9 (page 59), Section 4.3.6, Table 14 (page 78)

Total of [redacted] in UK, [redacted]. No UK centre in UNCOVER-3.

Systematic Review conducted in December 2014 (data from January 1990), updated November 2015.

Only PUVA (psoralen and longwave ultraviolet radiation) is in PICO (not UVB) **Source**: Company submission, Section 4.1.3, Table 7 (page 53).

ERG had some concerns about whether the systematic review was conducted according to best practice because of information lacking from the company submission, and some concerns about its potentially restrictive approach. However, they conducted their own search and did not find any additional evidence. **Source**: ERG report, Sections 4.1.1 (page 36), 4.1.3, 4.1.4 (page 39).

Company's clinical evidence

Dosing regimens

Dosing period	UNCOVER-1		UNCOVER-2		UNCOVER-3	
Ixekizumab						
Induction	Q2W (n=433)	Q4W (n=432)	Q2W (n=351)	Q4W (n=347)	Q2W (n=385)	Q4W (n=386)
Maintenance	Q4W (n=229)	Q12W (n=227)	Q4W (n=187)	Q12W (n=227)	N/A	N/A
Etanercept						
Induction	N/A		BIW (n=358)		BIW (n=382)	
Maintenance	N/A		N/A		N/A	
Placebo						
Induction	Q2W (n=431)		Q2W (n=168)		Q2W (n=193)	
Maintenance	Q4W (n=226)		Q4W (n=176)		N/A	
Patients re-randomised for maintenance period based on responder status: Responder = sPGA score of 0 or 1 with at least a 2-point improvement from baseline Non-responder = sPGA score of <1						

Q2W, every 2 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; BIW, twice weekly; sPGA, static Physician Global Assessment

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Source: Company submission, Section 4.2, Table 6 (page 59), Section 4.3.1, Table 10 (page 62), Figures 7,8,9 (pages 64-8), Section 4.3.5, Table 12 (page 72).

Company's clinical evidence

Baseline characteristics of patients – severity of disease

UNCOVER –x (arm)	PASI mean (SD)	PASI range	DLQI mean (SD)	DLQI range
-1 (Ixekizumab)	20.06 (7.65)	12.0 - 61.2	13.3 (7.02)	0 - 30
-1 (Placebo)	20.32 (8.64)	12.0 - 69.2	12.8 (7.11)	0 - 30
-2 (Ixekizumab)	19.69 (7.16)	12.0 - 57.5	12.0 (6.76)	0 - 30
-2 (Etanercept)	19.07 (6.70)	12.0 - 61.2	12.7 (7.03)	0 - 30
-2 (Placebo)	20.57 (8.37)	12.0 - 54.0	12.8 (7.24)	0 - 30
-3 (Ixekizumab)	20.94 (8.16)	12.0 - 63.0	12.1 (6.95)	0 - 30
-3 (Etanercept)	20.68 (8.17)	12.0 - 57.0	11.5 (6.84)	0 - 30
-3 (Placebo)	21.11 (8.39)	12.0 - 49.1	12.7 (7.00)	0 - 29

PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment; DQLI, Dermatology Life Quality Index

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Source: Company submission, Section 4.5.4, Tables 17,18,19 (pages 91-6)

Company's clinical evidence

Baseline characteristics of patients – previous treatment

	Systemic therapy never used	Previous non-biologic systemic therapy	Previous biologics	Previous non-biologics and biologics	Previous phototherapy
-1 Ixe	27.7%	32.8%	12.8%	26.6%	46.9%
-1 Pbo	30.6%	27.4%	13.2%	28.8%	42.9%
-2 Ixe	34.5%	41.3%	8.2%	16.0%	46.3%
-2 Eta	37.2%	41.6%	9.2%	12.0%	48.3%
-2 Pbo	38.1%	36.3%	11.3%	14.3%	44.0%
-3 Ixe	43.1%	41.9%	6.2%	8.8%	39.6%
-3 Eta	41.9%	42.4%	6.8%	8.9%	41.1%
-3 Pbo	45.6%	37.3%	8.3%	8.8%	31.1%
Note that prior use of etanercept excluded in UNCOVER-2,-3					

Ixe, Ixekizumab; Pbo, Placebo; Eta, Etanercept

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Source: Company submission, Section 4.5.4, Tables 17, 18, 19 (pages 91-6)

This is most relevant when considering the modelling.

Clinical evidence – ERG critique

Generalisability of UNCOVER trials to NHS patients

Thresholds	Source	Definition
PASI ≥12 + BSA ≥10%	UNCOVER trial eligibility criteria	Moderate to severe disease (and candidates for phototherapy and/or systemic therapy)
PASI ≥10 + DLQI >10	Company definition	Moderate to severe disease
PASI ≥10 + DLQI >10	NICE definition (previous technology appraisals)	Severe disease
PASI > 10 (or 12)	ERG's clinical experts	Moderate to severe disease (in context of systemic therapy)

- Do the UNCOVER trials include people with moderate/less severe disease?
- Are the UNCOVER trial populations representative of NHS patients?

PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area; DLQI, Dermatology Life Quality Index

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Source: ERG report, Section 4.2 (page 51)

See also: Company's clarification response B.1 (page 21) and B.2 (pages 22-3)

Quality assessment of UNCOVER trials – for UNCOVER -2 ERG say there were unexpected imbalances in drop-outs between the 2 groups, but agrees low risk of bias. **Source**: ERG report, Section 4.2 (pages 55-6).

Company's clinical evidence
Results – UNCOVER-1

Response rates (ITT) at week 12 – ixekizumab higher (p=<0.001)

		Ixekizumab Q2W n=433	Ixe total (Q2W & Q4W) n=865	Placebo n=431
PASI 75	%	89.1%	85.9%	3.9%
	Odds Ratio (95% CI)	223.94 (125.05, 401.03)	N/A	N/A
sPGA 0,1	%	81.8%	79.1%	3.2%
	Odds Ratio (95% CI)	146.51 (81.02, 264.92)	N/A	N/A

ITT, Intention-to-Treat; Q2W, every 2 weeks; Q4W, every 4 weeks; PASI, Psoriasis Area and Severity Index; CI, confidence interval; sPGA, static Physician Global Assessment

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Source: Company submission, Section 4.7.1, Table 21 (page 100)

Results – UNCOVER-2

Response rates (ITT) at week 12 – ixekizumab higher (p=<0.001 for all comparators)

		Ixe Q2W n=351	Ixe total (Q2W & Q4W) n=698	Eta n=358	Pbo n=168
PASI75	%	89.7%	83.7	41.6%	2.4%
	OR vs. Pbo (95% CI)	997.29 (173.11, 5745.5)	289.78 (88.85, 945.09)	30.73 (10.83, 87.16)	N/A
	OR vs. Eta (95% CI)	13.28 (8.66, 20.34)	7.63 (5.64, 10.31)	N/A	N/A
sPGA 0,1	%	83.2%	78.1	36.0%	2.4%
	OR vs. Pbo (95% CI)	282.24 (76.03, 1047.71)	174.63 (57.78, 527.84)	27.58 (9.40, 80.98)	N/A
	OR vs. Eta (95% CI)	10.70 (7.23, 15.85)	7.37 (5.44, 9.97)	N/A	N/A

ITT, Intention-to-Treat; Ixe, Ixekizumab; Eta, Etanercept; Pbo, Placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; PASI, Psoriasis Area and Severity Index; OR, odds ratio; CI, confidence interval; sPGA, static Physician Global Assessment

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Source: Company submission, Section 4.7.2, Table 33 (page 113)

Results – UNCOVER-3

Response rates (ITT) at week 12 – ixekizumab higher (p=<0.001 for all comparators)

		Ixe Q2W n=385	Ixe total (Q2W & Q4W) n=771	Eta n=382	Pbo n=193
PASI 75	%	87.3%	85.7%	53.4%	7.3%
	OR vs. Pbo (95% CI)	72.29 (36.11, 144.73)	70.51 (37.83, 131.44)	13.71 (7.61, 24.72)	N/A
	OR vs. Eta (95% CI)	6.46 (4.42, 9.45)	5.59 (4.15, 7.52)	N/A	N/A
sPGA 0,1	%	80.5%	78%	41.6%	6.7%
	OR vs. Pbo (95% CI)	50.47 (26.54, 95.98)	45.53 (24.75, 83.75)	11.30 (6.01, 21.25)	N/A
	OR vs. Eta (95% CI)	6.47 (4.55, 9.20)	5.55 (4.17, 7.38)	N/A	N/A

ITT, Intention-to-Treat; Ixe, Ixekizumab; Eta, Etanercept; Pbo, Placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; PASI, Psoriasis Area and Severity Index; OR, odds ratio; CI, confidence interval; sPGA, static Physician Global Assessment

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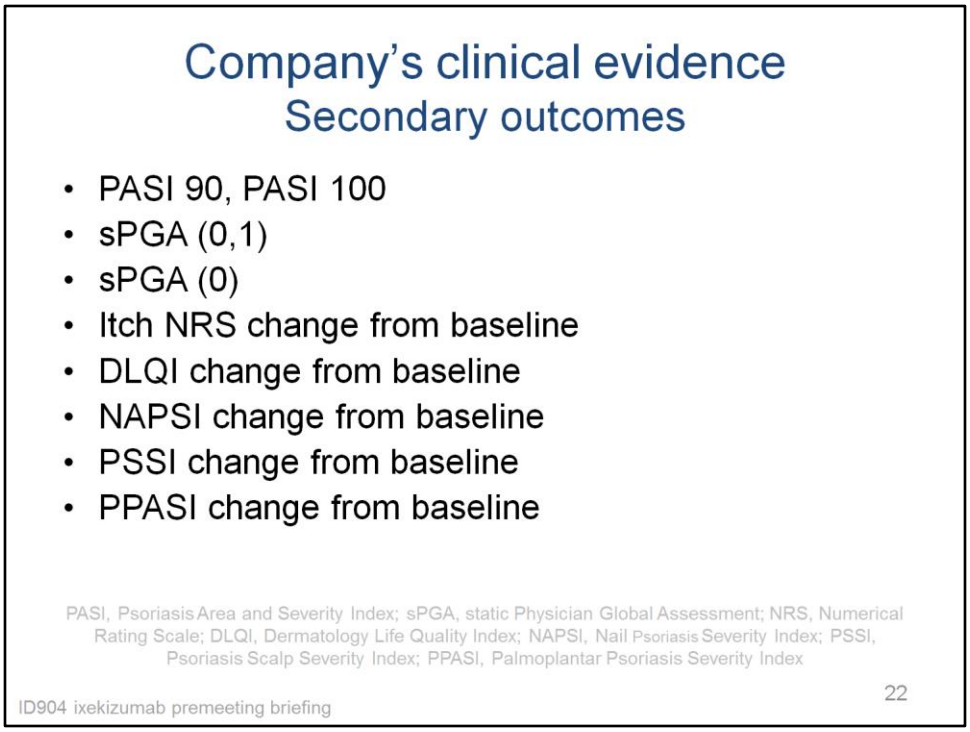
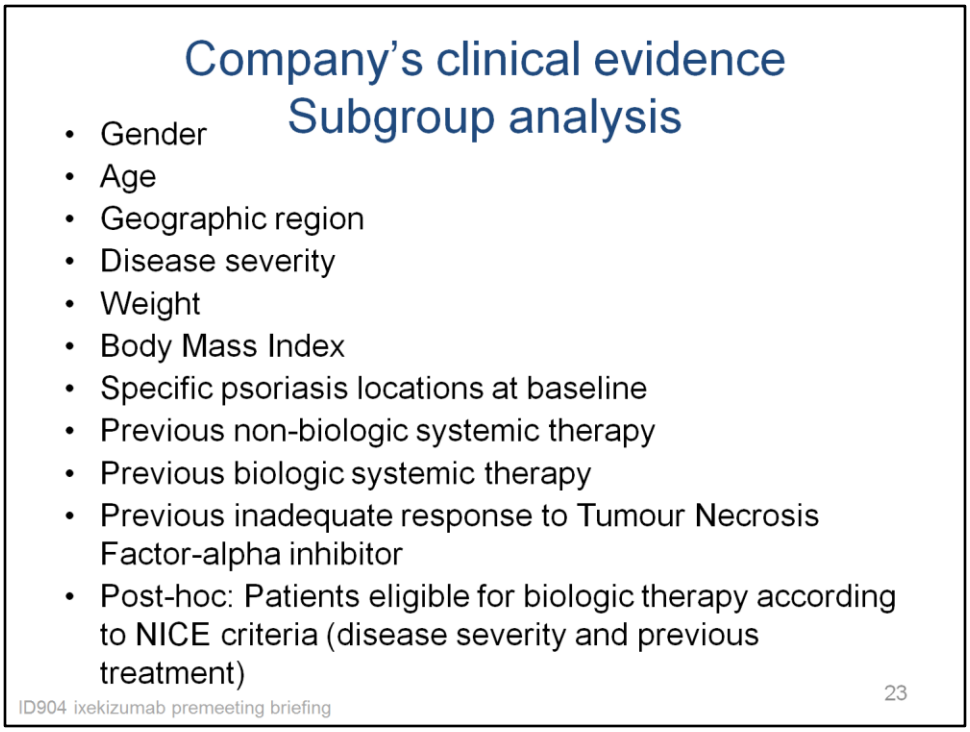
Source: Company submission, Section 4.7.3, Table 37 (page 119)

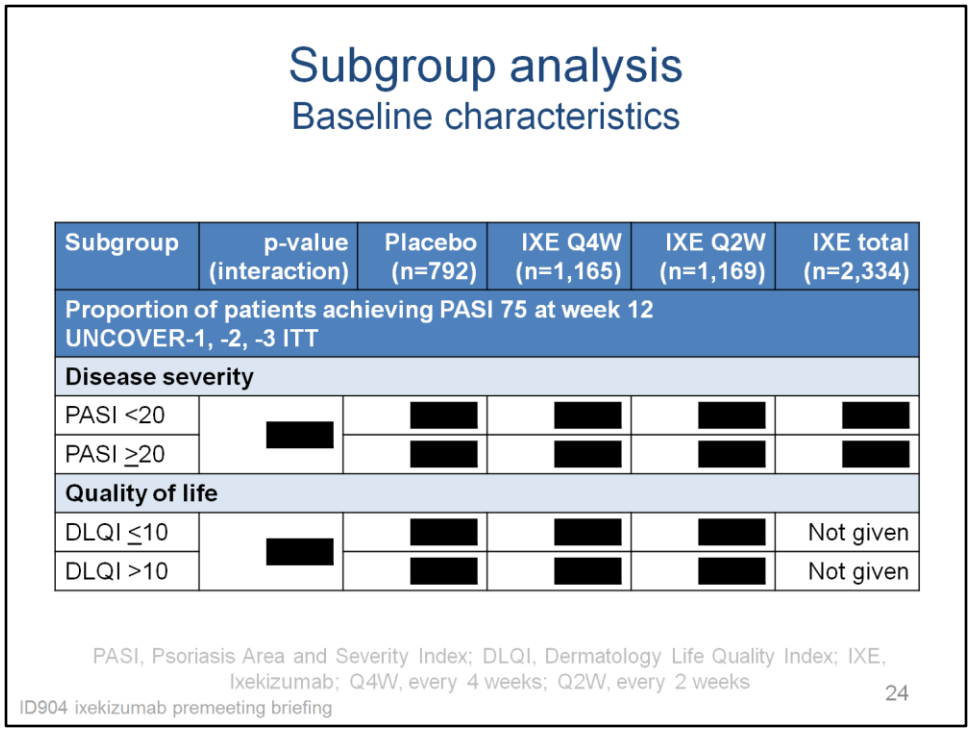


Source: Company Submission, Section 4.3.6, Table 14 (page 80)



Source: Company Submission, Section 4.3.6, Table 14 (page 81)

NICE requested evidence in subgroups of patients previously treated by systematic non-biological or biological therapies and in patients with different severity of psoriasis (moderate, severe) if data were available.



Subgroup analysis
Baseline characteristics

Subgroup	p-value (interaction)	Placebo (n=792)	IXE Q4W (n=1,165)	IXE Q2W (n=1,169)	IXE total (n=2,334)
Proportion of patients achieving PASI 75 at week 12 UNCOVER-1, -2, -3 ITT					
Disease severity					
PASI <20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI ≥20		[redacted]	[redacted]	[redacted]	[redacted]
Quality of life					
DLQI ≤10	[redacted]	[redacted]	[redacted]	[redacted]	Not given
DLQI >10		[redacted]	[redacted]	[redacted]	Not given

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; IXE, Ixekizumab; Q4W, every 4 weeks; Q2W, every 2 weeks

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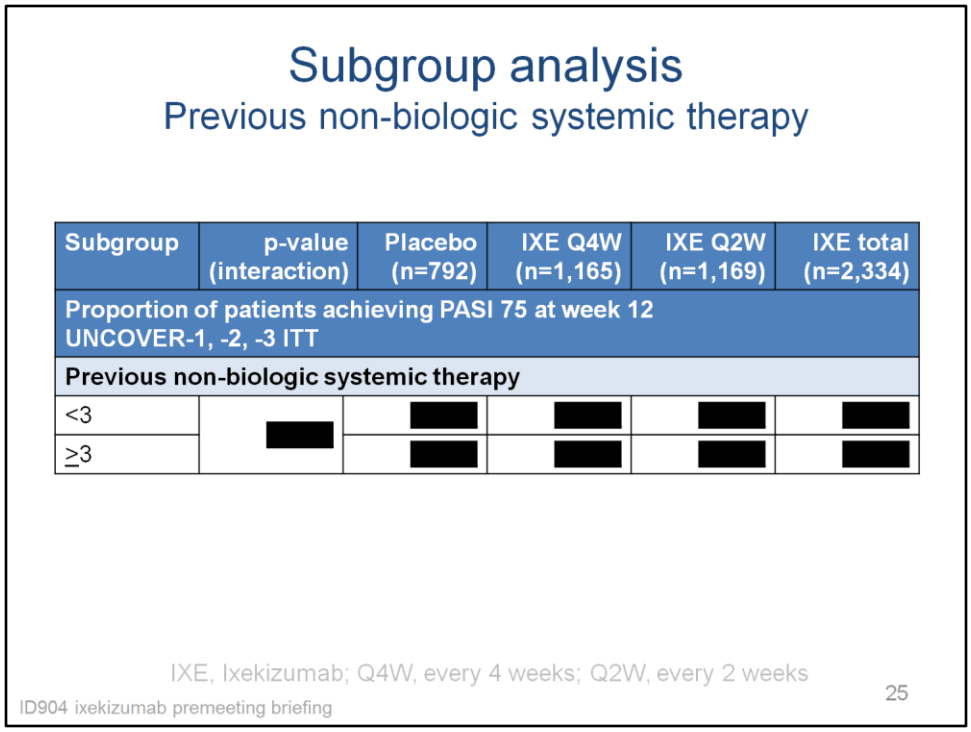
Source: Company submission, Section 4.8, Table 44 (page 132-3)

Source: Clarification response, Section B1.



Source: Company submission, Section 4.8, Table 44 (page 132-3)

Subgroup analysis

Previous biologic treatment

Proportion of patients achieving PASI 75 at week 12				
UNCOVER-2	Ixe Q2W	Ixe Q4W	Eta	Pbo
Prior biologic therapy (n=288)	92.9%	74.1%	30.3%	0%
Biologic-naïve (n=936)	88.8%	78.6%	44.3%	3.2%

Proportion of patients achieving PASI 75 at week 12					
UNCOVER-1, -2, -3 ITT, Placebo-Controlled. Previous biologic therapy n=883					
Discontinued previous biologic therapy due to inadequate response					
Ixe Q2W	[redacted]	Ixe Q4W	[redacted]	Placebo	[redacted]
Discontinued previous biologic therapy due to other reasons					
Ixe Q2W	[redacted]	Ixe Q4W	[redacted]	Placebo	[redacted]

PASI, Psoriasis Area and Severity Index; IXE, Ixekizumab; Q4W, every 4 weeks; Q2W, every 2 weeks

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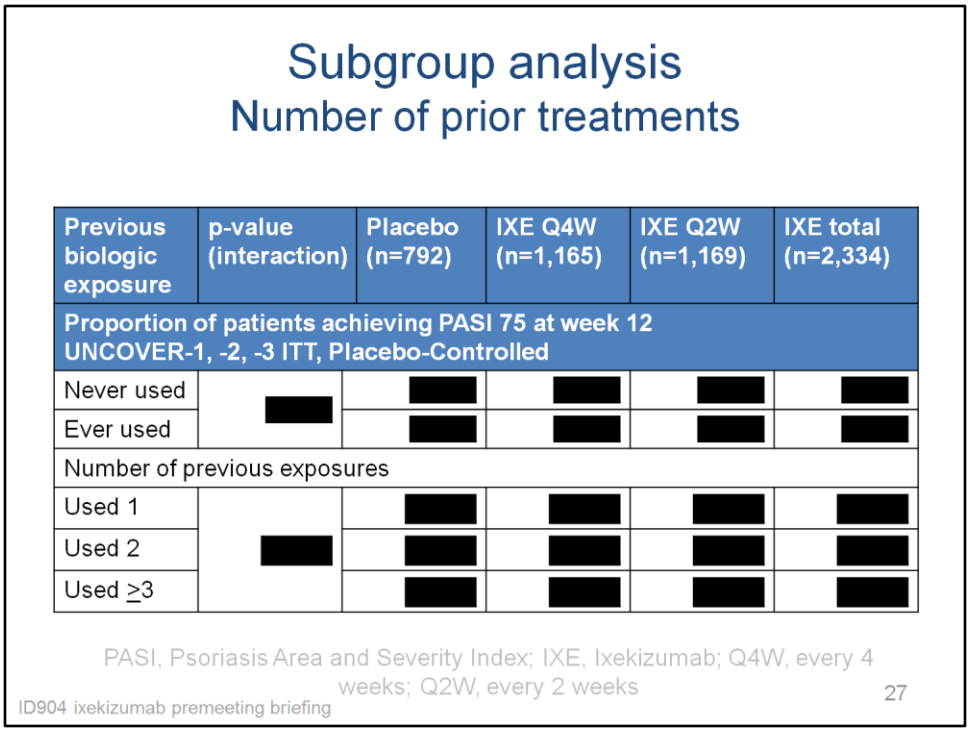
Source: Company submission, Section 4.8.2 (page 134-6)



Subgroup analysis
Number of prior treatments

Previous biologic exposure	p-value (interaction)	Placebo (n=792)	IXE Q4W (n=1,165)	IXE Q2W (n=1,169)	IXE total (n=2,334)
Proportion of patients achieving PASI 75 at week 12 UNCOVER-1, -2, -3 ITT, Placebo-Controlled					
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used		[redacted]	[redacted]	[redacted]	[redacted]
Number of previous exposures					
Used 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Used 2		[redacted]	[redacted]	[redacted]	[redacted]
Used ≥3		[redacted]	[redacted]	[redacted]	[redacted]

PASI, Psoriasis Area and Severity Index; IXE, Ixekizumab; Q4W, every 4 weeks; Q2W, every 2 weeks

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Source: Company submission, Section 4.8.2, Table 45 (page 137)

Subgroup analysis – ERG critique Summary of results

- Consistently high PASI 75 response rates shown for ixekizumab compared with placebo regardless of previous treatment (non-biologic systemic treatments or biologics)
- Company provided additional information at clarification that showed low heterogeneity across the UNCOVER studies by the results of study treatment interaction

PASI, Psoriasis Area and Severity Index

Source: ERG report, Section 4.2 (page 70)

See also: Company's clarification response A.13 (pages 12-20)

Adverse events – UNCOVER-1

	Ixekizumab Q2W (n=433)	Ixekizumab Q4W (n=432)	Ixekizumab Total (n=865)	Placebo (n=431)
Induction period				
Patients with ≥1 TEAEs	59.4%	61.1%	60.2%	48.7%
Discontinuations due to AEs	2.3%	2.3%	2.3%	1.4%
Deaths	0.0%	0.0%	0.0%	0.0%
SAEs	1.4%	2.8%	2.1%	1.2%
TEAEs possibly related to study drug	29.3%	25.7%	27.5%	11.4%
Per protocol population = 94.9% patients				
Company reported majority of TEAEs of mild to moderate severity and did not lead to stopping treatment				

Q2W, every 2 weeks; Q4W, every 4 weeks, TEAEs, Treatment Emergent Adverse Events; AEs, Adverse Events; SAEs, Serious Adverse Events

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Source: Company submission, Section 4.12.1, Table 57 (page 180)

Most frequent AESIs (Adverse Events of Special Interest) infection and injection site reactions.

After 12 weeks commonly observed types of infections were nasopharyngitis, upper respiratory tract infection, bronchitis and sinusitis.

Adverse events – UNCOVER-2

	Ixekizumab Q2W (n=350)	Ixekizumab Q4W (n=347)	Ixekizumab Total (n=697)	Etanercept (n=357)	Placebo (n=167)
Induction period					
Patients with ≥1 TEAEs	61.7%	58.8%	60.3%	59.1%	53.3%
Discontinuations due to AE	1.7%	1.4%	1.6%	1.4%	0.6%
Deaths	0.0%	0.0%	0.0%	0.0%	0.0%
SAEs	1.4%	2.3%	1.9%	2.2%	1.2%
TEAEs possibly related to study drug	33.4%	26.5%	30.0%	26.5%	18.0%
Per protocol population = 94.9% patients					
Company reported majority of TEAEs of mild to moderate severity and did not lead to stopping treatment					

Q2W, every 2 weeks; Q4W, every 4 weeks, TEAEs, Treatment Emergent Adverse E

 AEs, Adverse Events; SAEs, Serious Adverse Events

Source: Company submission, Section 4.12.2, Table 59 (page 184)

Most frequent AESIs (Adverse Events of Special Interest) infection and injection site reactions.

After 12 weeks commonly observed types of infections were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis and influenza.

Adverse events – UNCOVER-3

	Ixekizumab Q2W (n=384)	Ixekizumab Q4W (n=382)	Ixekizumab Total (n=766)	Etanercept (n=382)	Placebo (n=193)
Induction period					
Patients with ≥1 TEAEs	53.4%	56.3%	54.8%	49.0%	36.3%
Discontinuations due to AE	2.3%	2.1%	2.2%	1.0%	1.0%
Deaths	0.0%	0.0%	0.0%	0.0%	0.0%
SAEs	2.3%	1.6%	2.0%	1.3%	2.6%
TEAEs possibly related to study drug	26.8%	21.7%	24.3%	22.3%	12.4%
Per protocol population = 94.7% patients					
Company reported majority of TEAEs of mild to moderate severity and did not lead to stopping treatment					

Q2W, every 2 weeks; Q4W, every 4 weeks, TEAEs, Treatment Emergent Adverse E

ID904 ixekizumab premeeting briefing AEs, Adverse Events; SAEs, Serious Adverse Events 31

Source: Company submission, Section 4.12.3, Table 61 (page 188)

Most frequent AESIs (Adverse Events of Special Interest) infection and injection site reactions.

After 12 weeks commonly observed types of infections were nasopharyngitis, upper respiratory tract infection and urinary tract infection.

Network meta-analysis
Included studies

Comparator	Trials
Base case analysis	
Adalimumab	Gordon 2015, Bissonette, CHAMPION, Asahina, REVEAL, Gordon 2006*
Etanercept	UNCOVER-2, -3, ERASURE, FIXTURE, ACCEPT, Gottlieb 2003, Leonardi, Papp, Van de Kerkhof
Ustekinumab	ACCEPT, AMAGINE-2, AMAGINE-3, LOTUS, Igarashi, PEARL, PHOENIX-1, PHOENIX-2, CLEAR
Secukinumab	ERASURE, FIXTURE, FEATURE, JUNCTURE, CLEAR
Infliximab	EXPRESS II, Chaudhari, Yang, Torii, EXPRESS, SPIRIT
Scenario analyses **1 – etanercept 50mg BIW + systemic treatments; 2 – systemic treatments**	
Etanercept 50mg BIW	PRISTINE, Tyring, Bachelez, Bagel, Gottlieb 2011, Strober
Methotrexate	CHAMPION, RESTORE
Ciclosporin	Meffert
*additional study identified by ERG	

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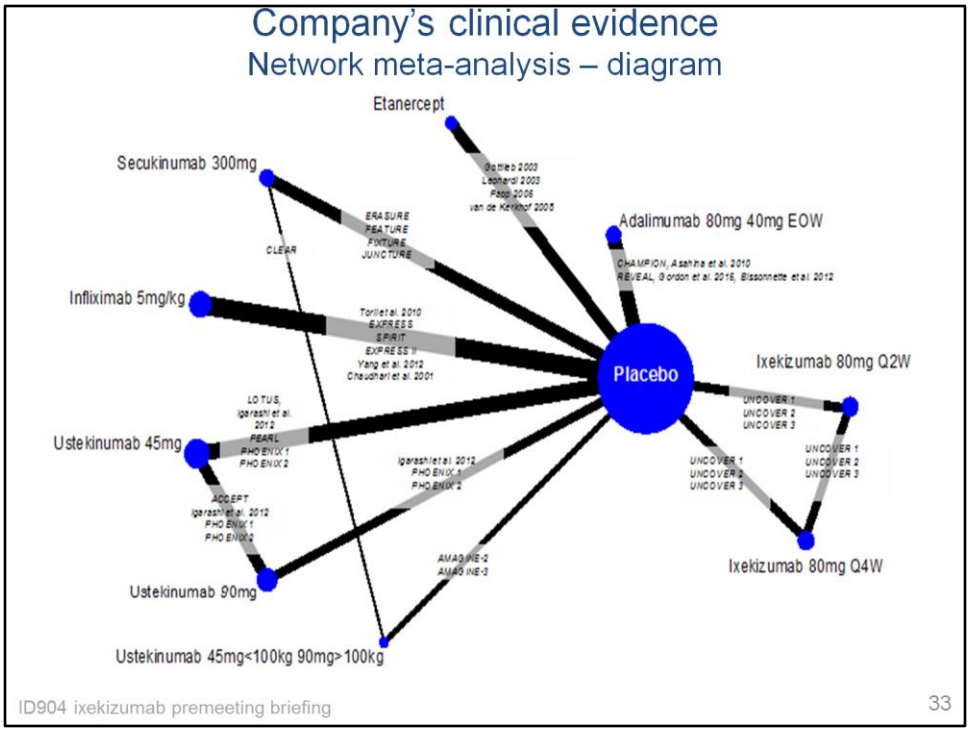
Source: Adapted from Company submission, Section 4.10.4, Table 48 (pages 145-54)

Gordon 2006 = Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomised controlled trial and open-label extension study; adalimumab + placebo

Gordon 2015 = A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis; adalimumab + guselkumab + placebo



Source: Company submission, Section 4.10.4, Figure 27 (page 143)

Clinical evidence – network meta-analysis

Trial populations generally similar

	Company	ERG
Baseline PASI score	• Entry criteria 'largely consistent' with PASI ≥10-12 • Baseline PASI score mean: 21.1 (standard deviation 2.8), median: 20.4	• Agrees no major imbalances of baseline characteristics, although some patients had PASI <10
Previous treatments	• Varied • Not all patients had inadequate response or contraindicated to standard systemic therapies	• Some trials had higher numbers of patients who had had biologic therapy before • Potential bias introduced as NICE guideline on psoriasis says effectiveness is lower when used as 2nd biologic treatment in a sequence

PASI, Psoriasis Area and Severity Index

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Source: Company submission, Sections 4.10.6, 4.10.7 (page 155), 4.10.8 (page 165)

Source: ERG report, Section 4.3 (pages 79, 96)

Company:

PASI response rate as primary outcome measure consistent with NICE STA submissions for biologics in psoriasis.

Aligns with efficacy inputs to inform cost-effectiveness model.

Baseline characteristics of patients in Table 49 (pages 156-9)

Results of each trial (PASI responses) in Table 50 (pages 160-3)

Subgroup of patients who had inadequate response to TNF-α inhibitors considered, but could not be progressed.

ERG:

Identified an additional study to include (Gordon, 2006) but it affected the results only slightly.

UNCOVER-1, FEATURE, NCT01483599, PHOENIX 1 and PHOENIX 2 trials had higher percentages of patients who had received biologic treatments before.

Random effects multinomial network meta-analysis for PASI 75 response – relative risk at week 12

Relative risk of Ixekizumab Q2W achieving PASI 75 significantly higher that all other biologic therapies except infliximab

Placebo	0.11 (0.06, 0.19)	0.09 (0.05, 0.16)	0.09 (0.05, 0.16)	0.07 (0.03, 0.15)	0.08 (0.04, 0.15)	0.06 (0.02, 0.14)	0.07 (0.03, 0.14)	0.07 (0.03, 0.14)	0.06 (0.02, 0.14)
9.48 (5.15, 15.87)	**Etanercept**	0.78 (0.49, 1.07)	0.76 (0.49, 1.04)	0.62 (0.36, 0.87)	0.66 (0.40, 0.92)	0.54 (0.28, 0.80)	0.57 (0.31, 0.83)	0.57 (0.31, 0.82)	0.53 (0.26, 0.79)
12.56 (6.15, 21.05)	1.34 (0.93 2.04)	**Adalimumab**	0.98 (0.77, 1.23)	0.80 (0.58, 0.96)	0.86 (0.65, 1.03)	0.69 (0.46, 0.89)	0.74 (0.51, 0.91)	0.73 (0.50, 0.91)	0.68 (0.44, 0.87)
12.85 (6.20, 21.60)	1.37 (0.96, 2.05)	1.03 (0.82, 1.31)	**Ustekinumab 45+90mg**	0.82 (0.60, 0.97)	0.88 (0.67, 1.05)	0.71 (0.47, 0.89)	0.75 (0.55, 0.91)	0.75 (0.53, 0.91)	0.69 (0.45, 0.88)
16.26 (6.82, 30.77)	1.71 (1.15, 2.79)	1.27 (1.04, 1.72)	1.25 (1.03, 1.65)	**Ustekinumab 90mg**	1.08 (1.01, 1.21)	0.87 (0.68, 0.98)	0.92 (0.77, 1.04)	0.91 (0.75, 1.04)	0.84 (0.66, 0.96)
14.96 (6.60, 27.03)	1.58 (1.09, 2.50)	1.18 (0.97, 1.54)	1.16 (0.96, 1.48)	0.93 (0.83, 0.99)	**Ustekinumab 45mg**	0.81 (0.60, 0.95)	0.86 (0.68, 0.98)	0.85 (0.66, 0.98)	0.79 (0.58, 0.93)
19.28 (7.18, 40.87)	2.00 (1.24, 3.62)	1.48 (1.13, 2.20)	1.45 (1.12, 2.12)	1.16 (1.02, 1.46)	1.25 (1.06, 1.66)	**Infliximab**	1.07 (0.95, 1.25)	1.06 (0.94, 1.23)	0.97 (0.85, 1.07)
17.86 (7.03, 35.65)	1.87 (1.21, 3.19)	1.39 (1.10, 1.95)	1.35 (1.10, 1.82)	1.09 (0.96, 1.31)	1.17 (1.02, 1.48)	0.94 (0.80, 1.05)	**Secukinumab**	0.99 (0.87, 1.12)	0.91 (0.78, 1.00)
18.09 (7.05, 36.40)	1.89 (1.21, 3.28)	1.40 (1.10, 1.98)	1.37 (1.09, 1.91)	1.10 (0.97, 1.34)	1.19 (1.02, 1.51)	0.95 (0.81, 1.07)	1.01 (0.89, 1.14)	**Ixekizumab Q4W**	0.92 (0.82, 0.98)
19.93 (7.24, 42.96)	**2.07 (1.26, 3.79)**	**1.53 (1.15, 2.29)**	**1.49 (1.14, 2.20)**	**1.20 (1.04, 1.52)**	**1.29 (1.08, 1.74)**	**1.03 (0.94, 1.17)**	**1.10 (1.00, 1.29)**	**1.09 (1.02, 1.22)**	**Ixekizumab Q2W**

Relative risk (credible interval)

NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; QIW=Once weekly dosing regimen; Q2W=Every second week

Source: Company submission, Section 4.10.14, Table 51 (page 167)

Company's clinical evidence

Results of network meta-analysis, base case, absolute probabilities of achieving PASI 75

Treatment	Probability	95% CrI	
Ixekizumab 80mg Q2W	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	81.8%	74.9%	88.1%
Infliximab 5mg/kg	81.1%	72.6%	88.1%
Ustekinumab 45mg	71.0%	62.2%	78.8%
Ustekinumab 90mg	75.1%	66.2%	82.7%
Ustekinumab 45mg<100kg & 90 mg>100kg	64.4%	54.0%	73.9%
Adalimumab 80mg/40mg EOW	57.5%	46.4%	68.2%
Etanercept 25mg BIW & 50mg QW	41.3%	30.3%	52.8%
Placebo	4.7%	3.1%	6.6%

Q2W, every 2 weeks; Q4W, every 4 weeks; EOW, every other week; BIW, twice weekly; PASI, Psoriasis Area and Severity Index; CrI, credible interval

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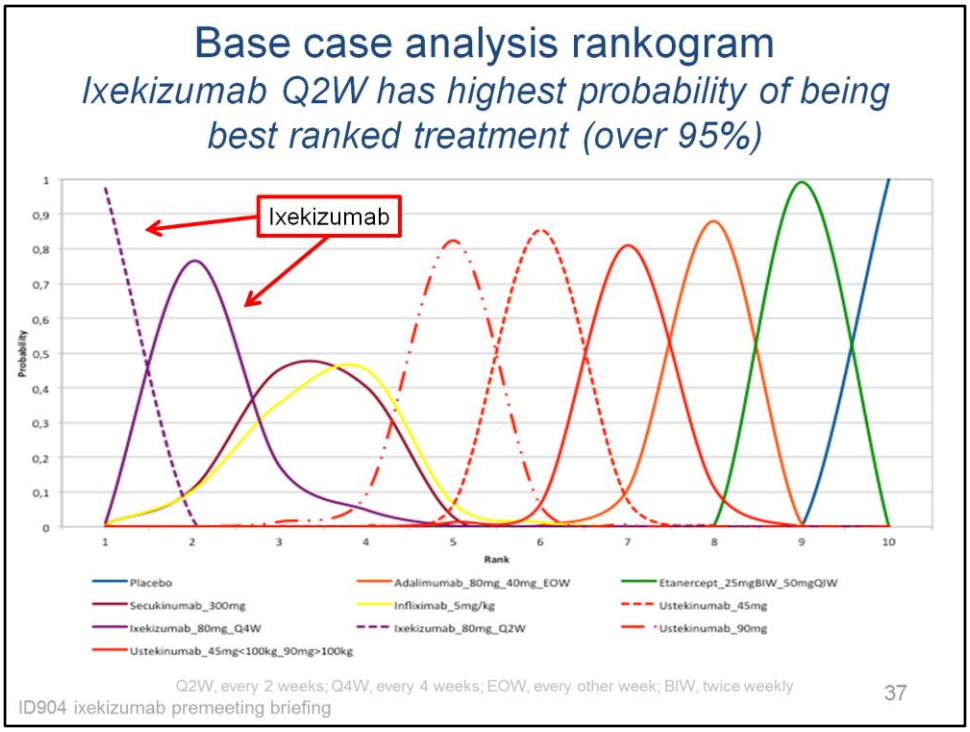
Source: Company submission, Section 4.10.14, Table 52 (page 168). Company also provided PASI 50, 90, 100 NWMA analysis results.

Includes ixekizumab Q4W dose but cost effectiveness analysis only includes Q2W

ERG re-ran results including the additional paper (Gordon, 2006); results shown in ERG report, Table 4.16 (page 101). Results were slightly different.



Source: Company submission, Section 4.10.4, Figure 30 (page 169)

Rankogram from base case Bayesian analysis with treatments ranked on the probability of best based on the posterior distributions for each intervention

Company's clinical evidence

Results of network meta-analysis, scenario analyses

- Company provided 2 additional network meta-analysis scenarios:
  - Scenario analysis 1: Ixekizumab vs etanercept 50mg BIW (unlicensed dose) and standard systemic treatments (including methotrexate and ciclosporin)
  - Scenario analysis 2: Ixekizumab vs standard systemic treatments (including methotrexate and ciclosporin)

BIW, twice weekly

Results of network meta-analysis, scenario analysis 1, absolute probabilities of achieving PASI 75

Treatment	Probability	95% CrI	
Ixekizumab 80mg Q2W	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	82.6%	75.8%	88.5%
Infliximab 5mg/kg	81.3%	72.3%	88.6%
Ustekinumab 45mg	69.2%	60.4%	77.4%
Ustekinumab 90mg	73.2%	64.5%	81.1%
Ustekinumab 45mg<100kg & 90 mg>100kg	64.3%	53.7%	74.2%
Adalimumab 80mg/40mg EOW	56.8%	45.2%	67.8%
Etanercept 25mg BIW & 50mg QW	37.1%	27.7%	47.2%
Etanercept 50mg BIW	51.7%	43.3%	60.2%
Ciclosporin 2.5mg/kg/day	37.1%	14.7%	64.4%
Methotrexate 15mg/week	40.6%	24.6%	58.2%
Methotrexate 7.5 to 25mg/week	19.5%	9.6%	32.5%
Placebo	4.4%	2.9%	6.3%

Q2W, every 2 weeks; Q4W, every 4 weeks; EOW, every other week; BIW, twice weekly; PASI, Psoriasis Area and Severity Index; CrI, credible interval

Source: Company submission, Section 4.10.14, Table 53 (page 170)

Scenario analysis 1 includes etanercept 50mg BIW (not NICE approved) and standard systemic therapies (methotrexate and ciclosporin)

Inclusion of etanercept 50mg BIW for a scenario analysis 'expanded the decision set and allowed inclusion of a number of studies that included an active head to head comparison with etanercept 50mg BIW'.

Company's clinical evidence

Results of network meta-analysis, scenario analysis 2, absolute probabilities of achieving PASI 75

Treatment	Probability	95% CrI	
Ixekizumab 80mg Q2W	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]
Ciclosporin 2.5mg/kg/day	43.5%	14.7%	76.8%
Methotrexate 7.5 to 25mg/week	20.4%	5.8%	43.4%
Placebo	6.8%	4.6%	9.4%

Q2W, every 2 weeks; Q4W, every 4 weeks; PASI, Psoriasis Area and Severity Index; CrI, credible interval

Source: Company submission, Section 4.10.14, Table 54 (page 172)

Scenario analysis 2 includes the 'decision set interventions' for ixekizumab and standard systemic treatments

Network meta-analysis – Heterogeneity & model fit

	Mean tau	Tau SD	Median tau	97.5 CrI	
Base case analysis	129.2	207.5	72.3	22.0	632.5
Scenario analysis 1 (etanercept 50mg BIW & standard systematic therapies)	75.9	62.8	58.7	22.6	244.0
Scenario analysis 2 (standard systemic therapies)	931.2	10760.0	30.5	1.8	3575.0

DIC	Random-effects model	Fixed-effects model
Base case analysis	1306.50	1313.19

Random effects model chosen as most appropriate analysis as it had lower deviance information criteria (DIC)

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Source: Company submission, Section 4.10.15, Table 55 (page 173), Section 4.10.16 (page 175)

ERG advised at pre-meet that random effects model generally preferred.

Network meta-analysis – ERG critique

- Methods in line with NICE Decision Unit (DSU) guidance
- ERG identified an additional 10 studies
  - 7 do not connect to the network due to unlicensed doses
  - 2 could not be added due to missing PASI information
  - Gordon 2006 (adalimumab vs placebo) met all inclusion criteria
    - Similar results when added to network
- "the selection of studies for inclusion in the NMA appears to be appropriate"

Cost effectiveness

Company's model
Consistent with NICE reference case

Type	Markov state transition
Population	Patients who had failed on prior systemic treatments and eligible for 1st line biologic therapy (as per NICE guidance)
Comparators	Biologic therapy only 1st line within a treatment sequence • Etanercept • Ustekinumab • Adalimumab • Secukinumab • Infliximab
Time horizon	Lifetime (44 years to 99.9 years) Patients expected to spend more than 10 years on active treatment
Cycle length	1 month Captures induction periods when patients switch to a new treatment
Measure of health effects	QALY
Discounting of utilities & costs	3.5%
Perspective	NHS/PSS

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Source: Company submission, Section 5.2.2, Table 66 (page 219)

The model facilitates analysis of ixekizumab in different actual treatment sequences. Company say this is important because it is reflective of clinical practice in UK, with potential variation in biologic treatment algorithms between CCGs.

Modelling treatment sequences means patients remain longer on treatment and so time horizon beyond 10 years needed.

Treatment sequence approach means cycle needs to be sufficiently short to capture induction periods when patients switch between treatments. Cycle is sufficiently short to not need half cycle correction.

44 years is average age of people in the trials.

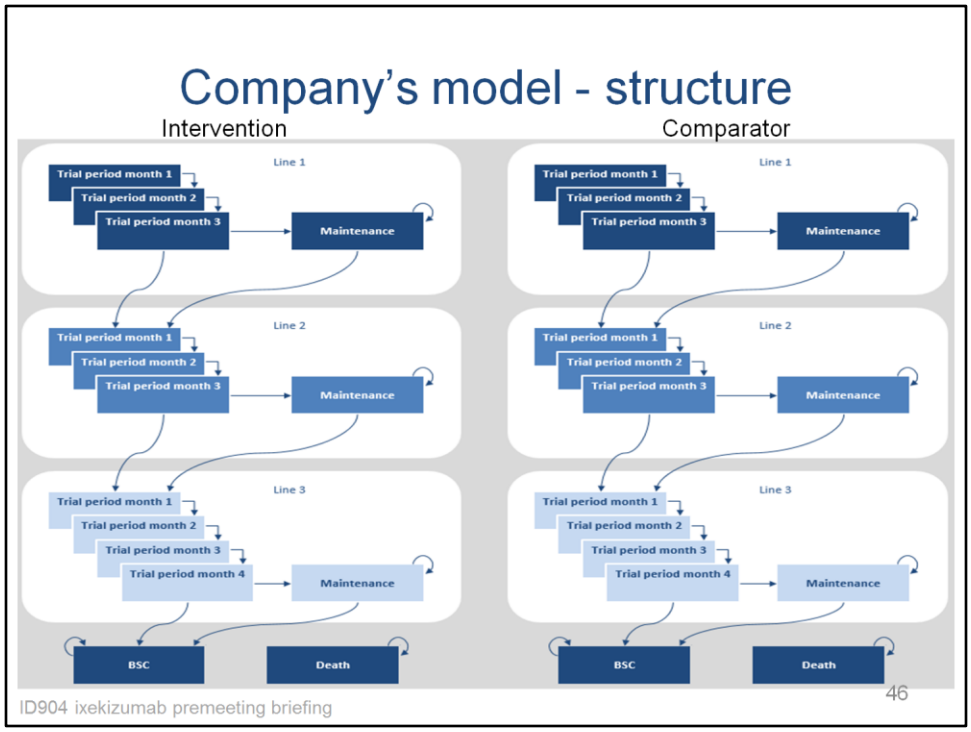
Company's model – ERG critique
Population inconsistent

- Company: 'Patients who had failed on prior systemic treatments and eligible for 1st line biologic therapy' (as per NICE guidance)
- Model results do not reflect biologic-naïve population because UNCOVER trials and indirect evidence included in network meta-analysis include patients who:
  - Have never had systemic treatments
  - Have had prior biologics
- Company explain that ixekizumab is modelled as 1st of 3 biologic treatments and only 26.4% UNCOVER patients had prior biologics
- ERG consider model population to be 'a population for whom biologic therapy is considered'.

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index

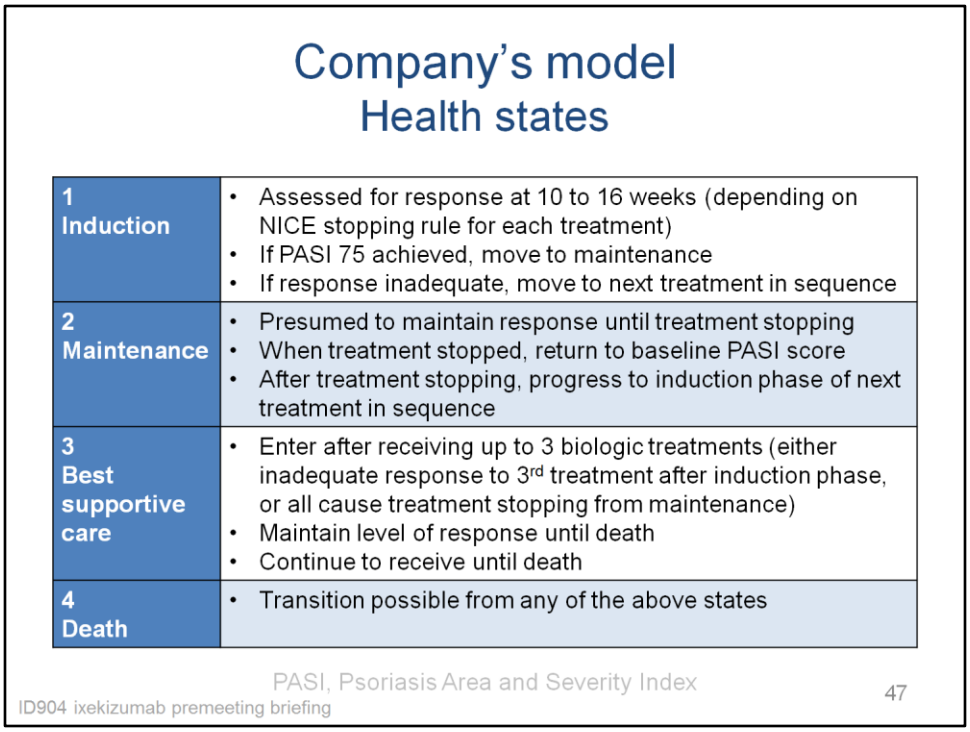
Source: ERG report, Section 5.2.3 (pages 115-6)

See also: Company's clarification response B.2 (pages 22-3)



Source: Company submission, Section 5.2.2, Figure 38 (page 217)

From ERG report (page 113): "The company states that the model consists of five PASI response categories (PASI<50 (no response), PASI 50-74, PASI 75-89, PASI 90-99, and PASI 100 (complete clearance of symptoms)) and four treatment-related health states. The PASI response states determine utility gains. The four treatment states determine the cost impact of a treatment in the model as they are associated with specific resource use rates: Induction (trial) period, Maintenance period, BSC and Death. The induction period consists of tunnel states, and the total length is dependent on the particular biologic and can last from 10 to 16 weeks in alignment with the response assessment time points reported in CG153.[76] At the end of the induction period, patients are assessed on the basis of PASI response and assigned in the model to one of the five PASI response health states. Patients who meet the minimum base case response criterion of PASI 75 continue treatment in the maintenance state. If patients do not have an adequate level of response, they enter another induction period upon initiating the next treatment line, either active treatment or BSC. At the end of the subsequent induction period, these patients are once again assessed for response. During the maintenance period, patients continue to receive the active therapy and are assumed to maintain their level of response until discontinuation due to any cause, such as loss of effectiveness or AEs. Upon discontinuing, a patient is assumed to revert to their baseline PASI score. Similar to the patients without adequate response to the induction therapy, these patients proceed to the induction period of the subsequent treatment in the sequence and are assumed to experience no improvement from baseline HRQoL until the next response assessment for the subsequent biologic therapy or BSC. BSC is the final treatment in the sequence, consisting of a bundle of non-biologic supportive therapies. The impact of adverse events of treatments on HRQoL is not incorporated in the model, the impact on costs is only explored in a scenario analysis. All patients, including non- or partial responders, continue to receive BSC and maintain the level of response until death. Patients can die from the induction, maintenance and BSC health states. Mortality is not conditioned on treatment or treatment response and has been derived from life tables for the UK. The cycle length is one month. The company did not apply a half-cycle correction because the cycle length was relatively short.



Source: Company submission, Section 5.2.2 (page 218)

End of induction period can vary from 10 to 16 weeks because it depends on the assessment time points reported in existing NICE TAs for comparator treatments (see slide 51)

No treatment effect on mortality

Company's model – ERG critique
Health states

- Model developed around PASI response: approach is common in disease area but there is a drawback
- Health states should be homogenous (in terms of quality of life and resources use)
- Because health states are based on relative PASI response this may not be the case
- Patients in specific PASI relative response states may differ in quality of life and resource use
- The true impact of treatment on quality of life and resource consumption may not be captured
- This may bias comparative effectiveness data (QoL/resource use PASI 75 on one treatment may not be the same as PASI 75 on another treatment)

PASI, Psoriasis Area and Severity Index; QoL, Quality of life

Source: ERG report, Section 5.2.2 (page 114-5)

Company's model
Treatment sequences

Sequence	1st line	2nd line	3rd line	4th line
1A	Ixekizumab	Ustekinumab 90mg	Infliximab	BSC
1B	Adalimumab	Ustekinumab 90mg	Infliximab	BSC
1C	Etanercept 50mg	Ustekinumab 90mg	Infliximab	BSC
1D	Infliximab	Ustekinumab 90mg	Adalimumab	BSC
1E	Secukinumab	Ustekinumab 90mg	Infliximab	BSC
1F	Ustekinumab 45mg	Adalimumab	Infliximab	BSC
1G	Ustekinumab 90mg	Adalimumab	Infliximab	BSC

Treatments	NICE rule – stop if inadequate response after:
Infliximab	10 weeks
Etanercept, Secukinumab	12 weeks
Adalimumab, Ustekinumab	16 weeks

Note that ustekinumab dose is weight based: 45mg for those with a weight of less than 100kg; 90mg for those who weight more than 100kg

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Source: Company submission, Section 5.2.3, Table 69 (page 225)

Best supportive care not included as a standalone comparator as patients eligible to receive a sequence of biologic treatments are unlikely to receive best supportive care following failure on conventional systemic or first biologic therapy for the remainder of their lifetime.

Specific treatments and ordering based on market shares in 2nd line, alternating between mechanisms of action where possible and maintaining a common treatment algorithm between sequences for easier comparison.

Each biologic therapy approved by NICE is assessed as first line in a treatment sequence.

Single dose of ustekinumab used in 2nd line to minimise duplicating sequences. 90mg has same acquisition cost but greater efficacy than 45mg – so company say this results in a conservative estimate of incremental costs and benefits of ixekizumab.

Disease severity progression not modelled (because psoriasis associated with an unpredictable natural history) but company assume infliximab would be given 3rd line because of its rapid onset of efficacy, and discontinuation from one TNF-α does not preclude use of another.

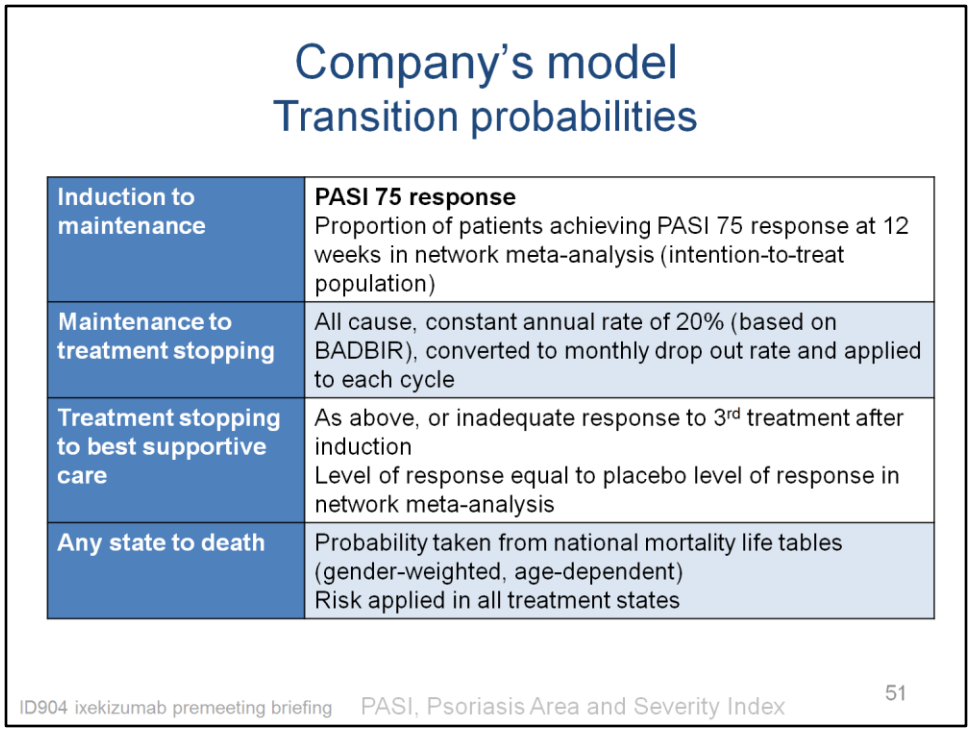
The model allows only logical treatments to be sequenced. For example, it is assumed that a patient who has not responded to treatment is not given a different dosage of the same treatment or its biosimilar counterpart later in the sequence, therefore treatment sequence restrictions have been incorporated into the model. A full list of restrictions is displayed below in Table 67 (page 222).

NICE defines adequate response as either PASI 75 or PASI 50 with 5 point increase in DLQI.

Company's model – ERG critique
Treatment sequences

- Treatment sequencing approach superior to comparing single treatments
- Non-biologics not included but this is reasonable if patients have failed these beforehand, although phototherapy may still be an option
- Most optimal treatment sequence should be included not just most widely used (based on market share)
- Plausible that ixekizumab could be positioned in the sequence as a 2nd biologic treatment (clinicians suggest it will probably be used as a 2nd biologic because there is more experience and safety data associated with other biologics)
- Do the treatment sequences reflect NHS practice?

Source: ERG report, Sections 5.2.2 (page 114), 5.2.4 (page 117)



Source: Company submission, Section 5.3.2 (page 228)

Fixed transition probabilities because of lack of data to model time-varying transition probabilities

BADBIR = British Association of Dermatologists Biologic Interventions Register. *Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study*

Gender-specific mortality rate combined into a blended rate, using the proportion of males across the UNCOVER trials (67.8%)

Company's model – ERG critique
Transition probabilities – treatment effectiveness

- Treatment response assumed not to vary with position in treatment sequence
  - Decrease in effectiveness of subsequent biologics not in base case analysis
  - Clinical expert suggests effect modification may not happen if subsequent biologics have different modes of action
- Treatment response based on intention-to-treat populations from network meta-analysis
  - Inconsistent with health utility inputs (sub-population of patients in UNCOVER trials with DLQI >10 used to derive health utilities)
  - In DLQI >10 sub-population, treatment response was lower
- Best supportive care treatment response based on placebo arm of UNCOVER trials, but:
  - Best supportive care can include systemic treatments that were prohibited in placebo arms of UNCOVER trials (for example, methotrexate)
  - Inconsistent with cost inputs (systemic treatment costs included)

DLQI, Dermatology Life Quality Index

Source: ERG report, Section 5.2.6 (pages 120-1)

Company say it was not possible to conduct network meta-analysis for sub-population PASI ≥10 and DLQI >10 as could not obtain data for all the studies

Company's model – ERG critique
Transition probabilities – treatment stopping

- Company: All cause, constant annual rate in line with previous NICE technology appraisals for biologics for psoriasis, and supported by data from BADBIR
- ERG: All cause constant annual rate not plausible or constant over time because adverse effects differ for treatments
- However, treatment-specific rates provided by company during clarification came from controlled and non-controlled evidence so more plausible to use equal rates for different treatments
- AEs not included in base case, but in scenario analysis

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Source: Company submission, Section 5.2.4 (pages 226-7)

Source: ERG report, Section 5.2.6 (pages 121-2)

ERG Report (page 121): In general, drop-out rates in observational or real-life studies are higher compared to trials, for instance because patients are able to switch to alternative biologic therapies

Company's model

Inputs: Health utilities – summary

- Health related quality of life expressed in terms of change from baseline EQ-5D-5L associated with PASI response
- EQ-5D-5L data collected in 3 UNCOVER trials (in all countries) at baseline and 12 weeks
- Used to derive health utility gains from baseline associated with specific PASI responses
- Change in utility calculated for each patient, then pooled across treatment arms and stratified by PASI response
- Only utility data for patients with DLQI >10 used
- Health utility gains only applied in maintenance period (so health utilities assigned in same way for all treatments within sequence)
- Utility assumed to be constant over time
- Impact of adverse events on health related quality of life not included in the model

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Source: Company submission, Section 5.4.1 (page 230), Section 5.4.4 (pages 246-7), Section 5.4.5 (pages 248-50)

The company say DLQI >10 population aligns to the NICE definition of moderate to severe disease, but this is not the case. It aligns to NICE's definition of severe disease (PASI $\geq$10 + DLQI >10). Health utility gains during induction phase excluded; company say this produces a more conservative outcome for ixekizumab, compared with instantaneous assignment of utility gains at the start of the induction period and linear gains throughout the induction period (include scenario analysis for this). The 12-week non-accrual is applied to those in the best supportive care state also.

EQ-5D-3L population norms for UK shown to decrease with age, but survival equivalent across treatments so company consider population norms to be incorporated in the model.

EQ-5D-5L data from UNCOVER trials within range identified from the literature, so company considered it was robust.

Utility values identified from the systematic literature review not included in the cost-effectiveness analysis as they did not stratify EQ-5D by PASI health states, were non-UK or reported without uncertainty estimates.

HRQOL impact of adverse events not included in the model because the impact of serious adverse events (aligned with secukinumab; non-melanoma skin cancer, severe infections) requiring hospitalisation likely to exceed duration of treatment. Because of delayed onset of malignancies it would be uncertain which element of the treatment sequence would be associated with it.

Also, information lacking on adverse event rates for several biologics. See: ERG report, Section 5.2.7 (page 122-3).

Company's model
Inputs: Health utilities – values

Summary of utility values (mean change from baseline) aligned to response category (all treatments)		
	EQ-5D-5L UNCOVER-1,-2,-3 2,085 patients (ITT, DLQI >10)	**EQ-PSO*** UNCOVER-3 663 patients (ITT, DLQI >10)
PASI <50 (no response)	0.012	0.021
PASI 50-74	0.100	0.117
PASI 75-89	0.131	0.141
PASI 90-99	0.144	0.148
PASI 100 (complete clearance)	0.153	0.198
*EQ-5D-5L with additional psoriasis-specific questions, used in sensitivity analysis		

ITT, intention-to-treat; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index

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Source: Company submission, Section 5.4.5, Tables 80 and 81 (pages 248-9)

Company's model – ERG critique

Health utility values lower compared with previous TAs

PASI response category		<50	50-74	75-89	90-99	100
Ixekizumab UNCOVER	**DLQI >10**	**0.01**	**0.10**	**0.13**	**0.14**	**0.15**
	Total	0.01	0.07	0.08	0.10	0.10
	Excluding PASI 100	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Adalimumab TA146	Total	0.05	0.14	0.14	0.22	NR
	DLQI ≤10	0.05	0.10	0.10	0.13	NR
	DLQI >10	0.06	0.18	0.18	0.31	NR
Etanercept TA103	Total	0.05	0.17	0.19	0.21	NR
	4th quartile DLQI	0.12	0.29	0.38	0.41	NR
Ustekinumab TA180	DLQI >10	0.04	0.17	0.22	0.25	NR
Secukinumab TA350	DLQI >10	0.11	0.19	0.23	0.26	NR
Infliximab TA134	4th quartile DLQI	0.12	0.29	0.38	0.41	NR

TAs, Technology Appraisals; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; NR, not reported

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Source: Adapted from ERG report, Section 5.2.8, Table 5.11 (page 127)

See also: Company submission, Section 5.4.3, Table 78 (pages 245-6), Section 5.8.3, Table 114 (page 300), Table 20 in response to clarification

PASI <50 = no response

PASI 100 = complete clearance

Company's model – ERG critique

Inputs: Health utilities

Population – inconsistent	• Using population with DLQI >10 matches scope better but inconsistent with ITT population used for effectiveness; also PASI response lower in DLQI >10 population (see slide 24): ERG agrees with using DLQI subset
Estimates of utility gains – uncertain	• One regression model (least square regression with baseline EQ-5D-5L & PASI response as covariates) used to convert EQ-5D-5L to health utilities. Alternative choices were available; but no model diagnostics provided: ERG unable to assess if model appropriate • 'Last observation carried forward' used for those who stopped treatment before end of induction. Unknown how many patients or why they stopped treatment
No utility gain applied in induction period – implausible	• Duration of induction phase differs between treatments; may impact on comparative effectiveness • Rapid onset of response with ixekizumab; likely gives a conservative estimate of health utility gains

DLQI, Dermatology Life Quality Index; ITT, Intention-to-Treat; PASI, Psoriasis Area and Severity Index

Source: ERG report, Sections 5.2.2 (page 115), 5.2.8 (pages 124-5)

ERG noted in pre-meeting that ideally the sub-population of patients with DLQI >10 should have been used for both treatment effectiveness and health utility data, because this sub-group better matches the scope. It was not possible to do because this sub-group data was not reported in the trials included in the network meta-analysis (which was used to estimate treatment effectiveness).

Company's model

Inputs: Resources and costs – summary

- Treatment acquisition costs
- Treatment administration costs
- Monitoring costs
- Best supportive care
- Non-responder cost (applied to induction period following discontinuation from treatment, reflecting higher disease activity and worse health after failure to respond, set at monthly cost of £274)
- Excluded from model: adverse event management costs (included in company sensitivity and scenario analyses; included in ERG's base case)

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Source: Company submission, Section 5.5 (page 250), 5.5.2 (page 261), 5.5.4 (page 262)

Non-responder cost applied to patients who have failed to respond to a prior biologic (both patients who are biologic-experienced at the start of the model or who have been treated with a biologic during the course of the model).

Cost is not applied during active therapy maintenance period, BSC induction period or BSC post-induction period.

Company's model
Inputs: Drug acquisition costs

	Pack size	Pack cost	Cost per dose	Total cost (induction)	Total cost (maintenance)
Ixekizumab 80mg	1	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg/0.8ml	2	£704	£352	£3,521	£9,156
Etanercept 50mg	4	£715	£179	£2,145	£9,295
Biosimilar etanercept 50mg	4	£656	£164	£1,968	£8,528
Infliximab 100mg	1	£420	£1,921	£5,763	£12,487
Biosimilar infliximab 100mg	1	£378	£1,729	£5,187	£11,238
Secukinumab 150mg	2	£1219	£1,219	£8,531	£15,844
Ustekinumab 45mg	1	£2,147	£2,147	£4,294	£9,304
Ustikinumab 90mg	1	£2,147	£2,147	£4,294	£9,304

PAS prices: ixekizumab (confidential), ustekinumab
List prices: infliximab, adalimumab, etanercept (no PAS), secukinumab ([redacted])
Biosimilar list prices for infliximab and etanercept used in base case analysis

Note that infliximab dose is based on a baseline weight of 91.56kg

ID904 ixekizumab premeeting briefing Source: MIMS (Monthly Index of Medical Specialities) 59

Source: Company submission, Section 5.5.2 (page 256), Table 84 (page 257)

Ustekinumab PAS is that the 90mg dose is provided at the same total cost as the 45mg dose

Infliximab dose – baseline weight of patients in UNCOVER x3 used to calculate weighted average of 91.56kg

Company consider that using biosimilar prices for infliximab and etanercept results in a more conservative estimate of cost effectiveness of ixekizumab

Biosimilar infliximab launched in UK February 2015

Biosimilar etanercept available in UK February 2016

Company's model
Inputs: Drug administration costs

Administration method	Sub-cutaneous self-injection (3 1-hour nurse training sessions)	Intravenous infusion, outpatient procedure
Admin cost	£36	£97
No. of administrations (induction)	3	3
No. of administrations (maintenance)	0	6.5
Total cost (induction)	£108	£291
Total annual cost (maintenance)	£0	£631

Source: PSSRU Unit Costs of Health and Social Care 2015, NHS Reference Costs 2014-15

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Source: Company submission, Section 5.5.2, Table 85 (page 259)

Infliximab is the only drug administered via IV

Where not available, costs inflated to 2015-16 levels using Special Aggregate: 06 Health component of the Consumer Price Index from Office for National Statistics (section 5.5, page 251)

Company's model
Inputs: Drug monitoring costs

		Sub-cutaneous admin		Intravenous admin	
Resource	Price	Induction	Maintenance (annual)	Induction	Maintenance (annual)
Physician visit	£102	2	4	1	0
Full blood count	£3	2	4	3	4
Test for urea and electrolytes	£1	2	4	3	4
Liver function test	£1	2	4	3	4

Non-responder costs were assumed to be £274.27 per monthly cycle (Fonia 2010, inflated to 2015 prices)

Source: NHS Reference costs (costs for monitoring), NICE Guideline 153 (resource use estimates)

Source: Company submission, 5.5.2, Tables 86 and 87 (page 260)

Frequency of physician visits and monitoring tests for ixekizumab assumed equivalent to resource use rates for other sub-cutaneously administered biologic treatments.

Where not available, costs inflated to 2015-16 levels using Special Aggregate: 06 Health component of the Consumer Price Index from Office for National Statistics (section 5.5, page 251)

Company's model

Inputs: Best supportive care costs

Drug cost	£1,251
Inpatient admissions and outpatient care	£2,957
Total annual cost (2014/15)	£5,082
Cost applied per model cycle	£424

- Data on hospital resource use and drug usage collected 12 months prior to and 6 months following the initiation of biologic treatment, to reflect costs for how moderate to severe psoriasis is managed without biologic treatment.
- Mean cost of inpatient admissions and outpatient care includes:
  - Inpatient admissions
  - Intensive Care Unit admissions
  - High Dependency Unit admissions
  - A&E visits
  - Outpatient visits
  - Day ward admissions
  - Phototherapy
- Source: Fonia et al (2010)

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Source: Company submission, Section 5.2.2 (page 260), Table 88 (page 261)

Where not available, costs inflated to 2015-16 levels using Special Aggregate: 06 Health component of the Consumer Price Index from Office for National Statistics (section 5.5, page 251)

Company's model – ERG critique

Inputs: Best supportive care costs

- Estimates from Fonia et al. (2010) do not represent best supportive care provision after multiple biologic treatment failures, for example:
  - Costs of systemic non-biologic treatment included, but these not likely to be given after multiple biologic treatment failures
- Resource use and costs for best supportive care uncertain, but lack of evidence in this area

Source: ERG report, Section 5.2.9 (pages 134-5)

Company's base case – deterministic results, fully incremental analysis (with ixekizumab PAS, secukinumab list price)

Treatment sequences	Total		Increments vs Ref		ICER
	Costs	QALYs	Costs	QALYs	
ETA→UST90→INF	£144,635	1.27	**Referent**	**Referent**	**Referent**
UST45→ADA→INF	£148,218	1.30	£3,583	0.04	**Extendedly dominated**
ADA→UST90→INF	£148,350	1.32	£3,715	0.05	**Extendedly dominated**
UST90→ADA→INF	£148,719	1.32	£4,083	0.06	**Extendedly dominated**
INF→UST90→ADA	£150,350	1.33	£5,714	0.06	**Extendedly dominated**
IXE→UST90→INF	£150,889	1.45	£6,254	0.18	**£33,858**
SEC→UST90→INF	£177,101	1.42	£32,466	0.15	**Dominated by IXE**

ETA, etanercept; UST45, ustekinumab 45mg; ADA, adalimumab; INF, infliximab; IXE, ixekizumab; SEC secukinumab; UST90, ustekinumab 90mg

Source: Company submission, Section 5.7.1, Table 91 (page 268)

Assumption in model summarised in company submission, Section 5.6.2 (pages 266-7)

Referent = comparator with lowest costs

Company's base case – deterministic results, pairwise comparison (with ixekizumab PAS, secukinumab list price)

Treatment sequences	Total		Increments vs Ref		Pairwise ICER IXE vs. comp
	Costs	QALYs	Costs	QALYs	
ETA→UST90→INF	£144,635	1.27	**Referent**	**Referent**	**£33,858**
UST45→ADA→INF	£148,218	1.30	£3,583	0.04	**£18,278**
ADA→UST90→INF	£148,350	1.32	£3,715	0.05	**£19,202**
UST90→ADA→INF	£148,719	1.32	£4,083	0.06	**£16,763**
INF→UST90→ADA	£150,350	1.33	£5,714	0.06	**£4,300**
IXE→UST90→INF	£150,889	1.45	£6,254	0.18	**N/A**
SEC→UST90→INF	£177,101	1.42	£32,466	0.15	**Dominated by IXE**

ICER, incremental cost effectiveness ratio; ETA, etanercept; UST45, ustekinumab 45mg; ADA, adalimumab; INF, infliximab; IXE, ixekizumab; SEC, secukinumab; UST90, ustekinumab 90mg

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Source: Company submission, Section 5.7.1, Table 91 (page 268)

Assumption in model summarised in company submission, Section 5.6.2 (pages 266-7)

Referent = comparator with lowest costs

Company's base case – probabilistic results, fully incremental analysis (with ixekizumab PAS, secukinumab list price)

Treatment	Incremental values		ICER
	Costs	QALYs	
ETA→UST90→INF	Referent	Referent	**Referent**
UST45→ADA→INF	£3,650	0.04	**Extendedly dominated**
ADA→UST90→INF	£3,774	0.05	**Extendedly dominated**
UST90→ADA→INF	£4,155	0.06	**Extendedly dominated**
INF→UST90→ADA	£5,991	0.06	**Extendedly dominated**
IXE→UST90→INF	£6,175	0.19	**£32,815**
SEC→UST90→INF	£33,642	0.15	**Dominated**

PAS, patient access scheme, QALYs, Quality-adjusted life years; ICER, incremental cost effectiveness ratio; ETA, etanercept; UST45, ustekinumab 45mg; ADA, adalimumab; INF, infliximab; IXE, ixekizumab; SEC, secukinumab; UST90, ustekinumab 90mg

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Source: Company submission, Section 5.8.1, Table 97 (page 278-9)

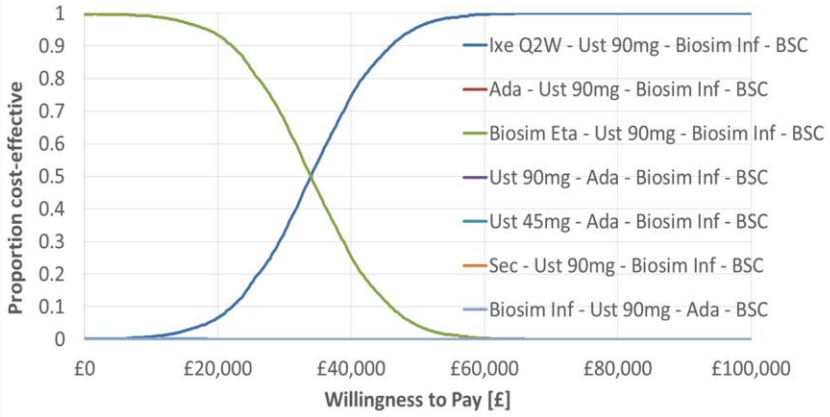
Source: ERG report, Section 5.2.11, Table 5.18 (page 138)

Full list of parameters included in the probabilistic sensitivity analysis in Table 69 in company submission (pages 276-278)

Referent = comparator with lowest costs

Company's cost effectiveness acceptability curve

	Maximum acceptable ICER (cost/QALY)	
Probability of cost-effectiveness at:	**£20,000/QALY**	**£30,000/QALY**
Ixekizumab	7%	33%
Etanercept	93%	67%



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Source: Company submission, Section 5.8.1, Figure 41 (page 280)

Source: ERG report, Section 5.2.11 (page 137)

All other comparators are dominated or extendedly dominated.

Company's deterministic sensitivity analysis
For pairwise comparisons

Greatest impact on ICER (consistent across all comparisons):

- Treatment acquisition costs (± 20% mean value)
- Annual all-cause treatment stopping rate (lower to upper 95% confidence interval)
- Discount rates: costs, QALYs (0-5%)

Greatest impact on ICER for ixekizumab sequence versus secukinumab sequence:

- PASI response rates (lower to upper 95% confidence interval)

ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; PASI, Psoriasis Area and Severity Index

Source: Company submission, Section 5.8.2 (page 284)

Source: ERG report, Section 5.2.11 (page 139)

Full list of parameters included in the deterministic sensitivity analysis in company submission, Table 98 (pages 281-3)

Tornado diagrams in company submission, Figures 43-7 (pages 285-9)

Company's scenario analysis
Summary

- Prior failure on or contraindication to TNF-α inhibitor
- Single treatment comparisons
- Comparison with non-biologic systemic therapy
- Varied model time horizon
- Effect modification of previous biologic treatment
- Branded prices for etanercept and infliximab
- Utility gain assignment (instantaneous in induction phase)
- Adverse events costs included
- PASI response criteria (varied to PASI 50 and PASI 90)
- Alternative utility sources*
- Best supportive care costs (from NICE guideline on psoriasis, 2012)
- Best supportive care efficacy (better than placebo)*

*greatest impact on ICER

TNF-α, tumour necrosis factor-alpha; PASI, Psoriasis Area and Severity Index

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Source: Company submission, Section 5.8.3 (pages 290-306)

Source: ERG report, Section 5.2.11 (pages 141-3)

Company's scenario analyses results (1)

Scenario	ICER ixekizumab vs. referent comparator (etanercept sequence unless stated)
Company's base case (deterministic)	**£33,858**
1) Prior failure/contraindication to TNF-α inhibitor (ixekizumab 2nd line)	ixekizumab dominant
2) Single treatment comparisons (no sequence)	**£39,563** vs. etanercept single treatment
3) Comparison with non-biologic systemic therapy (methotrexate, ciclosporin, best supportive care)	**£65,468** vs. methotrexate
4) Varied model time horizon (10 years)	**£24,216**
5) Effect modification of previous biologic treatment	**£38,034**
6) Branded prices for etanercept and infliximab	**£24,923**
7) Utility gain assignment (instantaneous in induction phase)	**£32,337**
8) Including costs of adverse events requiring hospitalisation	**£32,932**

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Source: Company submission, Section 5.8.3, Tables 99-118 (pages 290-306)
Source: ERG report, Section 5.2.11, Table 5.19 (pages 142-3)

Referent = comparator with lowest costs

1) Prior failure/contraindication to TNF-α inhibitor (IXE 2nd line)
New treatment sequences:
ADA-IXE-INF
ADA-SEC-INF
ADA-UST45-INF
ADA-UST90-INF

3) Comparison with non-biologic systemic therapy (methotrexate, ciclosporin, best supportive care)
Response rates taken from NMA scenario analysis 2
Assumed patients move onto BSC after discontinuing ixekizumab, methotrexate or ciclosporin

5) Effect modification:
To account for potentially decreased efficacy in patients previously treated with biologics
Odds ratio of drug survival for biologic naïve vs previous biologic exposed calculated as 1.24
Applied to increase drop out rate and decrease treatment response for non naïve population (applied to primary and secondary treatment failure [induction and after])
Applied to all biologic treatments and begins from second line treatment onwards
Company do not consider prior biologic treatment to be a treatment effect modifier (UNCOVER -2 and -3 showed similar response in biologic-naïve and biologic-experienced patients, and insufficient evidence to examine subgroups in network meta-analysis)

Note: secukinumab has same mechanism of action as ixekizumab

8) Including costs of adverse events requiring hospitalisation:
Non-melanoma skin cancer, malignancy other than non-melanoma skin cancer, severe infections
Follows approach used in secukinumab NICE submission.

Company's scenario analyses results (2)

Scenario	ICER ixekizumab vs. referent comparator (etanercept sequence unless stated)
Company's base case (deterministic)	**£33,858**
9a) PASI response criteria varied to PASI 50	**£30,146**
9b) PASI response criteria varied to PASI 90	**£35,506**
10a) Alternative utility sources – UNCOVERx3, all patients, baseline adjusted	**£47,235**
10b) Alternative utility sources – UNCOVER x3, patients with DLQI >10, baseline unadjusted	**£42,158**
10c) Alternative utility sources – UNCOVER x3, patients with DLQI >10, EQ-PSO bolt-on questions	**£27,615**
10d) Alternative utility sources – patients with 4th quartile DLQI score from York model	**£16,109**
10e) Alternative utility sources – patients with DLQI >10 from secukinumab submission	**£28,633**

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Source: Company submission, Section 5.8.3, Tables 99-118 (pages 290-306)

Source: ERG report, Section 5.2.11, Table 5.19 (pages 142-3)

Company's scenario analyses results (3)

Scenario	ICER ixekizumab vs. referent comparator (etanercept sequence unless stated)
Company's base case (deterministic)	**£33,858**
11) Best supportive care costs (from NICE CG153, 2012)	Ixekizumab dominant
12a) Best supportive care efficacy – 0% patients attain PASI 50-100	**£30,738**
12b) Best supportive care efficacy – 65% patients attain PASI 50; 0% PASI 75-100	**£50,047**
12c) Best supportive care efficacy – 83% patients attain PASI 50; 0% PASI 75-100	**£60,586**

Source: Company submission, Section 5.8.3, Tables 99-118 (pages 290-306)

Source: ERG report, Section 5.2.11, Table 5.19 (pages 142-3)

ERG's exploratory analyses – ERG's base case

- Fixed errors
  - Included adverse events (a. re-calculated unit costs, b. corrected error in rates)
  - Re-calculated standard error for NHS reference costs (for probabilistic sensitivity analysis) because company's method wrong
  - Corrected number of secukinumab administrations in maintenance period
- Different assumptions to company's base case:
  - Costs of adverse events included
  - Linear utility gains applied during induction period
  - Treatment sequence with ixekizumab as 2nd biologic included (adalimumab → ixekizumab → infliximab)
- Probabilistic analysis as base case

Source: ERG report, Section 5.2.9 (page 135), 5.3 (page 149-50), Table 5.26 (page 151-2), and Section 6, Table 6.1 (pages 160-3)

ERG's base case – probabilistic results, fully incremental analysis (with ixekizumab PAS, secukinumab list price)

Treatment sequences	Company's ICER (re-calculated by ERG)	ERG's ICER 1st line IXE	ERG's ICER 2nd line IXE
ETA→UST90→INF	**Referent**	**Referent**	**Referent**
ADA→IXE→INF	**Not reported**	**£25,532**	**£25,532**
UST45→ADA→INF	**Extendedly dominated**	**Dominated by ADA→IXE→INF**	**Dominated by ADA→IXE→INF**
ADA→UST90→INF	**Extendedly dominated**	**Dominated by ADA→IXE→INF**	**Dominated by ADA→IXE→INF**
UST90→ADA→INF	**Extendedly dominated**	**Dominated by ADA→IXE→INF**	**Dominated by ADA→IXE→INF**
IXE→UST90→INF	**£32,541**	**£39,129**	**Excluded**
INF→UST90→ADA	**Extendedly dominated**	**Dominated by IXE→UST90→INF**	**Dominated by ADA→IXE→INF**
SEC→UST90→INF	**Dominated by IXE→UST90→INF**	**Dominated by IXE→UST90→INF**	**£730,630**

ICER, incremental cost effectiveness ratio; ETA, etanercept; UST45, ustekinumab 45mg; ADA, adalimumab; INF, infliximab; IXE, ixekizumab; SEC, secukinumab; UST90, ustekinumab 90mg

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Source: ERG report, Section 5.3, Table 5.26 (page 151-2), and Section 6, Table 6.1 (pages 160-3)

ERG's base case – probabilistic results, pairwise comparison (with ixekizumab PAS, secukinumab list price)

Treatment sequences	Company's ICER (re-calculated by ERG)	ERG's ICER 1st line IXE vs comparator	ERG's ICER 2nd line IXE vs comparator
ETA→UST90→INF	**£32,541**	**£30,517**	**£25,532**
ADA→IXE→INF	**NR**	**£39,129**	-
UST45→ADA→INF	**£16,550**	**£15,024**	**Dominated**
ADA→UST90→INF	**£17,460**	**£15,281**	**Dominated**
UST90→ADA→INF	**£15,027**	**£13,147**	**Dominated**
IXE→UST90→INF	-	-	-
INF→UST90→ADA	**£602**	**Dominated**	**Dominated**
SEC→UST90→INF	**Dominated**	**Dominated**	**£730,630**

ICER, incremental cost effectiveness ratio; ETA, etanercept; UST45, ustekinumab 45mg; ADA, adalimumab; INF, infliximab; IXE, ixekizumab; SEC, secukinumab; UST90, ustekinumab 90mg

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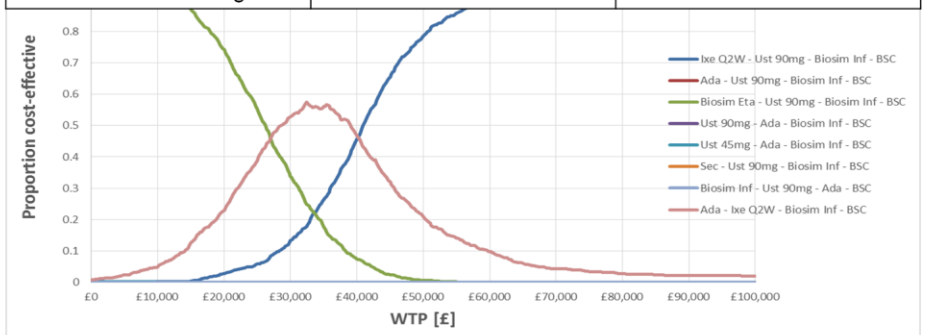
Source: ERG report, Section 5.3, Table 5.26 (page 151-2), and Section 6, Table 6.1 (pages 160-3)

ERG's cost effectiveness acceptability curve
Includes ixekizumab as 2nd biologic in sequence

	Maximum acceptable ICER (cost/QALY)	
Probability of cost-effectiveness at:	**£20,000/QALY**	**£30,000/QALY**
Ixekizumab 1st biologic	2.8%	13.2%
Ixekizumab 2nd biologic	22.8%	52.9%



ID904 ixekizumab premeeting briefing

Source: ERG report, Section 5.3.1, Figure 5.4 (page 153)

All other comparators are dominated or extendedly dominated.

ERG's exploratory analysis
Scenario analyses

- Using ITT population to estimate utility gains (without DLQI restriction)*
- Using treatment effectiveness data from subset population (UNCOVER trials population with DLQI >10). *Note that PASI response for other treatments still derived from network meta-analysis (without DLQI restriction) so results should be treated with caution*
- Applied effect modification (reduced effectiveness for subsequent biological treatments)
- Varied BSC costs (+/- 20%)*
- Added a new treatment sequence: secukinumab as 2nd biologic in sequence (Adalimumab → Secukinumab → Infliximab); replaces ustekinumab 90 mg sequence

*Greatest impact on ICER

TNF-α, tumour necrosis factor-alpha; PASI, Psoriasis Area and Severity Index

Source: ERG report, Section 5.3.2 (page 154-5)

Source: Company submission, Section 5.6.2 (pages 266-7)

Source: Company submission, Section 5.8.3, Table 105 (page 294)

ERG's scenario analyses results

Scenario	ICER (fully incremental) ixekizumab vs. referent comparator (etanercept sequence)	
	IXE 1st line	IXE 2nd line
ERG's base case (probabilistic)	**£39,129**	**£25,532**
Using ITT population from UNCOVER x3 to estimate utility gains	£55,243	£36,314
Using treatment effectiveness data from patients with DLQI >10 in UNCOVER x3	£40,308	£26,499
Applying effect modification of previous biologic treatment	£35,514	£35,191
Increasing best supportive care costs by 20%	£32,673	£17,532
Decreasing best supportive care costs by 20%	£45,709	£33,352
Including alternative treatment sequence Adalimumab → Secukinumab → Infliximab	£38,914	£25,423

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Source: ERG report, Section 6, Table 6.2 (pages 164-6)

Innovation

Company's comments

- Need for new, effective therapeutic options that maintain long-term responses
- Targeted approach that disrupts pro-inflammatory stimuli
- Achieves high levels of skin clearance, impact on health related quality of life
- Rapid onset of efficacy
- Sustained responses
- Improvements in difficult to treat areas
- Consistent benefits across subgroups
- Ease of use
- British Association of Dermatologists note different mode of action and extended activity of ixekizumab compared with secukinumab (another IL-17 inhibitor) because it binds to both IL-17 A and IL-17 F

Source: Company submission, Section 2.5 (pages 33-35), British Association of Dermatologists' submission (pages 3-4)

Equality considerations

- Current disease severity criteria for biologics may discriminate:
  - PASI score can underestimate disease severity in those with black or brown skin
  - DLQI has limited validity in those not working, older people, and may miss anxiety and depression
- Self-injecting a barrier, particularly for those with phobias or poor hand mobility? Feedback from patients suggests people appear to cope, or find ways to cope, with administration methods, as long as there is treatment benefit

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index

Source: British Association of Dermatologists' submission (page 6), Psoriasis and Psoriatic Arthritis Alliance submission (page 12)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ixekizumab for treating moderate to severe plaque psoriasis

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ixekizumab within its marketing authorisation for treating moderate to severe plaque psoriasis.

Background

Psoriasis is an inflammatory skin disease that is characterised by an increased turnover of the upper layer of the skin (epidermis). Although it is a chronic condition, its course may be unpredictable, with flare-ups and remissions. The most common form of psoriasis is chronic plaque psoriasis (psoriasis vulgaris), which is characterised by well-demarcated, often symmetrically distributed thickened, red, scaly plaques. Although the plaques can affect any part of the skin, they are typically found on the extensor surfaces of the knees and elbows, and on the scalp.

Psoriasis can be graded as mild, moderate or severe according to the body surface area affected or by using indices such as the Psoriasis Area Severity Index (PASI), which takes into account the size of the area covered with psoriasis as well as redness, thickness and scaling. In addition, the Dermatology Life Quality Index (DLQI) is a validated tool that can be used to assess the impact of psoriasis on physical, psychological and social wellbeing.

The prevalence of psoriasis in England is estimated to be 1.75%[1], which is about 951,000 people, of whom about 20% have moderate to severe psoriasis (15% moderate, 5% severe)[2], equating to approximately 190,000 people. About 90% of people with the condition have plaque psoriasis. There is no cure for psoriasis but there are a wide range of topical and systemic treatments that can manage the condition. Most treatments reduce severity rather than prevent episodes. Psoriasis has to be treated continually and on a long-term basis.

NICE clinical guideline 153 describes the care pathway for people with psoriasis. Initially, psoriasis is managed with topical treatments, including emollients and occlusive dressings, keratolytics (salicylic acid), coal tar, dithranol, corticosteroids and vitamin D analogues. Phototherapy may be used for people with plaque psoriasis that cannot be controlled with topical treatments. Systemic non-biological therapies (such as methotrexate, ciclosporin and acitretin) should be offered to people with any type of psoriasis if:

- it 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 **or**
    - psoriasis is localised and associated with significant functional impairment and/or high levels of distress **or**
    - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse.

NICE technology appraisals 103, 134, 146, 180 and 350 recommend biological therapies for people with psoriasis for whom other systemic therapies including ciclosporin, methotrexate and phototherapy with or without psoralen have been inadequately effective, not tolerated or contraindicated. Etanercept (technology appraisal [TA] 103), adalimumab (TA146), ustekinumab (TA180) and secukinumab (TA350) are recommended as treatment options for people with severe psoriasis (as defined by a total PASI score of 10 or more and a DLQI score of more than 10). Infliximab (TA134) is recommended as an option for people with very severe psoriasis (PASI score of 20 or more and a DLQI score of more than 18).

The technology

Ixekizumb (Taltz, Eli Lilly) is a humanised monoclonal antibody that neutralises interleukin-17A, which is a key T-cell-derived cytokine involved in inducing and mediating inflammation. It is administered by subcutaneous injection.

Ixekizumab has a marketing authorisation in the UK for treating moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Intervention(s)	Ixekizumab
Population(s)	Adults with moderate to severe plaque psoriasis

Comparators	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies (including acitretin, ciclosporin, fumaric acid esters, methotrexate) • Phototherapy with ultraviolet (UVB) radiation For people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Best supportive care
Outcomes	The outcome measures to be considered include: • severity of psoriasis • psoriasis symptoms on the face, scalp and nails • mortality • response rate • relapse rate • adverse effects of treatment • health-related quality of life.
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. 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 patient access schemes for the intervention or comparator technologies will be taken into account. For the comparators, the availability and cost of biosimilars should be taken into consideration.

Other considerations	If the evidence allows, the following subgroups will be considered: • previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe) Where the evidence allows, sequencing of different drugs and the place of ixekizumab in such a sequence will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** 'Etanercept and efalizumab for the treatment of adults with psoriasis' (2006) NICE Technology Appraisal 103. Note: guidance for efalizumab has now been withdrawn. 'Infliximab for the treatment of adults with psoriasis' (2008) NICE Technology Appraisal 134. Static list. 'Adalimumab for the treatment of adults with psoriasis' (2008) NICE Technology Appraisal 146. Static list. 'Ustekinumab for the treatment of adults with moderate to severe psoriasis' (2009) NICE Technology Appraisal 180. Static list. 'Secukinumab for treating moderate to severe plaque psoriasis' (2015) NICE Technology Appraisal 350. Review proposal date: July 2018 'Apremilast for treating moderate to severe psoriasis' (2015) NICE Technology Appraisal 368. Review proposal date: November 2018. **Related Guidelines:** 'Psoriasis. The assessment and management of psoriasis' (2013) NICE Clinical Guideline 153. Review Proposal Date: December 2016. **Related Interventional Procedures:** 'Grenz rays therapy for inflammatory skin conditions' (2007) NICE Interventional Procedures Guidance 236. **Related Quality Standards:** Quality Standard No. 40, August 2013, 'Psoriasis'.

	http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp **Related NICE Pathways:** 'Psoriasis' (2012) NICE Pathway http://pathways.nice.org.uk/pathways/psoriasis
Related National Policy	NHS England Manual for Prescribed Specialised Services 2013/14. Chapter 61, Highly specialist dermatology services. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England standard contract for specialised dermatology services, 2013/14. https://www.england.nhs.uk/wp-content/uploads/2013/06/a12-spec-dermatology.pdf Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 2–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1. NICE (2015) Psoriasis: assessment and management – costing template. Accessed December 2015.
2. Menter A, Korman NJ, Elmets CA et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol 2011; 65:137–74.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company Eli Lilly (ixekizumab) Patient/carer groups • Action Against Allergy • Allergy UK • Black Health Agency • Changing Faces • Muslim Council of Britain • Psoriasis Association • Psoriasis and Psoriatic Arthritis Alliance • Psoriasis Help Organisation • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • British Association of Dermatologists • British Dermatological Nursing Group • British Geriatrics Society • British Skin Foundation • British Society for Cutaneous Allergy • Primary Care Dermatology Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association Others • Department of Health • NHS England • NHS South Worcestershire CCG • NHS Tower Hamlets CCG	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • AbbVie Limited (adalimumab) • Accord Healthcare (methotrexate) • Allergan (acitretin) • B&S Colorama Pharmaceuticals (ciclosporin) • Cubic Pharmaceuticals (ciclosporin) • Dexcel Pharma (ciclosporin) • Genus Pharmaceuticals (acitretin) • Hameln Pharmaceuticals (methotrexate) • Hospira (infliximab, methotrexate) • Janssen (ustekinumab) • Medac Ltd (methotrexate) • Merck Sharp & Dohme (infliximab • Mylan UK (ciclosporin) • Napp (infliximab) • Novartis Pharmaceuticals

Consultees	**Commentators (no right to submit or appeal)**
• Welsh Government	(secukinumab, ciclosporin) • Orion Pharma UK (methotrexate) • Pfizer (etanercept, methotrexate) • Sandoz (methotrexate) • Teva UK (methotrexate) • Wockhardt UK (methotrexate) <u>Relevant research groups</u> • British Epidermo-Epidemiology Society • Centre of Evidence-based Dermatology, University of Nottingham • Cochrane Skin Group • MRC Clinical Trials Unit • National Institute for Health Research • Skin Research Centre • Skin Treatment & Research Trust <u>Associated Public Health groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ixekizumab for the treatment of moderate to severe plaque psoriasis [ID:904]

Eli Lilly and Company Limited

File name	Version	Contains confidential information	Date
Ixekizumab_psoriasis_main submission_ID904_Lilly_confidential information removed	1.0	No	21 September 2016

Please note academic in confidence (AIC) and commercial in confidence (CIC) information has been removed.

Contents

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Abbreviations

Abbreviation	Definition
ADA	Adalimumab
AE	Adverse event
AESI	Adverse event of special interest
AIC	Academic in confidence
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APR	Apremilast
AWMSG	All Wales Medicines Strategy Group
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BID	Twice daily
BI	Budget impact
BIM	Budget impact model
BIW	Twice weekly
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CCG	Clinical Commissioning Group
CE	Cost-effectiveness
CE mark	Conformité Européene mark
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CG153	Clinical Guidelines 153
CHMP	Committee for Medicinal Products for Human Use
CIC	Commercial in confidence
CICLO	Ciclosporin
CMH	Cochran Mantel Haenszel
CODA	Convergence Diagnostic and Output Analysis
CONSORT	Consolidated Standards of Reporting Trials
Cont.	Continuous
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval

Abbreviation	Definition
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
CVZ	College Voor Zorgverzekeringen
DARE	Database of abstracts of reviews of effects
DCE	Discrete choice experiment
DEF	Data extraction form
DIC	Deviance information criteria
DLQI	Dermatology Life Quality Index
DSA	Deterministic sensitivity analysis
DSR	Database of Systematic Reviews
DSU	Decision Support Unit
EADV	European Academy of Dermatology and Venerology
EDF	European Dermatology Forum
EED	Economic Evaluation Database
EFA	Efalizumab
EMA	European Medicines Agency
eow	Every other week
EQ-5D-3L	European Quality of Life – 5 Dimensions – 5 Levels
EQ-5F-5L	European Quality of Life – 5 Dimensions – 3 Levels
EQ-PSO	European Quality of Life – Psoriasis bolt-on
EQ-VAS	European Quality of Life – Visual Analogue Scale
ERB	Ethics Review Board
ERG	Evidence Review Group
ETN	Etanercept
ETV	Early termination visit
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FBC	Full blood count
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GP	General practitioner
GPRD	General Practice Research Database
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton Rating Scale for Depression
HAS	Haute Autorité de Santé
HEOR	Health economics and outcomes research
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment

Abbreviation	Definition
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive care unit
ICUR	Incremental cost-utility ratio
IGA	Investigator's Global Assessment
IL-17A	Interleukin-17A
IL-12/23	Interleukin-12/23
IM	Intramuscular
INF	Infliximab
Int.	intermittent
IP	Ixekizumab or placebo
IPC	International Psoriasis Council
IQR	Interquartile range
iQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRB	Institutional review board
ISE	Injection-site reaction
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IXE	Ixekizumab
LFT	Liver function test
LOCF	Last observation carried forward
LOS	Length of stay
LSM	Least squares mean
LTE	Long-term extension
LV	Date of last visit
LY	Ixekizumab
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular events
MAPP	Multinational Assessment of Psoriasis and Psoriatic Arthritis
MCS	Mental component summary
MI	Myocardial infarction
MIMS	Monthly Index of Medical Specialities
MOS	Medical Outcomes Study
MTC	Mixed treatment comparison
MTX	Methotrexate
N/A	Not applicable
NAPSI	Nail Psoriasis Severity Index

Abbreviation	Definition
NBST	Non-biologic systemic therapy
NBUVB	Narrow band ultraviolet B
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NMSC	Non-melanoma skin cancer
NNT	Number needed to treat
NOKC	Nasjonalt kunnskapssenter for helsetjenesten
NR	Not reported
NRI	Non-responder imputation
NRS	Numerical rating scale
OR	Odds ratio
OWSA	One-way sensitivity analysis
OXIS	Oxford Medical Information System
PAS	Patient Access Scheme
PASI	Psoriasis Area and Severity Index
PASLU	Patient Access Scheme Liaison Unit
PatGA	Patient's Global Assessment
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PCP	Pneumocystis pneumonia
PCS	Physical component summary
PDI	Psoriasis Disability Index
PGA	Physician's Global Assessment
PICOS	Patient, Intervention, Comparators, Outcome, Study design
PIIINP	Amino-terminal propeptide of type III procollagen
PPASI	Palmoplantar Psoriasis Severity Index
PQOL-12	Psoriasis Quality of Life 12
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
PRPA	Psoriasis-Related Pruritus Assessment
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analysis
PSI	Psoriasis symptom inventory
PSS	Personal Social Services
PSSI	Psoriasis Scalp Severity Index
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen and long-wave ultraviolet radiation
Q1W, QW	Every week

Abbreviation	Definition
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q12W	Every 12 weeks
QA	Quality assessment
QIDS	Quick inventory of depressive symptomatology
QOL	Quality of life
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RHAZ	UNCOVER-1 (NCT01474512)
RHBA	UNCOVER-2 (NCT01597245)
RHBC	UNCOVER-3 (NCT01646177)
RHBL	UNCOVER-A (NCT01777191)
RHBP	IXORA-P (NCT02513550)
RHBS	IXORA-S (NCT02561806)
SA	Sensitivity analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF-36	Short form 36
SF-6D	Short Form – 6 Dimension
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision-Making
SmPC	Summary of Product Characteristics
sPGA	Static Physician Global Assessment
STA	Single technology appraisal
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TA	Technology appraisal
TEAE	Treatment-related adverse event
TLV	Tandvårds- och läkemedelsförmånsverket
TNF	Tumour necrosis factor
TSD	Technical Support Document
TTO	Time trade-off
U&E	Urea and electrolytes test
UK	United Kingdom
USA	United States of America
UST	Ustekinumab

Abbreviation	Definition
UVB	Ultraviolet B
VAS	Visual Analogue Scale
WHO	World Health Organisation
WPAI	Work and activity impairment questionnaire
WTP	Willingness to pay

1 Executive summary

Ixekizumab

Ixekizumab (Taltz®) is a recombinant humanised IgG4 monoclonal antibody (mAb) designed and engineered to selectively inhibit interleukin-17A (IL-17A), a pro-inflammatory cytokine.[1] Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases, including plaque psoriasis.[2,3] In combination with other cytokines such as tumour necrosis factor alpha (TNF-α), IL-21, IL-22, and keratinocyte-derived chemokines, IL-17A contributes to keratinocyte activation and hyper-proliferation, production of antimicrobial peptides and further recruitment of inflammatory cells, that amplify skin inflammation.[4] Ixekizumab was granted marketing authorisation for the use of ixekizumab in the European Union (EU) on 26 April 2016 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.[1] The licensed dose of ixekizumab is 160 mg by subcutaneous injection (SC) injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.[1]

Psoriasis

Psoriasis is a common chronic inflammatory skin disease that is characterised by the appearance of prototypic red, thick and scaly plaques.[4] Plaque psoriasis (hereafter psoriasis) represents the most common form of the disease and has a substantial impact on overall health. Psoriasis manifests as well-defined, sharply demarcated, erythematous plaques varying in size which typically have a dry, thin, silvery-white or micaceous scale and tend to be symmetrically distributed over the body.[5,6] The course and progress of psoriasis is often unpredictable[7] but typically follows a relapsing and remitting course.[8]

Psoriasis has been shown to cause large detrimental effects on patients' physical, psychological, and social functioning, resulting in large impacts on health-related quality of life (HRQoL). Approximately 75% of psoriasis patients report burdensome symptoms associated with plaques (including itching, redness, scaling and flaking), regardless of whether they are receiving treatment.[9] Painful fissuring can occur if plaques are located on joints, soles or palms, adding to the burden on patients.[5] As a potential consequence of the systemic inflammatory nature of the disease, psoriasis is also associated with a range of comorbidities including obesity, hypertension, diabetes and hyperlipidaemia.[10] Many patients report being unhappy with their current psoriasis treatment.[9] Psoriasis also confers a substantial economic burden to society which increases with severity of disease.[11] The cost of psoriasis to healthcare systems is comparable to diseases such as pancreatic cancer,

melanoma, prostate cancer and asthma, and includes both direct costs (e.g. medication, physician visits, laboratory tests and hospitalisations) and indirect costs (e.g. loss of productivity).[12]

The prevalence of psoriasis in England has been estimated at 1.75% of the total, with approximately 2.55% of these patients being eligible for treatment with biologic therapy.[13]

The current treatment pathway for psoriasis in the UK according to NICE guidelines and technology appraisals consists of a combination of topical therapy, photo therapy and systemic therapy (which include conventional non-biologic agents and biologic agents). Biologic therapies are recommended for severe disease in patients who have failed to respond to standard systemic therapies and psoralen and long-wave ultraviolet radiation (PUVA); or the person is intolerant to, or has a contraindication to, these treatments.[8] Currently licensed biologics which have been recommended by NICE include etanercept, infliximab, adalimumab, ustekinumab and secukinumab.

Clinical effectiveness of ixekizumab

Treatment with ixekizumab can achieve complete clearance, high-level responses and relief from bothersome psoriasis symptoms (e.g. itch), thus improving the HRQoL of patients with moderate to severe psoriasis. Ixekizumab is also efficacious in difficult-to-treat areas, alleviating the burden of psoriasis symptoms in areas such as the nails, scalp and palmoplantar regions. Ixekizumab has a rapid onset of efficacy and is able to produce high-level responses in patients regardless of prior therapy, including biologics. Ixekizumab is well tolerated in patients with moderate to severe psoriasis with a predictable safety profile comparable to that of the commonly used biologic etanercept.

Cost-effectiveness of ixekizumab

A de novo Markov state-transition model was developed to estimate the cost-effectiveness of ixekizumab versus other biologic therapies approved in the UK as first line therapy within a treatment sequence in a fully incremental analysis framework. Mortality was assumed equivalent across all treatment sequences and HRQoL was modelled in terms of health utility gains associated with improvements in Psoriasis Area and Severity Index (PASI) symptoms relative to baseline. Cost and resources modelled included drug acquisition, administration, monitoring, best supportive care (BSC) and non-responder costs. A confidential discount on the list price of ixekizumab was approved under a patient access scheme (PAS) and applied in the analysis. The ixekizumab sequence was associated with the greatest QALY gains and an ICER of £33,858/QALY vs the referent comparator, the

etanercept sequence. No other sequence lay on the cost-effectiveness frontier.

1.1 *Statement of decision problem*

This submission presents the clinical- and cost-effectiveness data for ixekizumab in the treatment of patients with moderate to severe plaque psoriasis. The decision problem can be seen in Table 1.

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	Adults with moderate to severe plaque psoriasis	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy	As per summary of product characteristics (SmPC)
Intervention	Ixekizumab (Taltz®)	Ixekizumab 160 mg by subcutaneous injection (SC) injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks	As per reference case and final label
Comparator (s)	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies (including acitretin, ciclosporin, fumaric acid esters, methotrexate) • Phototherapy with ultraviolet (UVB) radiation For people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-α inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Best supportive care	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies (including ciclosporin and methotrexate) • Phototherapy with ultraviolet (UVB) radiation For people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-α inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Best supportive care	Fumaric acid esters, acitretin or phototherapy with UVB radiation have not been included in this submission as insufficient data for these comparators was identified from the systematic literature review (SLR) to allow indirect comparisons to be conducted in the network meta-analysis (NMA). However, it is anticipated that ixekizumab will have a similar place in the clinical pathway to NICE approved biologics, i.e. after standard therapies have failed/ are contraindicated or are not tolerated.
Outcomes	The outcome measures to be considered include: • severity of psoriasis • psoriasis symptoms on the face, scalp and nails • mortality • response rate • relapse rate	This submission includes a range of outcome measures to assess the clinical ixekizumab, including: • Psoriasis Area and Severity Index (PASI) – including PASI 75/90/100. The primary focus of the submission is PASI 75 as this was the co-primary endpoint of the included studies and is the measure of response used by NICE. • static Physician Global Assessment	Psoriasis symptoms of the face have not been included in the submission as there is no reference to this outcome measure in the SmPC, which focusses on psoriasis of the nails, scalp and palmoplantar areas. These outcomes measures have not been explicitly taken into account in the cost-effectiveness model which is based on standard overall PASI response. Mortality was included in the reporting of adverse

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• adverse effects of treatment • health-related quality of life	(sPGA) – a validated, standardised global score used in conjunction with PASI to assess efficacy • PASI 90 – high-levels of skin clearance used as an indicator of clear or almost clear skin • PASI 100 – complete clearance of skin symptoms used as an indicator of disease remission • Relapse rate will be assessed based on the maintenance of response at week 60. • Psoriasis of the nails, scalp and palmoplantar areas is assessed using area-specific measures including Nail Psoriasis Severity Index (NAPSI), Psoriasis Scalp Severity Index (PSSI) and Palmoplantar Psoriasis Severity Index (PPASI) • Adverse events (including background mortality) will be reported for ixekizumab and comparators based on the results from the clinical studies • Health-related quality of life (HRQoL) is measured using the Dermatology Life Quality Index (DLQI)	events. Treatment effect on mortality has not been included due to data limitations.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 (QALY). 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 patient access schemes (PAS) for the intervention or comparator technologies should be taken into account. For the comparators, the availability and cost of biosimilars should be taken into consideration.	Cost-effectiveness expressed as incremental cost per quality-adjusted life year, with a lifetime model horizon, considering costs from an NHS and PSS perspective.	As per the reference case
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe) Where the evidence allows, sequencing of different drugs and the place of ixekizumab in such a sequence will be considered.	Subgroup analyses have been reported according to the severity of psoriasis as measured by DLQI scores and previous use of systemic non-biological and biological therapies.	As per the reference case
Special considerations including issues related to equity or equality	No equity or equality issues identified.	No equity or equality issues identified.	As per the reference case

DLQI = Dermatology Life Quality Index; HRQoL = Health-related quality of life; NAPSI = Nail Psoriasis Severity Index; NHS = National Health Service; NMA = network meta-analysis; PAS = patient access scheme; PASI = Psoriasis Area and Severity Index; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Personal Social Services; PSSI = Psoriasis Scalp Severity Index; QALY = quality adjusted life year; SLR = systematic literature review; SmPC = summary of product characteristics; sPGA = static Physician Global Assessment; TNF-α = tumour necrosis factor alpha

1.2 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	Approved name: Ixekizumab Brand name: Taltz®
Marketing authorisation/CE mark status	On 26 April 2016, the European Commission granted a marketing authorisation for the use of ixekizumab in the European Union (EU)
Indications and any restriction(s) as described in the summary of product characteristics	Ixekizumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy
Method of administration and dosage	The recommended dose of ixekizumab is 160 mg by subcutaneous injection (SC) injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks

CE mark = Conformité Européene mark; EU = European Union; SC = subcutaneous

1.3 *Summary of the clinical effectiveness analysis*

1.3.1 Clinical efficacy

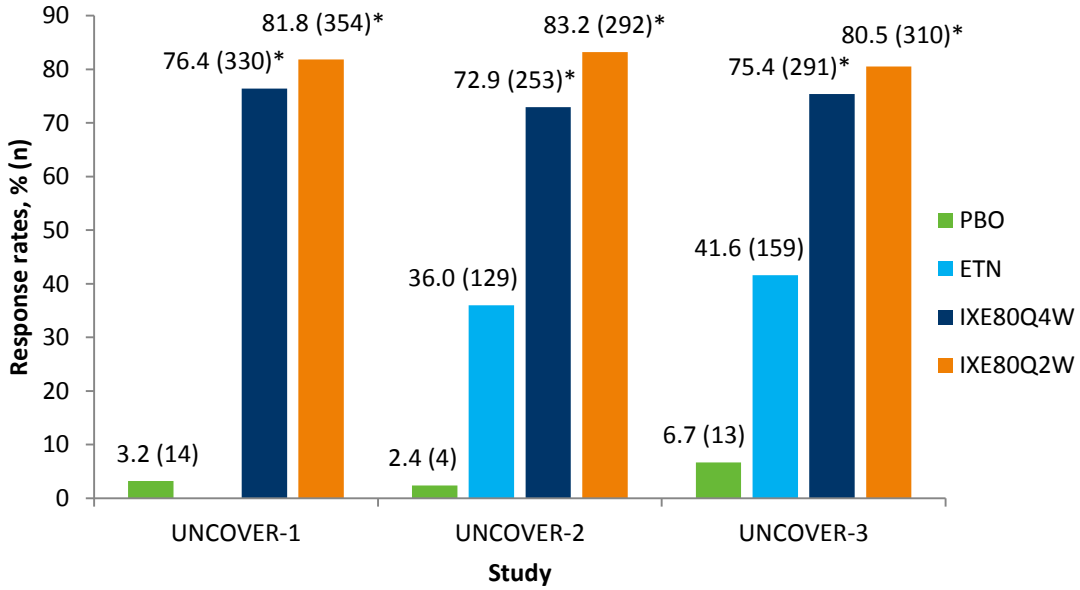
The efficacy and safety of ixekizumab has been evaluated in a comprehensive clinical development programme including three pivotal, double-blind, randomised, phase III studies in patients with moderate to severe psoriasis (UNCOVER-1, -2 and -3). The UNCOVER studies were all phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient trials comparing the efficacy and safety of ixekizumab to placebo in patients with moderate to severe plaque psoriasis. In addition, the UNCOVER-2 and UNCOVER-3 studies included an active comparator (etanercept) arm.

The UNCOVER studies included two dose regimens of ixekizumab in the 12 week induction period of the studies – ixekizumab 80 mg every two weeks (Q2W) and ixekizumab 80 mg every 4 weeks (Q4W). For completeness, the results of both these doses are presented in this submission, however it should be noted that the licensed dose regimen is 160 mg at week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg Q4W.

All three of the UNCOVER studies had similar patient populations and assessed the same co-primary endpoints. The co-primary endpoint measures used in the UNCOVER trials were the static Physician Global Assessment (sPGA) and the Psoriasis Area and Severity Index (PASI) responses after 12 weeks of treatment. The co-primary objectives were met in all three UNCOVER trials.

In all three UNCOVER studies statistically significantly higher sPGA (0, 1) response rates were achieved with ixekizumab compared with placebo at week 12 (p<0.001 for all comparisons). In addition, significantly higher sPGA (0, 1) response rates were achieved with ixekizumab compared with active comparator etanercept 50mg twice weekly at week 12 (p<0.001 for all comparisons) in the UNCOVER-2 and -3 studies (Figure 1).

Figure 1: sPGA (0,1) results at week 12 for all studies – NRI (ITT population)

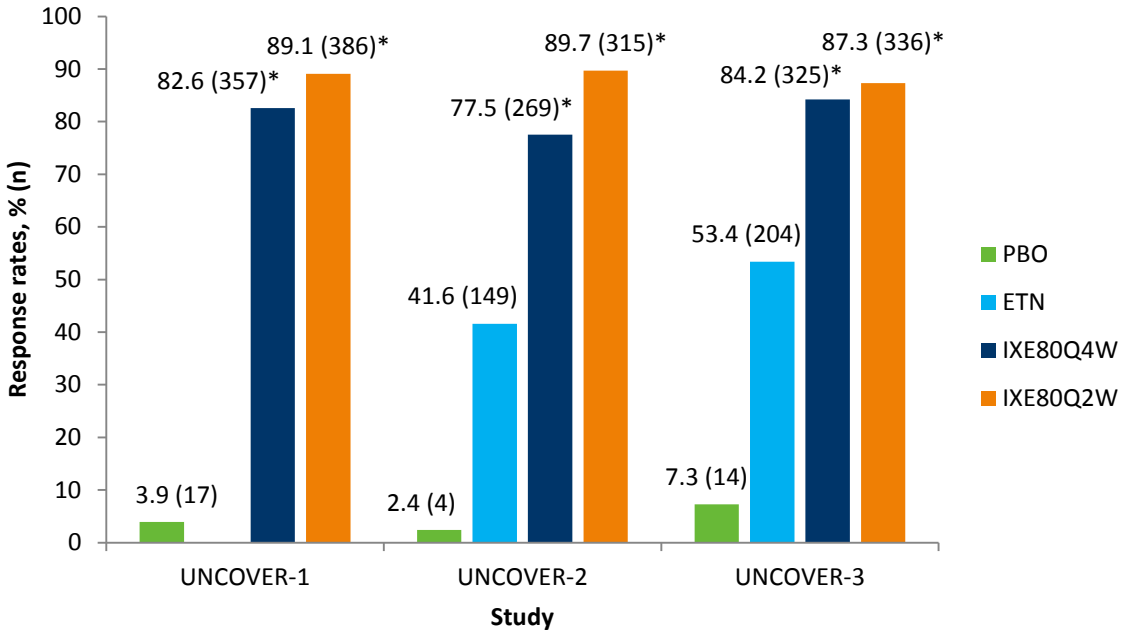


*p<0.001 versus placebo and etanercept

ETN = etanercept; ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

PASI 75 response rates at week 12 were statistically significantly higher with ixekizumab compared with both placebo and etanercept (UNCOVER-2 and -3 only) at week 12 (p<0.001 for all comparisons) (Figure 2).

Figure 2: PASI 75 response rates at week 12 for all studies – NRI (ITT population)



*p<0.001 versus placebo and etanercept

ETN = etanercept; ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

Ixekizumab also demonstrated significant improvements in the proportion of patients achieving complete clearance (PASI 100) and high-level responses (PASI 90) compared to etanercept (UNCOVER-2 and -3) and placebo at week 12 (p<0.001 for all comparisons).

Ixekizumab demonstrated rapid onset of efficacy in the UNCOVER-2 and -3 studies, with statistically significant differences in PASI 75 as early as week 2 compared with etanercept and placebo (p<0.001 for all comparisons). In the UNCOVER-2 study 18.2% of patients treated with ixekizumab Q2W achieved PASI 75 at week 2, compared with 0.6% of patients who received placebo, and 0.6% of patients who received etanercept, respectively. Similarly, in the UNCOVER-3 study 22.9% of patients treated with ixekizumab Q2W achieved PASI 75 at week 2, compared with 0% of patients who received placebo, and 2.4% of patients who received etanercept, respectively.

The UNCOVER-1 and -2 studies included a maintenance dosing period (week 12-60) in order to determine the optimum maintenance dosing interval of ixekizumab, the maintenance of response, relapse or rebound following treatment withdrawal and response to re-treatment with ixekizumab following relapse in a re-randomised patient population. sPGA (0,1) and PASI responses (including PASI 100) were generally achieved or maintained in the maintenance dosing period with ixekizumab.

Ixekizumab was also statistically significantly superior to etanercept (UNCOVER-2 and -3 only) and placebo in treating the symptoms of psoriasis in difficult-to-treat areas (including nail, scalp and palmoplantar areas), alleviating the burdensome symptom of itch associated with psoriasis and improving HRQoL as measured by Dermatology Life Quality Index (DLQI) scores at week 12 across all the UNCOVER studies ($p<0.001$ for all comparisons).

In order to facilitate the comparison of ixekizumab with all the comparators included in the NICE decision problem, a network meta-analysis (NMA) was conducted. The proportion of patients achieving four PASI outcome categories (PASI 50, 75, 90 and 100) was determined for ixekizumab and the relevant comparators. The NMA base case analysis included both induction doses of ixekizumab assessed in the UNCOVER studies (ixekizumab 80 mg Q2W and Q4W) as the final licensed dose of ixekizumab had not been determined at the time the NMA was conducted. The results of the base case NMA demonstrated that ixekizumab 80 mg Q2W was ranked as the therapy with the highest probability of being ranked best, achieving PASI 75 and PASI 90 responses at week 12 of 89.5% (95% credible intervals [CrI]: 84.1% to 93.7%) and 72.2% (95% CrI: 62.9% to 80.5%), respectively.

1.3.2 Safety

The safety profile of ixekizumab has been robustly evaluated through AE reporting in the UNCOVER studies, which included head-to-head assessments against etanercept (UNCOVER-2 and -3 only) and involved 3,866 patients.

There were no major safety signals identified in the UNCOVER clinical development programme. Ixekizumab was well tolerated across the UNCOVER studies with a predictable safety profile which was comparable to etanercept.

The incidence of ≥1 TEAEs and TEAEs judged to be possibly to study drug was generally higher in the ixekizumab groups compared with the placebo group at week 12. However, the majority of these TEAEs was of mild to moderate severity and did not lead to discontinuation of study medication. Importantly, the incidence of TEAEs was comparable between the ixekizumab treatment groups and the etanercept group after week 12.

The incidence of SAEs and discontinuations due to AEs did not differ between the ixekizumab, etanercept or placebo groups in any of the UNCOVER studies after 12 weeks.

The most frequent AESI which were reported in the UNCOVER studies included infection and injection site reactions. After 12 weeks of ixekizumab treatment, commonly observed types of infections in the studies were nasopharyngitis, upper respiratory tract infection, bronchitis, and sinusitis.

To assess the emergence of AEs following extended treatment, the safety of ixekizumab was evaluated beyond the 12-week efficacy primary endpoint into the maintenance dosing period (week 12-60). The results indicated that ixekizumab was well tolerated during the maintenance dosing period with similar AEs to those seen in the induction period.

1.4 *Summary of the cost-effectiveness analysis*

A de novo Markov state-transition model was developed in Visual Basic for Application with a Microsoft Excel interface to assess the cost-effectiveness of ixekizumab versus other biologic therapies approved in the UK.

In the base case analysis, the model assesses the cost-effectiveness of biologics as first-line therapy within a treatment sequence in a fully incremental analysis framework. Patients initiate treatment in an induction period and, in order to continue into maintenance therapy, are assessed for response measured as a percentage reduction in PASI symptoms relative to baseline. Patients may discontinue treatment due to inadequate response (attaining less than 75% reduction in baseline PASI score) at the end of induction or a constant annual rate of all-cause discontinuation during the maintenance period. After discontinuation, patients proceed to the next treatment in the sequence before finally receiving best supportive care (BSC) after discontinuing from three biologic therapies.

EQ-5D-5L data were collected in the UNCOVER trial programme and used to derive health utility gains from baseline associated with a specific level of PASI response. Health utility gains are applied each monthly model cycle only in the maintenance period until all-cause discontinuation. A gender-weighted, age-dependent risk of death is applied in all treatment state. No treatment effect on mortality is applied; the risk of death is assumed to be equivalent across all treatment sequences.

A confidential patient access scheme (PAS) discount on the list price of ixekizumab was approved by the Patient Access Scheme Liaison Unit (PASLU) and used in the analysis. List prices for other modelled interventions were obtained from the Monthly Index of Medical Specialities (MIMS). The costs for BSC were taken from a previously published UK study (Fonia *et al*- 2010) and other categories of resource use associated with biologic treatments (monitoring, administration, non-responder costs) were obtained from previous NICE appraisals.

The ixekizumab sequence was associated with the greatest QALY gains and an ICER of £33,858/QALY vs the referent comparator, the etanercept sequence. All other comparator treatment sequences were dominated (secukinumab, using the list price) or extendedly dominated by the ixekizumab sequence. Pairwise ICERs for ixekizumab versus adalimumab sequence, ustekinumab 45 mg sequence, ustekinumab 90 mg sequence and infliximab sequence all fell below £20,000/QALY.

Sensitivity analyses were conducted to assess the impact of variation in key parameters and assumptions on the results. Deterministic sensitivity analyses were undertaken for pairwise comparisons and indicated that acquisition costs, annual all-cause discontinuation rate and discount rates for costs and QALYs had the greatest impact on the ICER. The cost-effectiveness of ixekizumab versus ustekinumab 45 mg, ustekinumab 90 mg and secukinumab as second-line therapy was evaluated in patients who had inadequate response or contraindication to a TNF-α inhibitor. The ixekizumab sequence was associated with lower costs and greater QALY gains compared to the other sequences.

Table 3: Incremental cost-effectiveness results

1st line	2nd-line	3rd-line	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental analysis	Pairwise ICER: ixekizumab versus comparator
Etanercept	Ustekinumab 90 mg	Infliximab	£144,635	1.27	Referent	Referent	Referent	£33,858
Ustekinumab 45 mg	Adalimumab	Infliximab	£148,218	1.30	£3,583	0.04	Extended dominance	£18,278
Adalimumab	Ustekinumab 90 mg	Infliximab	£148,350	1.32	£3,715	0.05	Extended dominance	£19,202
Ustekinumab 90 mg	Adalimumab	Infliximab	£148,719	1.32	£4,083	0.06	Extended dominance	£16,763
Infliximab	Ustekinumab 90 mg	Adalimumab	£150,350	1.33	£5,714	0.06	Extended dominance	£4,300
Ixekizumab Q2W	Ustekinumab 90 mg	Infliximab	£150,889	1.45	£6,254	0.18	£33,858	N/A
Secukinumab 300 mg	Ustekinumab 90 mg	Infliximab	£177,101	1.42	£32,466	0.15	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; N/A = not applicable

2 The technology

2.1 *Description of the technology*

A summary of the technology being appraised in this submission can be seen in Table 4.

Table 4: Description of technology

Brand Name	Taltz®
Approved Name	Ixekizumab
Therapeutic Class	IL-17A inhibitor

IL = interleukin

Ixekizumab is a recombinant humanised IgG4 monoclonal antibody (mAb) designed and engineered to selectively inhibit interleukin-17A (IL-17A), a pro-inflammatory cytokine.[1] Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases, including plaque psoriasis.[2,3] In combination with other cytokines such as tumour necrosis factor alpha (TNF-α), IL-21, IL-22, and keratinocyte-derived chemokines, IL-17A contributes to keratinocyte activation and hyper-proliferation, production of antimicrobial peptides and further recruitment of inflammatory cells, that amplify skin inflammation.[4]

Selective inhibition of IL-17A represents a novel approach to disrupting pro-inflammatory cycles without interrupting a broader set of immunological pathways that may be affected by other biologic treatments, such as TNF-α inhibitors. The selective mechanism of action for ixekizumab provides an opportunity to enhance clinical efficacy with an acceptable safety profile.

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 Regulatory status in the UK

On 26 April 2016, the European Commission granted a marketing authorisation for ixekizumab for the following indication:

'Taltz® is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy'.

Ixekizumab is expected to be commercially available in England in July 2016.

The summary of product characteristics (SmPC) detailing contraindications and precautions for the use of ixekizumab can be seen in Appendix 1.

2.2.2 Regulatory status outside the UK

Ixekizumab was granted regulatory approval by the U.S. Food and Drug Administration (FDA) in March 2016 and by Health Canada in May 2016. In addition, ixekizumab is currently under review by regulatory authorities in Australia, Japan and Switzerland.

2.2.3 Other UK health technology assessment agencies

Ixekizumab is expected to be appraised by the National Centre for Pharmacoeconomics (NCPE) in [redacted] and the Scottish Medicines Consortium (SMC) in [redacted].

2.3 *Administration and costs of the technology*

The recommended dose of ixekizumab is 160 mg by subcutaneous injection (SC) injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.

The final label states that consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks. However, it should be noted that the blinded period for the primary endpoint of the included studies is 12 weeks (as noted above) and this is therefore the focus of the data presented.

The associated costs of ixekizumab can be seen in Table 5.

Table 5: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	80 mg solution for injection in pre-filled syringe or pen. Each pre-filled syringe/pen contains 80 mg ixekizumab in 1 ml.	SmPC[1]
Acquisition cost (excluding VAT)	**List price** Taltz® 80mg solution for injection in prefilled pen x 2 = £2,250 Taltz® 80 mg solution for injection in prefilled syringe = £1,125 **Approved PAS price** Taltz® 80mg solution for injection in prefilled pen x 2 = [redacted] Taltz® 80 mg solution for injection in prefilled syringe = [redacted]	
Method of administration	Administered via SC injection.	SmPC[1]

Doses and dose frequency	The recommended dose of ixekizumab is an initial dose of160 mg by SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.	SmPC[1]
Average length of a course of treatment	In patients who respond, treatment is expected to be continuous until loss of response or discontinuation for any reason.	
Average cost of a course of treatment	Per annum cost: **First year** 18 injections – [redacted] **Second year** 13 injections – [redacted]	
Anticipated average interval between courses of treatments	N/A – continuous treatment.	
Anticipated number of repeat courses of treatments	N/A – continuous treatment until discontinuation for any reason.	
Dose adjustments	No dose adjustments for ixekizumab are specified in the final label therefore patients are expected to remain on 80mg every 4 weeks until discontinuation for any reason	
Anticipated care setting	Initiation of treatment will be conducted by a dermatology specialist healthcare professional in secondary care. Patients may self-administer ixekizumab following proper training in SC injection technique if deemed appropriate by a healthcare professional.	SmPC[1]

N/A = not applicable; PAS = patient access scheme; SC = subcutaneous; SmPC = summary of product characteristics; sPGA = static Physician Global Assessment

2.4 *Changes in service provision and management*

There are no additional treatments, tests, investigations or monitoring requirements for patients prior to receiving ixekizumab or during therapy, compared with other available and NICE approved biologic therapies for psoriasis. In accordance with routine clinical practice for the use of biologics, patients should be evaluated for tuberculosis infection prior to initiation of therapy.[1]

Following proper training in SC injection technique patients may self-inject ixekizumab if a healthcare professional determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Comprehensive instructions for administration are given in the package leaflet in addition to a Lilly support programme.[1]

2.5 *Innovation*

There is a clear unmet need for new therapeutic options in the treatment of moderate to severe psoriasis as shown by a prospective observational cohort study of currently available biologics used in UK and Ireland clinical practice.[14] The study demonstrated that overall drug survival rates (defined as the length of time from initiation to discontinuation of therapy) fell to 53% by the third year of treatment.[14] The results demonstrate the clear need for new and effective therapeutic options which are able to maintain long-term responses.[14]

Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A have been implicated in the pathogenesis of psoriasis by promoting keratinocyte proliferation and activation. Inhibition of IL-17A selectively disrupts the pro-inflammatory stimuli that are responsible for the formation and perpetuation of psoriasis plaques, thus offering a targeted approach for psoriasis treatment. This mechanism of action may be postulated to be the primary factor influencing the results of the key phase III studies (Section 4.7) which demonstrated that a significant proportion of patients with moderate to severe psoriasis achieve complete clearance (PASI 100) and high-level responses (PASI 90), both highly clinically relevant measurement of efficacy.

The UNCOVER-1, -2 and -3 studies were all phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, trials comparing the efficacy and safety of ixekizumab with placebo, over a 12-week period. In addition, the UNCOVER-2 and UNCOVER-3 studies included an active comparator (etanercept) arm. Across the phase III UNCOVER studies the proportion of patients achieving complete clearance (PASI 100) and high-level responses (PASI 90) was significantly greater with ixekizumab compared with etanercept and placebo at week 12 ($p<0.001$ for all comparisons). Across the studies, PASI 100 response rates ranged from 35.3% to 41.0% in the ixekizumab Q2W group, 30.8% to 35.0% in the ixekizumab Q4W group, 5.3% to 7.3% in the etanercept group and only 0.6% in the placebo group (Section 4.7).[15,16] Improvements in health-related quality of life (HRQoL) are positively-linked with the level of skin clearance for patients with psoriasis.[17,18] Therefore, treatments which are able to achieve high-levels of skin clearance can have a substantial impact on patients' HRQoL.

Ixekizumab has also demonstrated a rapid onset of efficacy, another important factor for patients with psoriasis.[19] In the UNCOVER-2 study 18.2% of patients treated with ixekizumab Q2W achieved PASI 75 at week 2, compared with 0.6% of patients who received placebo, and 0.6% of patients who received etanercept, respectively. Similarly, in the UNCOVER-3 study 22.9% of patients treated with ixekizumab Q2W achieved PASI 75 at week 2, compared with 0% of patients who received placebo, and 2.4% of patients who received etanercept, respectively (Section 4.7).[16]

Long-term efficacy data from the UNCOVER studies also demonstrates the sustained responses achieved by patients treated with ixekizumab – an important factor in the treatment of chronic diseases such as psoriasis. In the UNCOVER-1 and -2 studies, which included a maintenance dosing period (week 12-60) significant proportions of patients treated with ixekizumab 80 mg Q2W in the induction dosing period and ixekizumab 80 mg Q4W during the maintenance dosing period achieved or maintained sPGA (0,1) compared with placebo ($p<0.001$ for all comparisons) at week 60 (Section 4.7).[15] Data from the long-term extension phase of the UNCOVER-3 study up to 108 weeks demonstrate that high-levels of clearance and complete clearance are achieved or maintained in patients receiving open-label fixed dosing of ixekizumab 80 mg Q4W between weeks 12 and 108.[20]

The presentation of skin symptoms in difficult-to-treat areas (e.g. nail, scalp and palmoplantar areas) can be an additional burden that further reduces patient HRQoL but the impact may not be adequately captured by the EQ-5D instrument.[9] Across all the UNCOVER trials, patients treated with ixekizumab demonstrated significant improvements in nail, scalp and palmoplantar psoriasis compared with etanercept and placebo at week 12 ($p<0.001$ all comparisons) (Section 4.7).[21-23]

Ixekizumab has demonstrated consistent benefits across a variety of subgroups in patients with moderate to severe plaque psoriasis (Section **Error! Reference source not found.**). Of particular note, ixekizumab demonstrated consistent levels of efficacy in patients who had been previously treated with biologic therapy and in patients who had inadequate response to etanercept. This is a particularly important factor considering the treatment paradigm for moderate to severe psoriasis in the UK and the drug survival rates for biologic therapies outlined above.

The ease of use and confidence in SC administration of biologic therapies is an important factor for patients with psoriasis. The ease of use of ixekizumab was assessed using a subcutaneous administration assessment questionnaire in the RHBL study (UNCOVER-A). The study demonstrated high-levels of patient satisfaction and confidence using both the ixekizumab pre-filled syringe and pre-filled pen.[24]

The considerable clinical benefit demonstrated by ixekizumab in the UNCOVER studies, in particular the proportion of patients achieving complete clearance of their symptoms, will result in the number of non-responders decreasing and less burden being placed on dermatology services. These potential benefits may not be captured in the Quality-Adjusted Life Year (QALY) calculation.

These factors all contribute to the argument that ixekizumab is an innovative step-change treatment option for psoriasis patients. Furthermore, there are aspects of the treatment benefits of ixekizumab that are unlikely to be captured in the QALY calculation which have been highlighted in previous NICE appraisals such as the potential social stigma associated with the condition, the likelihood that best supportive care is associated with unquantified disutility and the potential limitations of generic preference-based utility instruments such as EQ-5D for skin conditions.

3 Health condition and position of the technology in the treatment pathway

3.1 *Overview of disease*

Psoriasis is a common chronic inflammatory skin disease that is characterised by the appearance of prototypic red, thick and scaly plaques.[4] Plaque psoriasis (hereafter psoriasis) represents the most common form of the disease and has a substantial impact on overall health. In moderate to severe cases, it can be associated with a range of systemic comorbidities (Section 3.1.2).[4] Psoriasis manifests as well-defined, sharply demarcated, erythematous plaques varying in size which typically have a dry, thin, silvery-white or micaceous scale and tend to be symmetrically distributed over the body.[5,6] Common locations for the development of plaques can include the scalp, trunk, buttocks, and limbs, with a particular tendency for occurrence on the elbows and knees.[25] The course and progress of psoriasis is often unpredictable[7] but typically follows a relapsing and remitting course.[8] The chronic and relapsing nature of the disease can often impact patients QoL and psychological wellbeing.[26]

3.1.1 Pathophysiology

Psoriasis results from the interplay of genetic predisposition, environmental triggers and dysregulation of the auto-immune system. Specifically, psoriasis is now known to be primarily a T-cell mediated condition that leads to accumulation of inflammatory cells, angiogenesis and epidermal hyperproliferation.[27,28] The interleukin-23 (IL-23)/ T-helper 17 cells (Th17) pathway and associated pro-inflammatory mediators, cytokines, and antimicrobial peptides stimulate amplification of the immune response, leading to the clinical features of psoriasis (e.g. red, elevated, scaly plaques).[4,29]

Recent studies have identified IL-17A as a major cytokine in the psoriasis disease pathway and the most critical T-cell-derived cytokine in alterations of skin function.[2,3] Moreover, evidence suggests that TNF-α inhibitors produce efficacy in psoriasis by indirectly modifying the IL-17A pathway.[30] Selective inhibition of IL-17A therefore represents a biologically plausible target for new psoriasis therapies.

3.1.2 Comorbidities

Patients with psoriasis have an increased risk of depression, anxiety, and suicidality compared with patients without psoriasis.[31] Patients with psoriasis are significantly more likely to show depressive symptoms and use antidepressants, compared with controls. In a UK population-based cohort study from 1987 to 2002, the risk of depression according to the severity of psoriasis was assessed.[31] The adjusted relative risk for receiving a diagnosis of depression was higher in patients with severe psoriasis, compared with mild psoriasis (Table 6). RR of depression was higher in younger patients compared to older patients.[31]

Table 6: Age and sex adjusted hazard ratios of depression, anxiety, or suicidality in patients with psoriasis compared with controls

Condition	Mild Psoriasis* HR (95% CI)	Severe Psoriasis* HR (95% CI)	All Psoriasis HR (95% CI)
Depression	1.38 (1.35, 1.40) p<0.001	1.72 (1.57, 1.88) p<0.001	1.39 (1.37, 1.41) p<0.001
Anxiety	1.31 (1.29, 1.34) p<0.001	1.29 (1.15, 1.43) p<0.001	1.31 (1.29, 1.34) p<0.001
Suicidality	1.44 (1.32, 1.57) p<0.001	1.51 (0.92, 2.49) p=0.103	1.44 (1.32, 1.57) p<0.001

CI = confidence interval; HR = hazard ratio

Note: Disease was classified using Oxford Medical Information System (OXIS) and Read codes

*Severe psoriasis was defined by both a diagnostic code for psoriasis and a code indicating a systemic treatment modality. Psoriasis patients who did not receive systemic therapy were classified as mild

Psychiatric disorders represent substantial morbidity; it is important to identify these disorders, so that they can be potentially improved using pharmacological and non-pharmacological approaches.[31]

As a potential consequence of the systemic inflammatory nature of the disease, psoriasis is also associated with a range of comorbidities including obesity, hypertension, diabetes and hyperlipidaemia.[10] Meta-analysis of several observational studies has demonstrated the increased risk of major adverse cardiovascular events (MACE) in patients with psoriasis, including increased rates of cardiovascular (CV) mortality, myocardial infarction (MI) and stroke.[32] A UK cohort study, using data from the General Practice Research Database (GPRD) showed that (after adjusting for age, gender, diabetes, hypertension, tobacco use and hyperlipidemia) severe psoriasis confers an excess 6.2% absolute risk of a 10-year rate of MACE, when compared to the general population.[33]

Results from recent surveys suggest that physicians are unaware of the association between psoriasis and cardiovascular disease (CVD), and that patients are not adequately screened for the presence of medical co-morbidities. Identification of these modifiable conditions is important, as they may warrant significant lifestyle modification and medical intervention.[32] In particular, appropriate pharmacological treatment strategies may have an impact on CV outcomes in patients with psoriasis.[34]

3.1.3 Economic burden

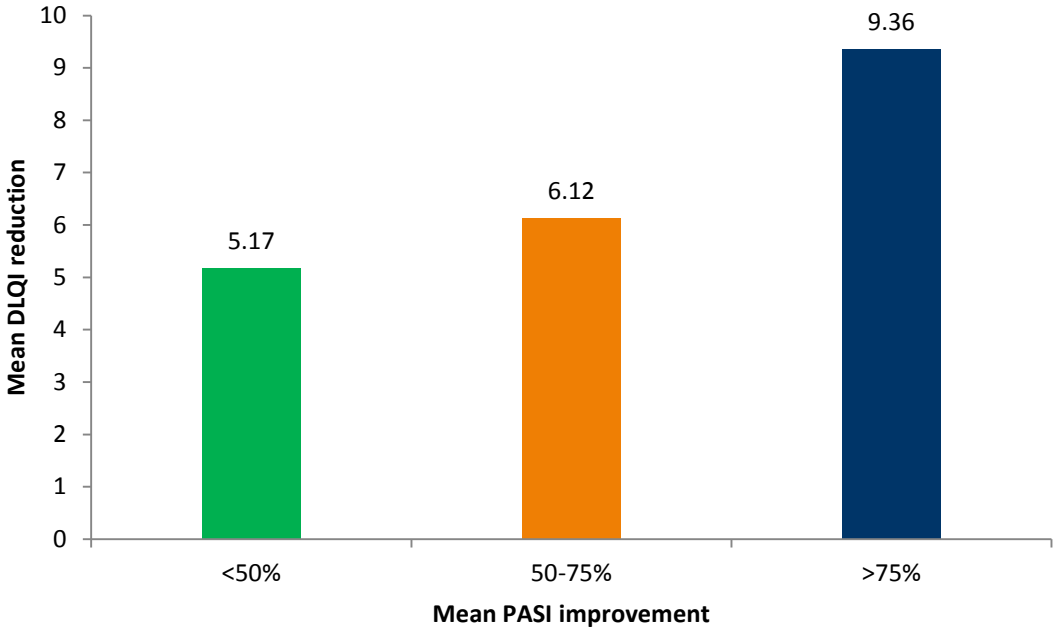
Due to the chronic nature of the condition, and the requirement for lifetime treatment, psoriasis confers a substantial economic burden to society. The cost of psoriasis to healthcare systems is comparable to diseases such as pancreatic cancer, melanoma, prostate cancer and asthma, and includes both direct costs (e.g. medication, physician visits, laboratory tests and hospitalisations) and indirect costs (e.g. loss of productivity).[12] Patients with more severe disease represent the biggest burden on healthcare resource utilisation, as a result of lengthy hospital stays and more outpatient physician visits.[11] In addition, patients with facial psoriasis and those with an increasing severity of itch are more likely to be hospitalised.[35,36] Indirect costs associated with psoriasis are also positively-linked to the severity of disease. Patients with severe disease are associated with overall lower productivity and a greater number of work days missed due to their condition compared with patients with milder forms of the disease.[37,38]

3.2 *Health-related quality of life*

Psoriasis has been shown to cause large detrimental effects on patients' physical, psychological, and social functioning, resulting in large impacts on HRQoL. Approximately 75% of psoriasis patients report burdensome symptoms associated with plaques (including itching, redness, scaling and flaking), regardless of whether they are receiving treatment.[9] Painful fissuring can occur if plaques are located on joints, soles or palms, adding to the burden on patients.[5]

The positive-link between the degree of skin clearance and HRQoL has been demonstrated in clinical studies.[17] Patients who achieve high-levels of skin clearance (e.g. those achieving PASI 90 and PASI 100) have substantially greater improvements in HRQoL as measured by the Dermatology Life Quality Index (DLQI).[17] Mean PASI and DLQI scores have been found to correlate predictably in patients with moderate to severe psoriasis (Figure 3).[18] There is therefore a need for treatments that can demonstrate high-level clearance and alleviate the detrimental HRQoL impact of psoriasis.

Figure 3: Mean DLQI reduction by PASI improvement category[18]



DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index.
Adapted from Matte *et al.* 2014[18]

Itch represents one the most bothersome symptoms of psoriasis and is associated with worsening of patients' HRQoL.[9,39] Itch negatively impacts the HRQoL of psoriasis patients, affecting daily activities (e.g. sleep and ability to attend work/school), mood, concentration, sexual desire and appetite.[40-42] Itch worsens with self-reported disease severity, with moderate to severe psoriasis patients experiencing greater symptoms than those with mild psoriasis (79.1% vs 43.1%, respectively).[39]

Psoriasis is also associated with substantial psychosocial impact in addition to affecting patients physically. Large-scale cross-sectional studies have demonstrated that a high proportion of patients with psoriasis report hiding their condition due to feeling embarrassed or for fear of stigmatisation, with over 75% of respondents having experienced stigmatisation.[43] Psoriasis also affects personal and social relationships, with patients reporting reluctance to engage in social and normal daily activities.[44] Qualitative data show that patients experience low self-esteem, feelings of rejection, isolation, despair and anger.[45]

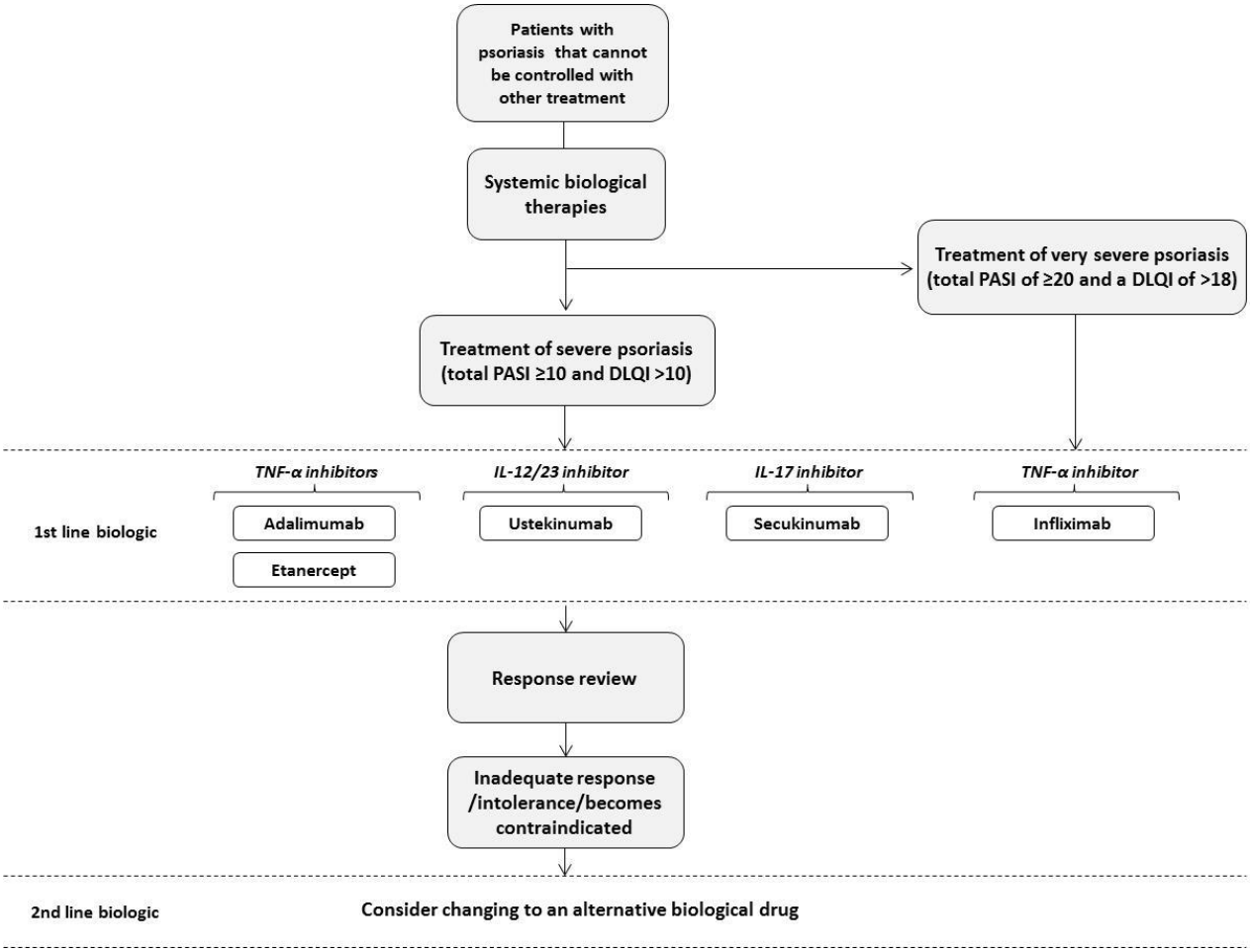
Psoriasis can present in many areas of the body, with some areas being particularly difficult to treat, including nails (10-56%),[46] scalp (48%), and genitals (7%) posing an additional burden that further reduces patient HRQoL.[9] Psoriasis involvement on the face (15%) leads to more emotional stress related to poorer HRQoL. Patients with facial psoriasis frequently report early onset, long duration and tend to have more extensive disease.[47]

3.3 *Clinical pathway of care showing the context of the proposed use of the technology*

A number of treatment options are currently available for the treatment of psoriasis including topical therapy, photo therapy and systemic therapy (which includes conventional non-biologic agents and biologic agents). In general, topical therapies are recommended as first-line therapy for milder forms of psoriasis, with phototherapy being recommended as second-line therapy, or for more extensive disease. Conventional non-biologic systemic therapy can be used as a first-line treatment option in severe psoriasis. A proportion of patients with moderate to severe disease may require treatment with biologics in order to achieve clinically acceptable outcomes. The majority of treatment guidelines recommend biologic agents as second- or third-line therapies following on from when treatment with standard systemics and/or phototheray has failed/is contra-indicated or not tolerated. In the UK, biologic therapies are recommended for severe disease in patients who have failed to respond to standard systemic therapies and PUVA; or the person is intolerant to, or has a contraindication to, these treatments.[8] However, even with the development of more efficacious treatments for psoriasis, patients may not reach high-level responses or lose efficacy over time, which means there is a high unmet need for new treatment options.

The current clinical pathway of care using biologic therapy according to published NICE clinical guidelines and technology appraisals can be seen in Figure 4.

Figure 4: Overview of current treatment pathway for moderate to severe psoriasis (total PASI≥10 and DLQI>10) in accordance with NICE recommendations



DLQI = Dermatology Life Quality Index; IL = interleukin; PAS I = Psoriasis Area and Severity Index; TNF-α = tumour necrosis actor alpha

3.3.1 Limitations of current treatment pathway

Despite a variety of treatment options, currently available systemic therapies (conventional non-biologic agents and biologic agents) for the treatment of moderate to severe psoriasis are associated with a number of limitations. Several studies report poor levels of patient satisfaction and adherence, with many patients considering treatments to be time-consuming (50%) and/or ineffective (32%).[48]

Limitations of conventional non-biologic systemic therapies

Currently available conventional non-biologic systemic therapies (e.g. methotrexate and ciclosporin) are associated with a number of adverse events (AEs) including renal, hepatic and gastrointestinal AEs.[49] These AEs contribute to the higher likelihood of conventional non-biologic systemic treatment discontinuation, in comparison with biologic treatments.[50] In addition, these therapies are rarely able to produce the high-level of response that is considered important for patients with moderate to severe psoriasis. For example, results from a randomised controlled study found that 64.5% of methotrexate-treated patients did not achieve PASI 75 after 16 weeks of treatment.[51]

A substantial proportion of patients also report dissatisfaction with conventional non-biologic systemic therapies options. In the Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey (MAPP) study, 75% of patients receiving conventional non-biologic systemic therapies were dissatisfied; specifically, 74% of patients were not satisfied with efficacy over time, whilst 50% were concerned about the long-term health risks associated with oral therapies.[9] Important factors in patient concerns over conventional non-biologic systemic therapies include treatment tolerability, long-term safety, life-style modifications and lack/loss of response.[52]

Furthermore, conventional non-biologic systemic therapies can prove burdensome in terms of lifestyle adaptions for patients, with some therapies requiring frequent laboratory analyses. For example, in patients receiving methotrexate therapy, NICE recommend fortnightly full blood count, liver function, and urea and electrolytes tests, until six weeks after the last dose increase; these regular tests can prove extremely inconvenient for patients.[53]

Limitations of biologic systemic therapies

Despite offering greater efficacy relative to conventional non-biologic systemic therapies, currently available biologic systemic therapies for the treatment of moderate to severe psoriasis often fail to achieve optimal levels of skin clearance and there is a need for more efficacious treatments which are able to produce high-levels of skin clearance and HRQoL benefit for patients with psoriasis.

There is a substantial unmet need for therapies which are able to provide patients with complete clearance in difficult-to-treat areas, such as the face and scalp.[35,54] For example, a phase III study of ustekinumab reported that 67.5% of patients with nail involvement did not achieve complete clearance at week 52.[55] As unresolved involvement in difficult-to-treat areas is associated with a substantial impact on HRQoL[56,57], patients may still experience substantial disease burden in spite of treatment with more efficacious biologic therapies.

There is also a requirement for new biologic treatments which are efficacious in patients who have previously failed on other biologic treatments. Currently available biologic therapies achieve lower PASI response rates when used as a second-line treatment. For example, following 16 weeks of treatment with adalimumab, 38.3% of TNF-α inhibitor experienced patients did not achieve PASI 75 compared with 28.3% of patients who were TNF-α inhibitor naïve.[58]

As previously mentioned, overall drug survival rates for biologic therapies is poor, with the survival rate associated with current biologics decreasing from 77% in the first year to 53% in the third year.[14] Given the chronic nature of psoriasis, the long-term efficacy of biologic therapies is of particular importance. A common reason for treatment cessation and lack of drug survival has been shown to be loss of efficacy, as exemplified by a loss of PASI response. Loss of response was cited as one of the main reasons for discontinuing treatment in a survey of psoriasis patients (n=4,862).[59]

Results from the MAPP study also highlight that only approximately 45% of patients treated with a biologic reported being very satisfied on their treatment, with 85% of patients surveyed feeling that there is a need for better therapies.[9] High-levels of patient dissatisfaction is linked to non-adherence in many patients with psoriasis.[60] Furthermore, 28% of dermatologists reported feeling dissatisfied with currently available biologic therapies.[52]

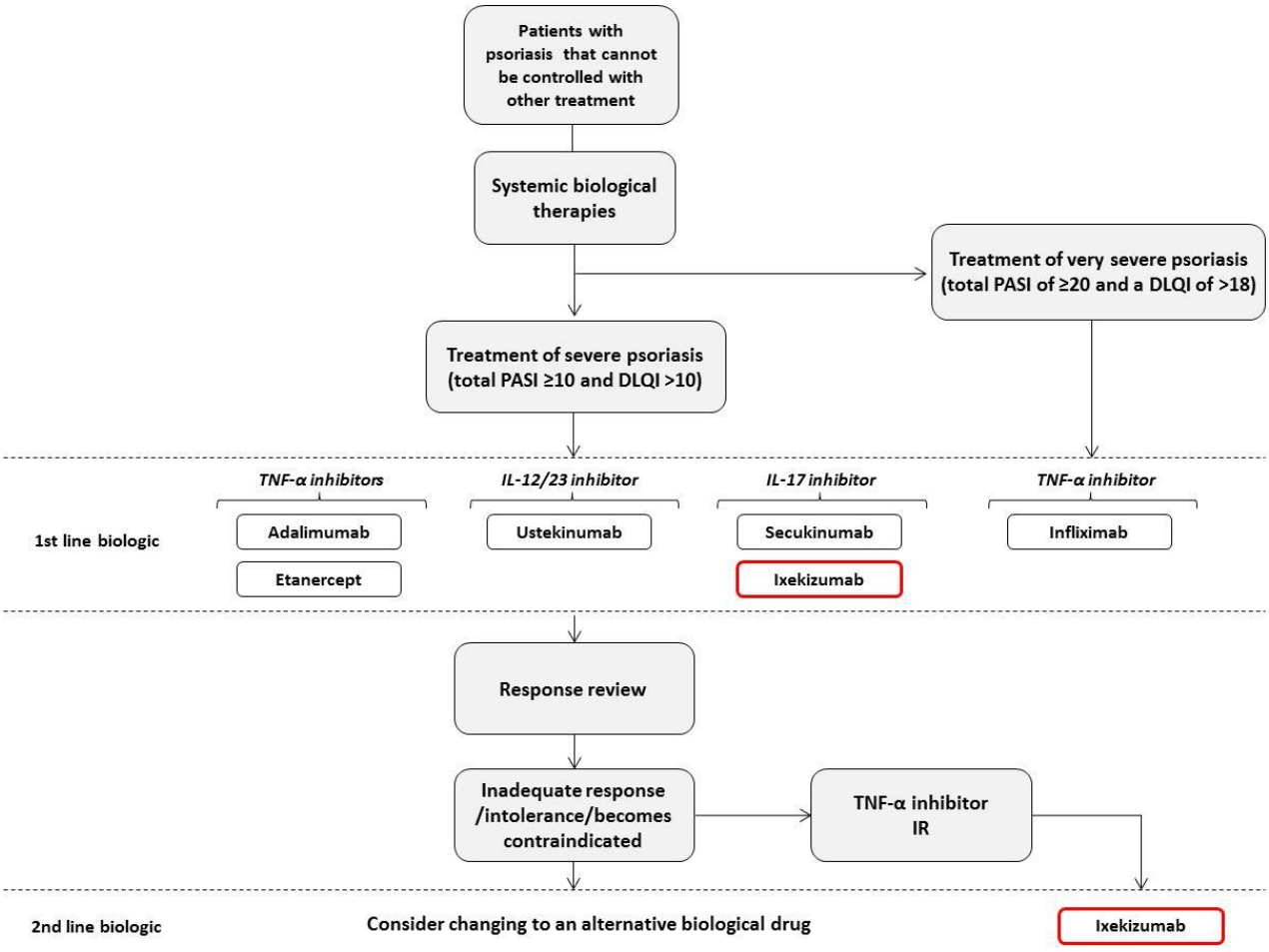
Given the limitations of currently available systemic non-biologic and biologic therapies for moderate to severe psoriasis, there is an important unmet need for new treatments that can achieve high-levels of skin clearance with an acceptable safety profile.

3.3.2 Proposed positioning of ixekizumab in the current treatment pathway

As detailed in Section 2.5 and Section 4.7, ixekizumab is an IgG4 monoclonal antibody that binds with high affinity and specificity to IL-7A which has demonstrated high-levels of skin clearance in clinical trials which are consistently maintained in the long-term and lead to significant improvements in HRQoL as measured by DLQI scores. Ixekizumab has demonstrated a rapid onset of response and has been shown to be efficacious in patients who have been previously exposed to biologic therapies, including TNF-α inhibitors. Ixekizumab has also demonstrated efficacy in patients with psoriasis in difficult-to-treat areas, such as nail, scalp and palmoplantar psoriasis. The improvement in patients' psoriasis symptoms associated with ixekizumab is accompanied by acceptable safety and tolerability, with an AE profile consistent with currently available biologics (Section 4.11).

Ixekizumab should therefore be considered as a treatment option for first-line biologic therapy in patients who have failed to respond to standard systemic therapies or in patients who are intolerant to or have a contraindication to these treatments. Ixekizumab may also be considered as a treatment option in patients who have failed, are contraindicated to, or are intolerant to one or more TNF-α inhibitors. The proposed positioning of ixekizumab in the current treatment pathway can be seen in Figure 5.

Figure 5: Proposed position of ixekizumab within the treatment pathway for patients with moderate to severe psoriasis (total PASI≥10 and DLQI>10) in accordance with NICE recommendations



DLQI = Dermatology Life Quality Index; IL = interleukin; PAS I = Psoriasis Area and Severity Index; TNF-α = tumour necrosis actor alpha

3.4 *Epidemiology*

The prevalence of psoriasis in England has been estimated at 1.75%, with approximately 2.55% of these patients being eligible for treatment with biologic therapy.[13] Assuming an estimated total adult population in England and Wales (working and pension age population) of 47.6 million[61], the number of patients eligible for treatment with a biologic would be approximately 21,242. In 2014-15, there were 1,253 hospital admissions in England as a result of psoriasis (International Statistical Classification of Diseases and Related Health Problems, ICD-10 L40.0), equating to 1,341 finished consultant episodes and 3,727 bed days.[62]

Patients with severe psoriasis have a 50% increased risk of mortality, for example, male and female patients with severe psoriasis die younger (by 3.5 and 4.4 years respectively), than patients without psoriasis.[63] Increased risk of mortality can stem from comorbidities (e.g. CVD, malignancies, chronic lower respiratory disease, diabetes, dementia, infection, and kidney disease), life-style factors (e.g. smoking and alcohol intake), chronic and cumulative drug-toxicity, or from the disease itself.[63] Sixteen deaths from psoriasis were registered in England and Wales during 2014 (ICD-10 L40.0).[64]

3.5 *Relevant NICE guidance*

The following NICE guidance is relevant to the current submission:

- NICE quality standard. Psoriasis [QS40]. August 2013.[65]
- NICE clinical guideline. Psoriasis: The assessment and management of psoriasis [CG153]. October 2012.[8]
- NICE interventional procedure guidance. Grenz rays therapy for inflammatory skin conditions [IPG236]. November 2007.[66]

In addition the following NICE technology appraisals (TAs) are of relevance:

- NICE technology appraisal. Apremilast for treating moderate to severe plaque psoriasis [TA368]. November 2015.[67]
- NICE technology appraisal. Secukinumab for treating moderate to severe plaque psoriasis [TA350]. July 2015.[68]
- NICE technology appraisal. Ustekinumab for the treatment of adults with moderate to severe psoriasis [TA180]. September 2009.[69]
- NICE technology appraisal. Adalimumab for the treatment of adults with psoriasis [TA146]. June 2008.[70]
- NICE technology appraisal. Etanercept and efalizumab for the treatment of adults with psoriasis [TA103]. July 2006.[71]

With the exception of apremilast which is not recommended by NICE, the technology appraisals listed above are relevant for the following patient population:

Patients with a total PASI≥10 and DLQI >10, where the psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the patient is intolerant to, or has a contraindication to, these treatments.

- NICE technology appraisal. Infliximab for the treatment of adults with psoriasis [TA134]. January 2008.[72]

The relevant patient population for the technology appraisal listed above is:

Patients with a total with a total PASI of ≥20 and a DLQI of >18, where the psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and longwave ultraviolet radiation); or the patient is intolerant to, or has a contraindication to, these treatments.

Other than the definition of very severe psoriasis applied to infliximab, no sub-groups were explicitly addressed in any of the above appraisals.

3.6 *Other relevant clinical guidelines*

Treatment guidelines have also been published by a multidisciplinary consortium of clinical societies, namely the European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC).[49] These guidelines largely correspond with clinical guidelines and technology appraisals published by NICE and recommend the use of biologics including adalimumab, etanercept, infliximab and ustekinumab if phototherapy and conventional non-biologic systemic agents were inadequate in response or if they are contraindicated or not tolerated. The British Association of Dermatologists (BAD) has also published treatment guidelines on the use of biologics in 2009.[73] However, as a result of the rapidly evolving treatment paradigm in psoriasis, not all currently available treatment options are included in these guidelines (e.g. newer biologic therapies).

In accordance with guidance issued by NICE, the treatment guidelines listed above recommend the use of biologic therapies in patients with moderate to severe psoriasis (total PASI of ≥ 10 and DLQI >10) where treatment with standard systemic therapies has failed or the patient is intolerant to, or has a contraindication to, these treatments.

3.7 *Issues relating to clinical practice including any variations or uncertainty about best practice*

The management of moderate to severe psoriasis is rapidly evolving with several ongoing clinical trials and there is uncertainty about where these therapies will fit in the current treatment pathway. Despite the emergence of new systemic biologic therapies in recent years, there is still an unmet need for treatments which are able to provide high-levels of skin clearance, with an acceptable tolerability profile and convenient dosing schedule. There may also be some variations between clinical localities with regard to access to further biologic therapy for patients who may lose treatment response or have other reasons to discontinue their initial therapy.

3.8 *Equality issues*

We are unaware of any equality issues that could impact the appraisal of ixekizumab.

4 Clinical effectiveness

Summary of ixekizumab clinical effectiveness:

- A systematic literature review (SLR) was conducted to identify evidence of the clinical efficacy and safety of ixekizumab in addition to relevant comparators for the treatment of moderate to severe psoriasis (Section 4.1).
- Four studies identified in the SLR assessed the clinical efficacy and safety of ixekizumab (including one phase II study and three phase III studies). The phase three studies were considered to be relevant to the decision problem and were detailed in the submission (Section 4.2):
    - UNCOVER-1 was a phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient trial comparing the efficacy and safety of ixekizumab to placebo in 1,296 patients with moderate to severe plaque psoriasis.
    - UNCOVER-2 was a phase III, multicentre, randomised, double-blind, active- and placebo-controlled, parallel-group, outpatient trial comparing the efficacy and safety of ixekizumab to etanercept and placebo in 1,224 patients with moderate to severe plaque psoriasis.
    - UNCOVER-3 was a phase III, multicentre, randomised, double-blind, active- and placebo-controlled, parallel-group, outpatient trial comparing the efficacy and safety of ixekizumab to etanercept and placebo in 1,346 patients with moderate to severe plaque psoriasis.
- The co-primary endpoints of the UNCOVER studies were sPGA (0, 1) and PASI 75 response rates at week 12.
- In all three UNCOVER studies significantly higher sPGA (0, 1) and PASI 75 response rates were achieved with ixekizumab compared with placebo at week 12 ($p<0.001$ for all comparisons). In addition, significantly higher sPGA (0, 1) and PASI 75 response rates were achieved with ixekizumab compared with etanercept at week 12 ($p<0.001$ for all comparisons) in the UNCOVER-2 and -3 studies (Section 4.7).
- Ixekizumab demonstrated significant improvements in the proportion of patients achieving complete clearance (PASI 100) and high-level responses (PASI 90) compared with etanercept (UNCOVER-2 and -3 only) and placebo at week 12 ($p<0.001$ for all comparisons) (Section 4.7).

- Ixekizumab demonstrated rapid onset of efficacy in the UNCOVER-2 and -3 studies, with significant differences in PASI 75 response rates as early as week 2 compared with etanercept and placebo ($p<0.001$ for all comparisons) (Section 4.7).
- The UNCOVER-1 and -2 studies included a maintenance dosing period (week 12-60) in order to determine the optimum dosing interval of ixekizumab, the maintenance of response, relapse or rebound following treatment withdrawal and response to re-treatment with ixekizumab following relapse in a re-randomised patient population. sPGA (0,1) and PASI responses (including PASI 100) were achieved or maintained in the maintenance dosing period with ixekizumab (Section 4.7).
- Ixekizumab was significantly superior to etanercept (UNCOVER-2 and -3 only) and placebo in treating the symptoms of psoriasis in difficult-to-treat areas (including nail, scalp and palmoplantar psoriasis), alleviating the burdensome symptom of itch associated with psoriasis and improving HRQoL as measured by DLQI scores at week 12 across all the UNCOVER studies ($p<0.001$ for all comparisons) (Section 4.7).
- Ixekizumab demonstrated significant improvements in PASI 75 response rates compared with placebo in patients who had been previously treated with biologics, patients who had responded inadequately to TNF-α inhibitors and patients who are eligible for biologic therapy according to NICE criteria
- A network meta-analysis (NMA) demonstrated that ixekizumab has superior efficacy to other biologic comparators including adalimumab, infliximab, ustekinumab and secukinumab as measured by the probability of achieving a given PASI response (Section 4.9). The consistency and robustness of the NMA was confirmed with the results of the scenario analyses reported here which were consistent with the base case
- Ixekizumab was well tolerated across the UNCOVER studies with a predictable safety profile which was comparable to etanercept. Adverse events (AEs) which occurred following treatment with ixekizumab were generally of mild to moderate severity and did not lead to discontinuation from ixekizumab (Section 4.11).

4.1 *Identification and selection of relevant studies*

4.1.1 Systematic literature review (SLR)

A systematic search of the published literature was performed on 11 December 2014 (data from January 1990-November 2014) and updated on 18 November 2015 (data from November 2014-November 2015). The literature review was designed as a combined search to identify both randomised controlled trials (RCTs) of ixekizumab and of potential relevant comparators in patients with moderate to severe plaque psoriasis.

4.1.2 Search Strategies

The main literature search was conducted through the OVID platform, in which the following databases were systematically searched using the specific search strategies provided in Appendix 2.

- Embase
- Ovid MEDLINE(R), Ovid MEDLINE(R) Daily Update and Ovid MEDLINE In-Process & Other Non-Indexed Citations
- PsycINFO
- Econlit
- American College of Physicians Journal Club
- Cochrane Library:
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Cochrane Database of Systematic Reviews (DSR)
    - Cochrane Methodology Register
    - Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment
- NHS Economic Evaluation Database (DARE)

In addition, the following databases (not included within OVID) were also searched manually or by using database specific syntax:

- PharmNet.bund
- Clinicaltrials.gov (see specific search strategies used in Appendix 2)
- European Union (EU) Clinical Trial Registry

- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP)
- European Medicines Agency (EMA)
- NICE
- SMC

A grey literature review was conducted using 'Google' (original and update) and 'duckduckgo.com' (update only) to identify and review supplementary evidence to augment findings from both the systematic literature searches for areas not well reported in the published literature yet relevant in the context of the research question. To ensure that the search was comprehensive and that sources were fully interrogated, pre–specified search terms were not used, as many websites did not include a search function and the different sources featured a wide range of terminology.

In addition a review of conference proceedings from 2013 to 2014 (original SLR) and from November 2014 to November 2015 (updated SLR) was conducted. Alongside conference abstracts, key databases relevant to psoriasis were searched in a structured, non-systematic fashion to provide additional strategic insight and supplementary data (see Appendix 2 for details of conference proceedings searched).

4.1.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria were the same for both the original and the update SLR (Table 7). The comparators included within the PICOS criteria were those currently used to treat moderate to severe psoriasis, as informed by treatment guidelines and previous Health Technology Assessment (HTA) submissions. In addition, experimental therapies in clinical development (phase II or III) and off-label therapies were included in the search strategy to ensure that all data sources were exhausted, even though they may not have been relevant for subsequent inclusion to address the decision problem in the NMA.

Key outcome measures included were those within the ixekizumab clinical trial program, along with additional outcomes used within previous HTA submissions, e.g. to the Gemeinsamer Bundesausschuss (G-BA), Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Benefits Advisory Committee (PBAC) and NICE.

Outcomes were recorded for 10, 12 and 16 weeks to record initial treatment effect (induction period) and for 24, 52 and 60 weeks or longer to record the long-term treatment effect (maintenance period) where available. If these exact time points were not recorded in the primary publication, data for the nearest recorded time points were extracted and any variances recorded.

The PICOs criteria used as a basis to include/exclude publications can be seen in Table 7.

Table 7: Inclusion and exclusion PICOS criteria for both the original and update SLR

Criteria	Inclusion	Exclusion
Population	Patients with moderate, severe, or very severe psoriasis	Patients with mild psoriasis
Comparators and intervention (and placebo)	Placebo Non-biologic approved treatments: Acitretin Apremilast Cyclosporine/ Ciclosporin Fumaric acid esters† Methotrexate PUVA Approved Biologic treatments: Adalimumab Etanercept Infliximab Ustekinumab Secukinumab Biosimilars of the above (where appropriate) Experimental treatments: Ixekizumab Brodalumab Guselkumab Namilumab Ponesimod Tildrakizumab Tofacitinib Biosimilars of the above (where appropriate)	Interventions not listed within the inclusion criteria, including those specifically for mild to moderate psoriasis: corticosteroids, vitamin A & analogues, vitamin D & analogues, tar preparations

Criteria	Inclusion	Exclusion
Outcomes	Key clinical outcomes: PASI, relative and absolute: PASI 50* PASI 75 PASI 90 PASI 100 Global assessments, relative and absolute: (Physician's) PGA 0, 1 (Static Physician's) sPGA 0, 1 (Investigators) IGA 0, 1 Key quality of life outcomes: SF-36 DLQI Safety outcomes: Infections Adverse events Death Malignancy Immunogenicity Injection site reactions Infusion reactions Withdrawals Serious and severe adverse events Treatment-emergent adverse events Cardiovascular adverse events Additional outcomes: Patient's global assessment Skin pain VAS Healthcare resource utilisation** Health status* (e.g. EuroQol five dimensions (EQ-5D)) Depression** (e.g. hospital anxiety and depression scale (HADS), quick inventory of depressive symptomatology (QIDS)) (Work) productivity** (e.g. work and activity impairment questionnaire (WPAI)) Itch** (E.g. itch VAS, itch NRS)	Any outcomes not listed in the following subsets of inclusion criteria: Key clinical outcomes Key quality of life outcomes Safety outcomes

Criteria	Inclusion	Exclusion
Trial design	Clinical trials, including RCTs and open-label trials, phase II-IV Publications presenting un-pooled data relating to moderate to severe psoriasis NMAs/MTCs of comparators listed above Human trials	Trials pooling moderate to severe psoriasis results with other comorbidities (e.g. PsA), and not presenting results separately Cohort trials Cross-sectional trials Epidemiological/ecological trials Observational trials Case-control trials Editorials Single case reports Letters Animal trials

† Not licensed in the UK

* PASI 50 added after the initial approval of the protocol as an additional inclusion criterion. PASI 50 was only considered for the data extraction stage of this SLR. PASI 50 was not considered an inclusion criterion for the abstract screening phase.

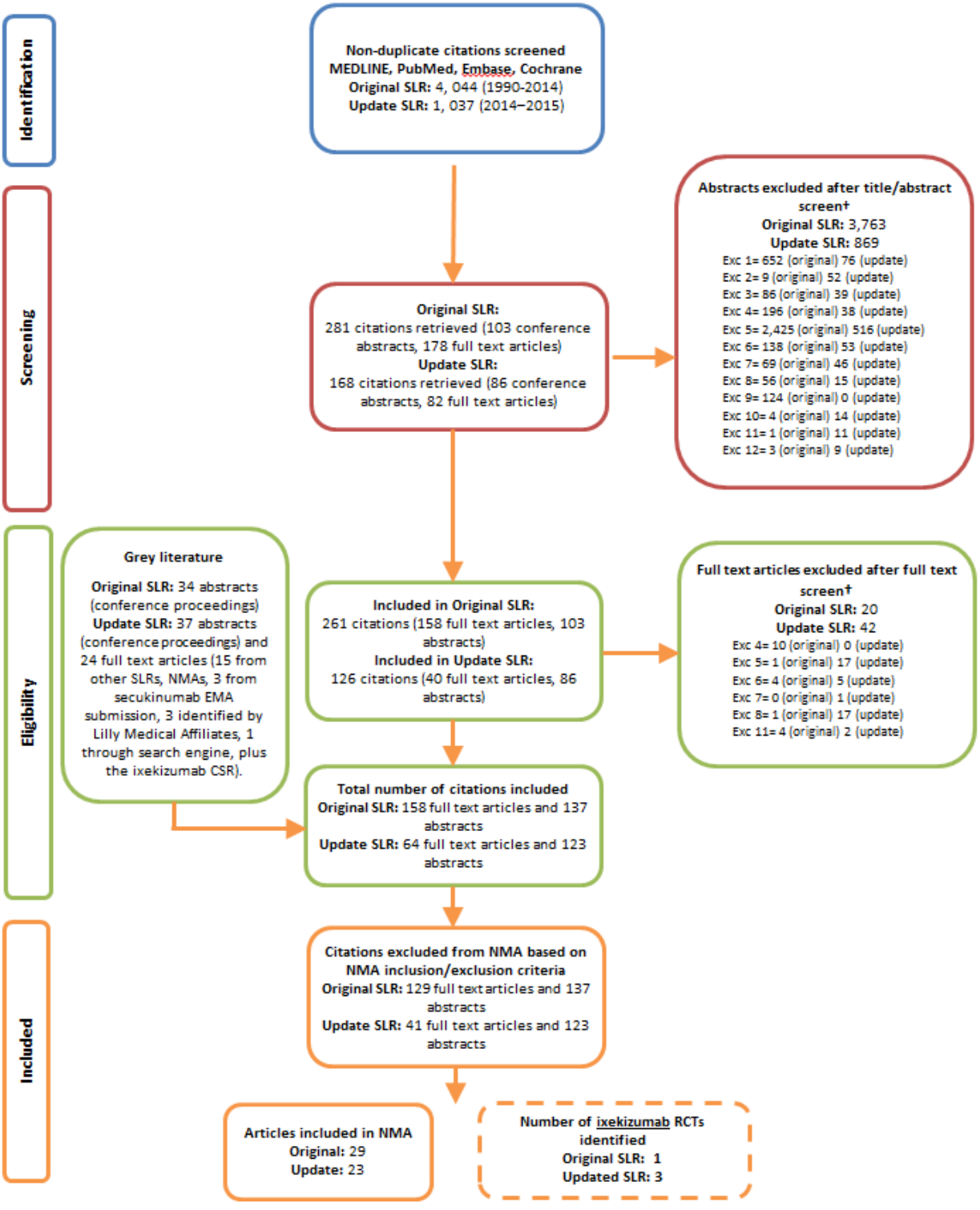
** Additional outcome measures were reported within the DEF where data were available. As there are a broad range of instruments that can be used to capture data on healthcare resource utilisation, health status, depression, work productivity and itch, the reported measures used to capture these data were recorded within the DEF and data ranges captured where data were available.

DEF = data extraction form; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol five dimensions; HADS = hospital anxiety and depression scale; MTC = mixed treatment comparison; NMA = network meta-analysis; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; PUVA = psoralen and longwave ultraviolet radiation; QIDS = quick inventory of depressive symptomatology; RCT = randomised controlled trial; SF-36 = short form 36; SLR = systematic literature review; VAS = visual analogue scale; WPAI = work and activity impairment questionnaire

4.1.4 Results of the SLR

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) work flow charts showing the number of publications included and excluded at each stage of both SLRs are detailed in Figure 6.

Figure 6: PRISMA diagram for both the original and update SLR



Further details on excluded publications can be seen in Appendix 3

EMA = European Medicines Agency; NMA = network meta-analysis; RCT = randomised controlled trial; SLR = systematic literature review

Four RCTs investigating the effects of ixekizumab in patients with psoriasis were identified through the original SLR (one RCT), updated SLR (two RCTs) and the ixekizumab clinical study report (CSR) (one RCT). The phase II study NCT01107457 has been published in full[74-76] as have the UNCOVER studies[15,16] Where necessary, supplementary data has been taken form the respective CSRs.

Table 8: Summary of ixekizumab RCTs identified in the SLR

Trial name (acronym)	Trial overview	Primary trial reference
Phase II		
NCT01107457	20-week, phase II, double-blind, placebo-controlled RCT. Patients with <PASI 75 at week 20 entered an open-label extension (≤240 weeks)	Leonardi *et al.* 2012[74] Gordon *et al.* 2014[77] Zhu *et al.* 2014[76]
Phase III		
UNCOVER-1 (RHAZ)	60-week, phase III, double-blind, placebo-controlled RCT, followed by an open-label long-term extension period of up to 264 weeks.	Gordon *et al.* 2016[15]
UNCOVER-2 (RHBA)	60-week, phase III, double-blind, multicentre, placebo-controlled RCT	Griffiths *et al.* 2015[16]
UNCOVER-3 (RHBC)	12-week, phase III, double-blind, multicentre, placebo-controlled RCT followed by a 5 year open label extension	Griffiths *et al.* 2015[16]

PASI = Psoriasis Area and Severity Index; PASI 75 = 75% reduction from baseline PASI score; RCT = randomised controlled trial; SLR = systematic literature review

4.2 *List of relevant randomised controlled trials*

This submission is based on clinical data from three phase III RCTs:

- I1F-MC-RHAZ (RHAZ) – UNCOVER-1
- I1F-MC-RHBA (RHBA) – UNCOVER-2
- I1F-MC-RHBC (RHBC) – UNCOVER-3

An additional phase II RCT was identified through the SLR (study NCT01107457) however will not be discussed in any detail in this section due to the availability of data from the three phase III UNCOVER trials. In addition, the ixekizumab dosing regimen investigated in the phase II study was different to the licensed dose of ixekizumab (ixekizumab 10 mg, 25 mg, 75 mg or 150 mg of at week 0, 2, 4, 8, 12, and 16).

The UNCOVER studies were all phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient trials comparing the efficacy and safety of ixekizumab to placebo in patients with moderate to severe plaque psoriasis. In addition, the UNCOVER-2 and UNCOVER-3 studies included an active comparator (etanercept) arm. An overview of the UNCOVER is provided in Table 9.

Table 9: List of relevant RCTs

Trial name (acronym)	Population	Intervention (n=number randomised in dosing period)	Comparator(s) (n=number randomised in dosing period)	Primary trial reference
UNCOVER-1 (RHAZ)	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who were candidates for phototherapy and/or systemic therapy	Induction dosing period Ixekizumab Q2W (n=433) Ixekizumab Q4W (n=432) Maintenance dosing period Ixekizumab Q4W (n=229) Ixekizumab Q12W (n=227)	Induction dosing period Placebo (n=431) Maintenance dosing period Placebo (n=226)	Gordon *et al.* 2016[15]
UNCOVER-2 (RHBA)	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who were candidates for phototherapy and/or systemic therapy. Patients with prior use of etanercept were excluded.	Induction dosing period Ixekizumab Q2W (n=351) Ixekizumab Q4W (n=347) Maintenance dosing period Ixekizumab Q4W (n=187) Ixekizumab Q12W (n=227)	Induction dosing period Placebo (n=168) Etanercept (n=358) Maintenance dosing period Placebo (n=176)	Griffiths *et al.* 2015[16]
UNCOVER-3 (RHBC)	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who were candidates for phototherapy and/or systemic therapy. Patients with prior use of etanercept were excluded.	Induction dosing period Ixekizumab Q2W (n=385) Ixekizumab Q4W (n=386)	Induction dosing period Placebo (n=193) Etanercept (n=382)	Griffiths *et al.* 2015[16]

CSR = clinical study report; RCT = randomised controlled trial

4.3 *Summary of methodology of the relevant randomised controlled trials*

The methodology and results for all the UNCOVER studies have been published in full. week 12 data for UNCOVER-2 and -3 have been published in the Lancet in June 2015(Griffiths *et al.* 2016)[16], with week 60 data published in the New England Journal of Medicine in June 2016 (Gordon *et al.* 2016).[15] Methodology and results from the UNCOVER-1 study have also been published in Gordon *et al.* 2016. Where necessary, information has also been presented from the individual CSRs.

4.3.1 Trial designs

All the UNCOVER studies consisted of a 'Screening Period', followed by a 12-week, double-blind 'Induction Dosing Period' in which the efficacy and safety of two dose regimens of ixekizumab [80 mg every two weeks (Q2W) and 80 mg every four weeks (Q4W)] were compared with placebo (UNCOVER-1, -2 and -3) and to etanercept 50 mg twice weekly (UNCOVER-2 and UNCOVER-3 only). The primary efficacy objectives of the trials (see Section 4.3.6) were evaluated at the end of the Induction Dosing Period (week 12).[15,16]

Following the Induction Dosing period patients in UNCOVER-1 and -2 were assigned treatments in the 'Maintenance Dosing Period' – a randomised withdrawal design. Patients were re-randomised based on their responder status according to the following criteria:[15,16]

- Responder = sPGA score of 0 or 1 with at least a 2-point improvement from baseline.
- Non-responder = sPGA score of >1.

Patients were assigned treatments in the Maintenance Dosing Period as follows:

- Patients who received ixekizumab and were classified as responders were re-randomised (1:1:1) to ixekizumab 80 mg Q4W, ixekizumab 80 mg Q12W, or placebo.
- Patients who received ixekizumab and were classified as non-responders were assigned to ixekizumab 80 mg Q4W.
- Patients who received placebo or etanercept (UNCOVER-2 only) and were classified as responders received two injections of placebo at week 12 and remained on placebo Q4W until relapse (defined as a loss of response equal to a sPGA score of ≥3).

- Patients who received placebo and were classified as non-responders received two injections of ixekizumab (160 mg starting dose) at week 12 followed by ixekizumab 80 mg Q4W.
- Patients who received etanercept (UNCOVER-2 only) and were classified as non-responders received two injections of placebo at week 12 followed by ixekizumab 80 mg Q4W starting at week 16.

The Maintenance Dosing Period (week 12 to week 60) was designed to determine the optimum dosing interval of ixekizumab (80 mg Q4W or every 12 weeks [Q12W]), the maintenance of response, relapse or rebound following treatment withdrawal, and response to re-treatment with ixekizumab 80 mg Q4W following relapse in a re-randomised patient population. The UNCOVER-3 study had a double-blind Induction Dosing Period as in UNCOVER-1 and -2, however, at week 12 patients received open-label ixekizumab 80 mg Q4W in a Long-Term Extension Period which allows for up to 264 weeks follow-up. In UNCOVER-1 and -2, patients who maintained their efficacy response with adequate overall safety during the Maintenance Dosing Period (UNCOVER-1 and -2) were permitted to enter an open-label Long-Term Extension Period where safety and efficacy continued to be monitored.[15,16]

Patients who maintained their efficacy response with adequate overall safety during the Induction Dosing Period (UNCOVER-3) and Maintenance Dosing Period (UNCOVER-1 and -2) were permitted to enter the open-label 'Long-Term Extension Period' where safety and efficacy continued to be monitored. In this period, all treatments from the previous period were continued unless a patient experienced relapse (defined as a loss of response equal to a sPGA score of ≥3). Patients who relapsed whilst on ixekizumab or placebo were continued on or switched to 80 mg ixekizumab Q4W. Following relapse, patients were removed from the Maintenance Dosing Period Primary Population and subsequently censored from all analyses performed on data derived from this population.[15,16]

Finally, all patients who received at least one dose of investigational product entered the 'Post-Treatment Follow-Up Period' for a minimum of 12 weeks after their last regularly scheduled visit or the date of their Early Termination Visit (ETV) for safety monitoring.[15,16]

A summary table of the trial designs of the UNCOVER studies can be seen in Table 10.

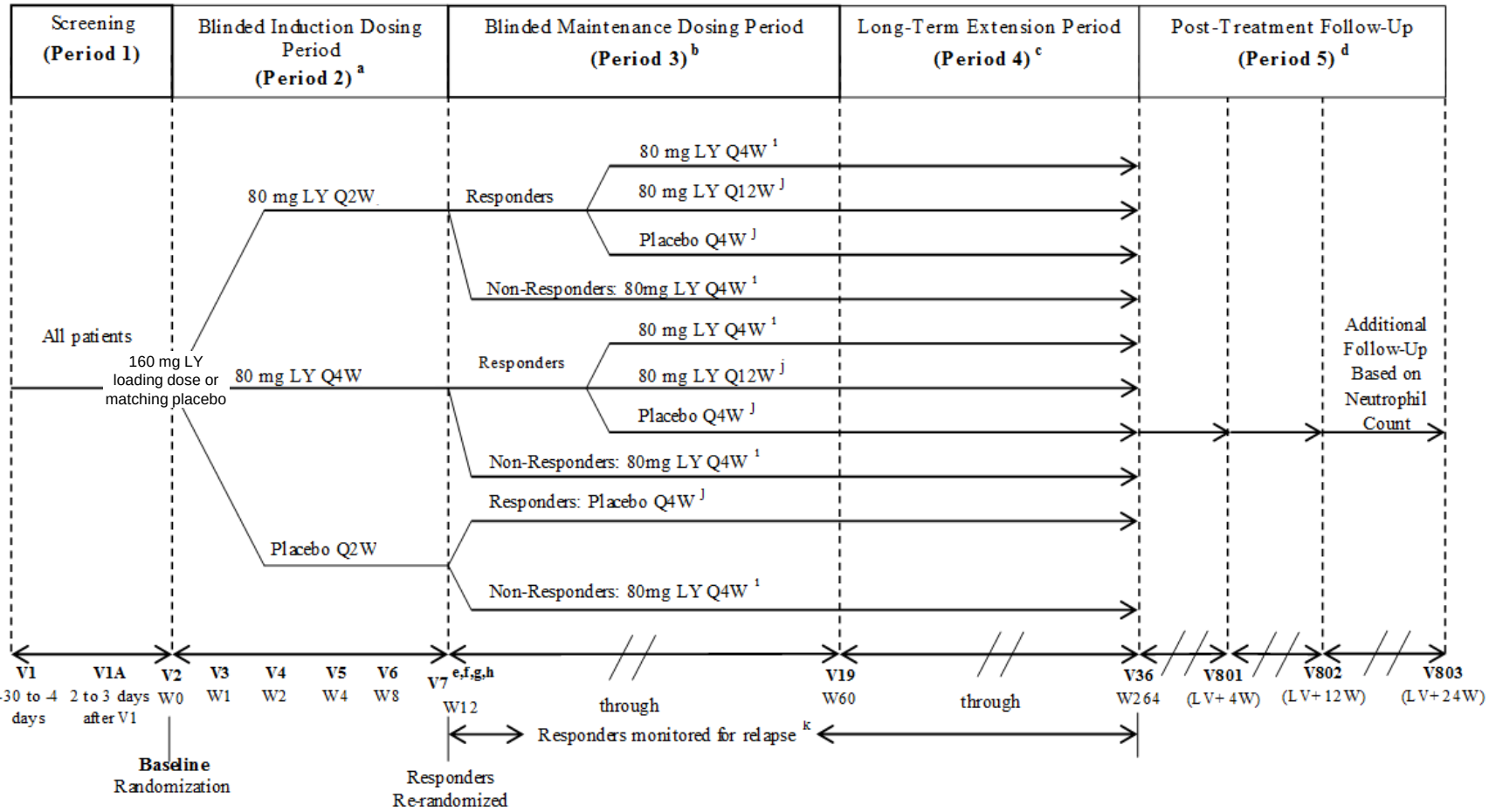
Table 10: Key trial design features of the UNCOVER studies

	UNCOVER-1[15] (N=1,296)	**UNCOVER-2[15,16] (N=1,224)**	**UNCOVER-3[15,16] (N=1,346)**
Induction treatment groups (Weeks 0-12)	160 mg starting dose, then 80 mg Q2W 160 mg starting dose, then 80 mg Q4W Placebo Randomisation (1:1:1)	160 mg starting dose, then 80 mg Q2W 160 mg starting dose, then 80 mg Q4W Placebo Etanercept 50 mg BIW Randomisation (2:2:1:2)	160 mg starting dose, then 80 mg Q2W 160 mg starting dose, then 80 mg Q4W Placebo Etanercept 50 mg BIW Randomisation ratio (2:2:1:2)
Maintenance treatment groups: Maintenance Dosing Period Primary Population[a] (Weeks 12-60)	80 mg Q4W 80 mg Q12W Placebo (Randomisation ratio: 1:1:1, re-treatment with 80 mg Q4W upon relapse)	80 mg Q4W 80 mg Q12W Placebo (Randomisation ratio: 1:1:1, re-treatment with 80 mg Q4W upon relapse)	N/A
Maintenance treatment groups: Maintenance Dosing Period Secondary Population[b] (Weeks 12-60)	80 mg Q4W (non-responders to any treatment at week 12)[c] Placebo (responders to placebo at week 12, re-treatment with 80 mg Q4W upon relapse)	80 mg Q4W (non-responders to any treatment at week 12)[c] Placebo (responders to placebo or etanercept at week 12, re-treatment with 80 mg Q4W upon relapse)	N/A
Treatment groups (LTE Phase)	80 mg Q4W 80 mg Q12W Placebo	80 mg Q4W 80 mg Q12W Placebo	80 mg Q4W
Duration blinded	60 weeks	60 weeks	12 weeks
Efficacy/health outcome data included in this submission[d]	Data up to 60 weeks	Data up to 60 weeks	Data up to 108 weeks

[a] Ixekizumab-treated patients who responded to treatment, that is, who achieved sPGA (0,1), during the Induction Dosing Period
[b] Patients randomised to either placebo or etanercept at week 0 or ixekizumab-treated patients who did not respond to therapy (achieve sPGA 0,1) during the Induction Dosing Period
[c] Etanercept non-responders received placebo for a 4-week washout period, before commencing treatment with ixekizumab 80 mg Q4W at week 16.
[d] For the Maintenance Dosing Period, efficacy data reported are from patients who completed week 60, discontinued prior to week 60, or relapsed prior to week 60
BIW = twice weekly; BSA = body surface area; LTE = long-term extension; N/A = not applicable; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; sPGA = static Physician's Global Assessment

Diagrammatic representations of the trial design of each of the UNCOVER studies can be seen in Figure 7, Figure 8 and Figure 9.

Figure 7: UNCOVER-1: Schematic of trial design[15]



LV = date of last visit; LY = ixekizumab; n = number of patients; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous; sPGA = static Physician's Global Assessment; V = study visit; W = study week.

[a] All patients received 2 SC doses of investigational product at week 0 (Visit 2) and 1 SC dose Q2W from week 2 (Visit 4) through week 10.

[b] All patients received 2 SC doses of investigational product at week 12 (Visit 7) and 1 SC dose Q4W from week 16 (Visit 8) through week 60 (Visit 19). Study visits occurred at least Q4W during Period 3.

[c] Study visits occurred at least Q12W during Period 4. Treatment remained blinded to investigators, study site personnel, and patients until all patients reached week 60 (Visit 19) or discontinued from the study (moved into Period 5).

[d] All patients who received investigational product entered into Period 5 and completed through Visit 802. Patients were to be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed or if determined by the sponsor/investigator that additional monitoring was needed.

[e] Responders to ixekizumab at week 12 (Visit 7; responders were defined as those who achieved an sPGA score of 0 or 1) were randomly assigned at a 1:1:1 ratio to ixekizumab Q4W, Q12W, or placebo.

[f] Non-responders to ixekizumab at week 12 (Visit 7; non-responders were defined as having an sPGA score of >1) received ixekizumab 80 mg Q4W.

[g] Responders to placebo at week 12 (Visit 7) received 2 injections of placebo at week 12 and remained on placebo Q4W until relapse.

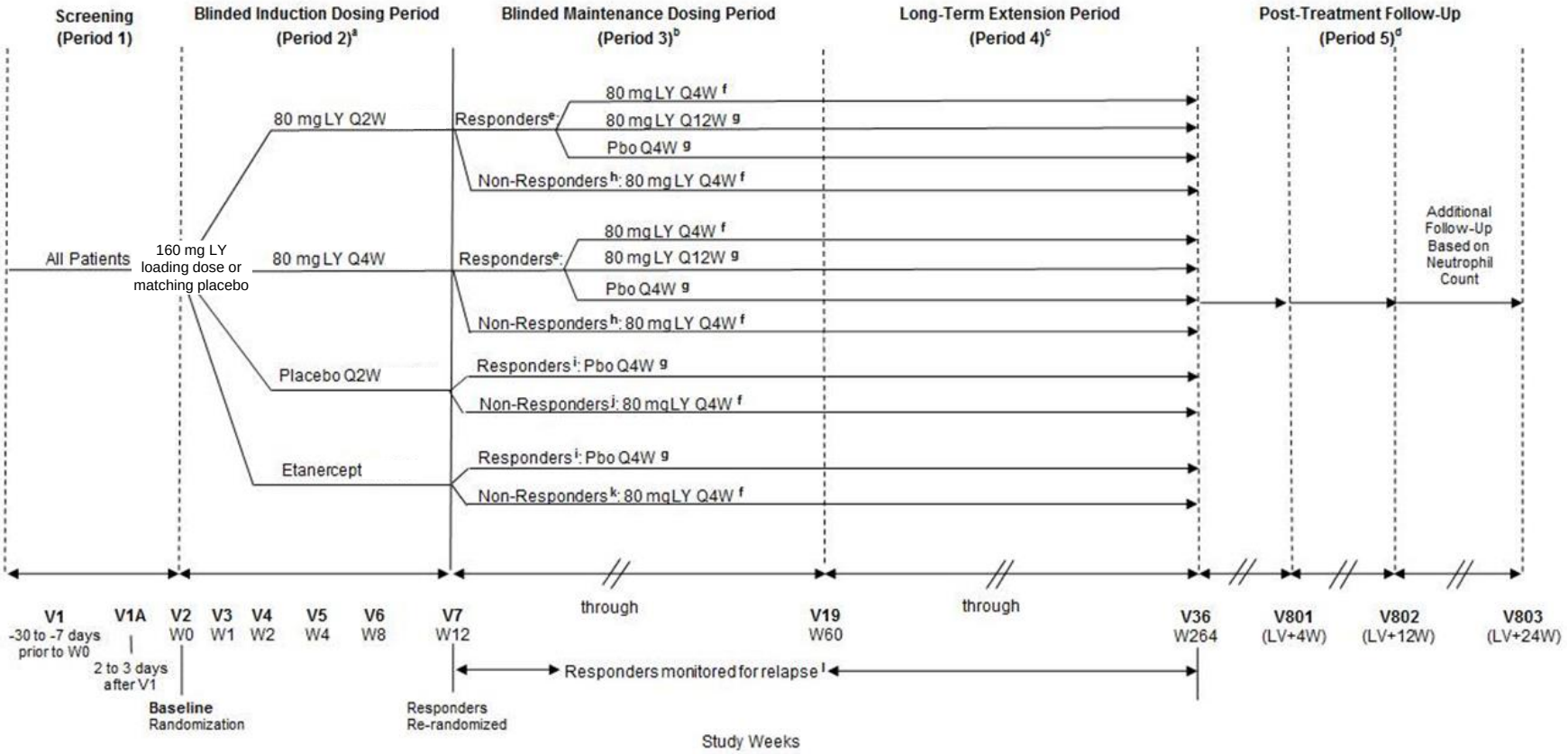
[h] Non-responders to placebo at week 12 (Visit 7) received 2 injections of ixekizumab (starting dose) at week 12 followed by ixekizumab 80 mg Q4W.

[l] Patients who experienced loss of treatment efficacy (relapse) during Period 3 remained on 80 mg ixekizumab Q4W to maintain the blind.

[j] Patients who experienced loss of treatment efficacy (relapse) during Period 3 were switched to 80 mg ixekizumab Q4W.

[k] Relapse occurring after week 12 (Visit 7) was defined as a loss of response equal to an sPGA score of ≥3.

Figure 8: UNCOVER-2: Schematic of trial design[16]



LV = date of last treatment period visit; LY = ixekizumab; n = number of patients; Pbo = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous; sPGA = static Physician's Global Assessment; V = study visit; W = study week.

[a] All patients received SC doses of IP (ixekizumab [Q2W or Q4W], placebo, or etanercept [twice weekly]) starting at week 0 (Visit 2) up to week 12.

[b] All patients will receive 2 SC doses of IP (ixekizumab or placebo) at week 12 (Visit 7) and 1 SC dose Q4W from week 16 (Visit 8) through week 60 (Visit 19). Study visits will occur at least Q4W during Period 3.

[C] Study visits will occur at least Q12W during Period 4. Treatment (ixekizumab and placebo) will remain blinded to investigators, study site personnel, and patients until all patients reach week 60 (Visit 19) or have discontinued from the study (moved into Period 5).

[d] All patients receiving investigational product must enter into Period 5 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed, or if determined by the sponsor/investigator that additional monitoring is needed.

[e] Responders to ixekizumab at week 12 (Visit 7; responders are defined as achieving an sPGA score of 0 or 1) were randomly assigned at a 1:1:1 ratio to ixekizumab (Q4W, Q12W), or to placebo.

[f] Patients who experience loss of treatment efficacy (relapse) during Period 3 will remain on ixekizumab 80 mg Q4W in order to maintain the blind.

[g] Patients who experience loss of treatment efficacy (relapse) during Period 3 will be switched to ixekizumab 80 mg Q4W.

[h] Non-responders to ixekizumab at week 12 (Visit 7; nonresponders are defined as having an sPGA score >1) will receive ixekizumab 80 mg Q4W.

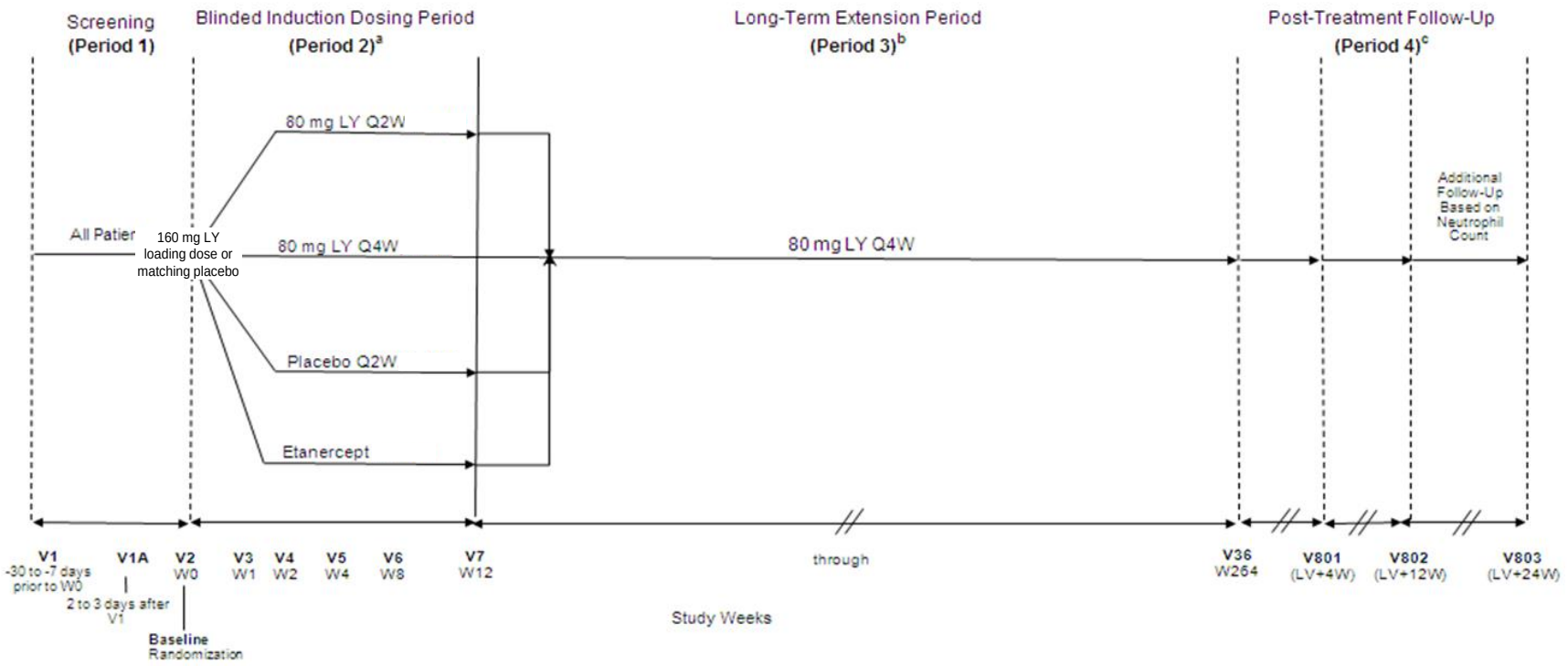
[i] Responders to placebo or etanercept at week 12 (Visit 7) will receive 2 injections of placebo at week 12 followed by placebo Q4W until relapse.

[j] Non-responders to placebo at week 12 (Visit 7) will receive 2 injections of ixekizumab (starting dose) at week 12 followed by ixekizumab 80 mg Q4W.

[k] Non-responders to etanercept at week 12 (Visit 7) will receive 2 injections of placebo at week 12 followed by ixekizumab 80 mg Q4W starting at week 16.

[l] Relapse occurring after week 12 (Visit 7) is defined as a loss of response equal to an sPGA score ≥3

Figure 9: UNCOVER-3: Schematic of trial design[16]



LV = date of last visit; LY = ixekizumab; n = number of patients; Pbo = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = study visit; W = study week.

[a] All patients received SC doses of investigational product (ixekizumab [Q2W or Q4W], placebo, or etanercept [twice weekly]) starting at week 0 (Visit 2) up to week 12.

[b] All patients received 2 SC doses of investigational product (ixekizumab or placebo) at week 12 (Visit 7) and 1 SC dose of ixekizumab Q4W from week 16 (Visit 8) through week 264 (Visit 36). Treatment at week 12 remained blinded until all patients completed week 12 (Visit 7) or discontinued from the study treatment (moved into Period 4).

[c] All patients receiving investigational product must enter into Period 4 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed, or if determined by the sponsor/investigator that additional monitoring is needed

4.3.2 Randomisation and blinding

The UNCOVER trials were all double-blind studies; patients and study site personnel were blinded to study treatment until after all patients discontinued from treatment (moved into Post Treatment Follow-Up Period) or completed week 12 (UNCOVER-3) or week 60 (UNCOVER-1 and -2).[15,16]

In all the UNCOVER trials, patients who met the criteria for enrolment following screening were randomised by a computer-generated random sequence using an interactive voice response system (IVRS) to one of the double-blind treatment groups in the Induction Dosing Period. Patients were stratified as follows:

- UNCOVER-1:[78]
    - Geographic regions
    - Previous non-biologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or ≥3 conventional non-biologic systemic therapies)
    - Weight (<100 kg or ≥100 kg)
- UNCOVER-2 and -3:[16]
    - Pooled centre.

At week 12, patients who had responded to treatment with ixekizumab in UNCOVER-1 and -2 who entered the Maintenance Dosing Period (as the Maintenance Dosing Period Primary Population) were re-randomised using IVRS. Patients were stratified as follows:

- UNCOVER-1 and -2:[15]
    - Ixekizumab induction dosing regimen in the Induction Dosing Period (80 mg Q2W or 80 mg Q4W).

In UNCOVER-1 and -2 placebo-responders and non-responders from any treatment group were assigned using the IVRS to continue to receive placebo or change to ixekizumab 80 mg Q4W, respectively, until relapse.[21,22]

To preserve the blinding of the study, a minimum number of sponsor personnel not in direct contact with study sites had access to the randomisation table and treatment assignments before the study was unblinded. Site personnel confirmed that they had located the correct assigned investigational product package by entering a confirmation number found on the package into the IVRS.[21,79]

A double dummy design was used, in which the pre-filled syringes containing either ixekizumab or placebo (for ixekizumab), or etanercept or placebo (for etanercept) for UNCOVER-2 and -3, were visibly indistinguishable from each other.[79]

Study protocols and informed consent forms were approved by applicable ethics review boards, and all patients signed informed consent before undergoing study-related procedures.

4.3.3 Eligibility criteria

Key eligibility criteria for the UNCOVER studies can be seen in Table 11. A complete list of all inclusion and exclusion criteria is given in Appendix 4.

Table 11: Key eligibility criteria for the UNCOVER studies[15,78,79]

Trial Code	Inclusion Criteria	Exclusion Criteria
UNCOVER-1, -2 and -3	• Are male or female patients 18 years or older • Present with chronic plaque psoriasis based on a confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to baseline • Have ≥10% BSA involvement at screening and baseline • Have both an sPGA score of ≥3 and PASI score ≥12 at screening and at baseline • Are a candidate for phototherapy and/or systemic therapy	• Have pustular, erythrodermic, and/or guttate forms of psoriasis • Have a history of drug-induced psoriasis • Had a clinically significant flare of psoriasis during the 12 weeks prior to baseline • Have received systemic nonbiologic psoriasis therapy or phototherapy within 4 weeks prior to baseline or had topical psoriasis treatment within the previous 2 weeks prior to baseline • Cannot avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline and during the trial • Concurrent or recent use of any biologic agent within specified washout periods • Have ever received natalizumab or other agents that target alpha-4-integrin • Had a live vaccination within 12 weeks prior to baseline, or intend to have a live vaccination during the course of the trial or within 12 months of completing treatment in this trial • Have current or a history of lymphoproliferative disease; or signs or symptoms of lymphoproliferative disease; or have active or history of malignant disease • Presence of significant uncontrolled cerebrocardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders • Presence of significant uncontrolled neuropsychiatric disorder, have history of a suicide attempt, have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the QIDS-SR16 at screening (Visit 1) or baseline (week 0; Visit 2), or are clinically judged by the investigator to be at risk for suicide. • Had a serious infection, have been hospitalized, or have received IV antibiotics for an infection, within 12 weeks prior to baseline
UNCOVER-2 and -3		• Prior use of etanercept

BSA = body surface area; ERB = ethics review board; IRB = institutional review board; IV = intravenous; PASI = Psoriasis Area and Severity Index; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report (16 items); sPGA = static Physician Global Assessment

4.3.4 Settings and locations where the data were collected

UNCOVER-1, -2 and -3 were international, multicentre trials conducted in outpatient settings in 21 countries across Europe, North America, Australia, Asia, and Central and South America. Across the three studies there were a total of [redacted] based in the UK which enrolled a total of [redacted].[21-23]

The summary of trial data collection locations are provided in Table 14 with more detailed information in Appendix 5.

4.3.5 Study drugs and concomitant medications

Study drugs

An overview of the study drugs in the UNCOVER studies can be seen in Table 12.

Please note the licensed dose of ixekizumab is 160 mg by SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) Q2W, then maintenance dosing of 80 mg (one injection) Q4W. As the co-primary endpoints for the UNCOVER studies included both the Q2W and Q4W dosing regimens in the induction period, the results for both these treatments groups are presented in this submission. In addition, the NMA includes the Q4W induction dosing regimen, as the final licensed dose of ixekizumab had not yet been determined at the time these analyses were conducted. However, the cost-effectiveness analyses only report the Q2W induction regimen to comply with the final licensed treatment regimen.

The results of the Q12W dosing regimen in the maintenance dosing period are not presented in this submission as this treatment group was assessed only in secondary objectives which were not all successfully met. The Q12W maintenance dosing regimen is not licensed for use in patients with moderate to severe psoriasis.

Table 12: Overview of the study drugs in the UNCOVER studies[15,16]

Study drugs	UNCOVER-1	UNCOVER-2	UNCOVER-3
Ixekizumab	*Induction dosing period*		
	A single starting dose of ixekizumab 160 mg (2 x SC injections) followed by ixekizumab 80 mg given as 1 x SC injection every 2 weeks (80 mg Q2W) A single starting dose of ixekizumab 160 mg (2 x SC injections) followed by ixekizumab 80 mg given as 1 x SC injection every 4 weeks (80 mg Q4W)		
	Maintenance dosing period		
	Ixekizumab 80 mg given as 1 x SC injection every 4 weeks (80 mg Q4W) Ixekizumab 80 mg given as 1 x SC injection every 12 weeks (80 mg Q12W)		-
Placebo	*Induction dosing period*		
	A single starting dose of placebo given as 2 x SC injections followed by placebo for ixekizumab Q2W (Weeks 2, 4, 6, 8, and 10)	A single starting dose of placebo given as 2 x SC injections followed by placebo for ixekizumab Q2W (Weeks 2, 4, 6, 8, and 10) Placebo for etanercept (1 SC injection) given twice weekly (every 3 to 4 days) starting at week 0 up to week 12	
	Maintenance dosing period		
	Placebo given as 2 x SC injections at week 12 followed by placebo given as 1 SC injection Q4W thereafter until the study was unblinded		-

Etanercept	*Induction dosing period*	
	-	Etanercept 50 mg (1 x SC injection) administered twice weekly (every 3 to 4 days) starting at week 0 and up to week 12

Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous

Identity of investigational product and treatment administration

In addition to the treatment regimens outlined above in Table 12 patients were also administered placebo injections in varying regimens in order to maintain study blind.

- UNCOVER-1:[15]
    - **Ixekizumab 80 mg Q4W group** - Placebo given as 1 x SC injection at Weeks 2, 6, and 10
- UNCOVER-2 and -3:[15]
    - **Ixekizumab 80 mg Q2W group** - Placebo for etanercept (1 x SC injection) given twice weekly starting at week 0 up to week 12.
    - **Ixekizumab 80 mg Q4W group** - Placebo for ixekizumab given as 1 x SC injection at Weeks 2, 6, and 10. Placebo for etanercept (1 x SC injection) given twice weekly starting at week 0 up to week 12.
    - **Etanercept 50 mg twice weekly group** - Placebo for ixekizumab given as 2 x SC injections (week 0) followed by placebo for ixekizumab Q2W given as 1 x SC injection (Weeks 2, 4, 6, 8, and 10).

Concomitant therapies

During UNCOVER-1 and -2, prior to week 60, patients could use topical moisturizers or emollients, bath oils, oatmeal bath preparations, or topical salicylic acid (≤3%), α- or β-hydroxyl acids, corticosteroids, or vitamin D3 analogue preparations for skin conditions, as needed. During the UNCOVER-3 open-label long-term extension period, more potent topical steroids and shampoos with corticosteroids, coal tar, or vitamin D3 analogues could be used, as needed. Patients in all three studies could use medications consistent with the protocol requirements for treatment of adverse events (AEs); other medications were allowed if reviewed and approved by Lilly. Weak topical steroids (class VI or VII only) were permitted only on the face, axillae, or genitalia as required. Topical medications were to be discontinued approximately 24 hours before PASI and sPGA assessments. No other topical preparations were allowed within 2 weeks before randomization or during the study unless medically required to treat an AE.[78]

4.3.6 Primary, secondary and tertiary outcomes

Primary efficacy outcomes

The co-primary efficacy measures used in the UNCOVER trials were the static Physician Global Assessment (sPGA) and the Psoriasis Area and Severity Index (PASI) responses after 12 weeks of treatment.

Using these measures, the co-primary objectives of the trials were:[15,16]

- To assess at week 12 of treatment whether ixekizumab 80 mg Q2W or 80 mg Q4W were:
    - superior to placebo (UNCOVER-1, -2 and -3)
    - non-inferior to etanercept (UNCOVER-2 and -3)
    - superior to etanercept (UNCOVER-2 and -3).
- Measured by the proportion of patients:
    - with an sPGA (0,1) with at least a 2-point improvement from baseline
    - achieving at least 75% improvement from baseline in PASI score (PASI 75).

Definitions of primary efficacy outcomes

sPGA (static Physician Global Assessment)

The sPGA is the physician's determination of the severity of the patient's psoriasis lesions overall at a given time point.[80] Overall lesions are categorised by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). A sPGA score of (0, 1) indicates clear or minimal psoriasis which is indicative of treatment success. The EMA considers that PASI alone is not sufficient to evaluate psoriasis severity at baseline and on treatment and recommends using 2 endpoints to assess efficacy: a validated, standardised global score (e.g. PGA) in conjunction with the PASI.[80] The assessment was carried out by site investigators who had been trained in specific assessment techniques.

PASI (Psoriasis Area and Severity Index)

The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease.[81] The PASI has been the most frequently used endpoint and measure of psoriasis severity in clinical trials. An improvement of ≥75% from baseline in PASI score (or PASI 75) is considered clinically meaningful and the main indication of treatment effectiveness in patients with moderate to severe psoriasis.[25,80] Higher levels of clearance, including 90% to 99% and 100% improvements from baseline in PASI score (PASI 90 and PASI 100, respectively) were also measured in the UNCOVER trials. Clear or almost clear has been defined as an improvement of PASI >90%.[80] The assessment was carried out by site investigators who had been trained in specific assessment techniques.

Secondary efficacy measures

Major secondary efficacy measures assessed in the three UNCOVER trials included additional sPGA and PASI comparisons (defining a higher degree of treatment response than PASI 75) as well as evaluations of itch severity, HRQoL and nail psoriasis.

An overview of secondary efficacy outcomes assessed in the UNCOVER studies and included in this submission can be seen in Table 13. The definitions for these secondary efficacy measures have been presented in Appendix 6.

Table 13: Major secondary efficacy objectives assessed in UNCOVER-1, -2 and -3[78,79]

	UNCOVER-1	UNCOVER-2	UNCOVER-3
Superiority of Ixe Q2W or Ixe Q4W to placebo during the Induction Dosing Period			
sPGA (0) at week 12	✓	✓	✓
PASI 90 at week 12	✓	✓	✓
PASI 100 at week 12	✓	✓	✓
Itch NRS ≥4 point reduction from baseline to week 12 for patients who had baseline Itch NRS ≥4	✓	-	✓
Change from baseline in DLQI at week 12	✓	-	✓
Change from baseline in NAPSI score in patients with fingernail involvement at week 12	✓	-	✓
Superiority of Ixe Q2W or Ixe Q4W to etanercept during the Induction Dosing Period			
sPGA (0) at week 12	-	✓	✓
PASI 90 at week 12	-	✓	✓
PASI 100 at week 12	-	✓	✓
Superiority of Ixe Q12W or Ixe Q4W to placebo during the Maintenance Dosing Period			
Maintenance of sPGA (0,1) from week 12 to week 60	✓	✓	-

DLQI = Dermatology Life Quality Index; Ixe = ixekizumab; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; sPGA = static Physician's Global Assessment

Other secondary measures

In addition to the primary and secondary efficacy measures listed above, selected other secondary endpoints have been presented in this submission including:[21-23]

- UNCOVER-1:
    - PASI 75, PASI 90 and PASI 100 at week 60
    - Nail psoriasis at week 60
    - Psoriasis with scalp involvement at week 12 and 60
    - Psoriasis with palmoplantar involvement at week 12 and 60.
- UNCOVER-2:
    - PASI 75, PASI 90 and PASI 100 at week 60.
- UNCOVER-3:
    - Psoriasis with scalp involvement at week 12
    - Psoriasis with palmoplantar involvement at week 12.

A summary of the measures for the major secondary measures have been presented in Table 14 (trial comparative table). Not all pre-specified secondary and exploratory objectives were deemed critical for this submission (as presented in the final scope for this appraisal) and have therefore not been discussed in detail.

Table 14: Comparative summary of trial methodology

Trial number (acronym)	UNCOVER- 1[15,21]	UNCOVER-2[16,22]	UNCOVER-3[16,23]
Settings and locations where the data were collected (Further details can be seen in Appendix 5)	108 sites in 11 countries: Japan, Australia, Germany, Denmark, United Kingdom, Hungary, Italy, Poland, Romania, Canada, United States	127 sites in 12 countries: Australia, Austria, Czech Republic, Germany, Spain, France, United Kingdom, Netherlands, Poland, Romania, Canada, United States	125 sites in 10 countries: Argentina, Chile, Mexico, Bulgaria, Germany, Hungary, Poland, Russia, Canada, United States
Duration of trial and time trial was conducted	• Blinded Induction Dosing Period (week 0-12 – primary endpoint assessment) • Blinded Maintenance Dosing Period (week 12-60) • Long-term Extension Period (week 60-264) • Post-Treatment Follow-Up Period (from the last treatment period visit or ETV up to a minimum of 12 weeks after that visit) Duration of trial (including long-term safety and efficacy follow up): 5 years	• Blinded Induction Dosing Period (week 0-12 – primary endpoint assessment) • Blinded Maintenance Dosing Period (week 12-60) • Long-term Extension Period (week 60-264) • Post-Treatment Follow-Up Period (from the last treatment period visit or ETV up to a minimum of 12 weeks after that visit) Duration of trial (including long-term safety and efficacy follow up): 5 years	• Screening Period (prior to week 0) • Blinded Induction Dosing Period (week 0-12 – primary endpoint assessment) • Open-label long-term extension period (week 12-264) • Post-Treatment Follow-Up Period (from the last treatment period visit or ETV up to a minimum of 12 weeks after that visit) Duration of trial (including long-term safety and efficacy follow up): 5 years
Trial design	Randomised, double-blind, placebo-controlled, parallel-group	Randomised, double-blind, placebo-controlled, active-comparator, parallel-group. Non-inferiority/superiority to active comparator study	Randomised, double-blind, placebo-controlled, active-comparator, parallel-group. Non-inferiority/superiority to active comparator study
Main eligibility criteria for participants	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who were candidates for phototherapy and/or systemic therapy	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who were candidates for phototherapy and/or systemic therapy Patients with prior use of etanercept were excluded.	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who were candidates for phototherapy and/or systemic therapy Patients with prior use of etanercept were excluded.
Number of patients randomised	1,296	1,224	1,346

Trial number (acronym)	UNCOVER- 1[15,21]	UNCOVER-2[16,22]	UNCOVER-3[16,23]
Trial arms (n=number randomised/not randomised; treatment period) including how and when they were administered	Induction dosing period • Ixekizumab Q2W (n = 433) • Ixekizumab Q4W (n = 432) • Placebo (n =431) Maintenance dosing period • Ixekizumab Q4W (n = 229) • Ixekizumab Q12W (n= 227) • Placebo (n = 226)	Induction dosing period • Ixekizumab Q2W (n = 351) • Ixekizumab Q4W (n= 347) • Etanercept (n = 358) • Placebo (n =168) Maintenance dosing period • Ixekizumab Q4W (n = 187) • Ixekizumab Q12W (n = 181) • Placebo (n = 176)	Induction dosing period • Ixekizumab Q2W (n = 385) • Ixekizumab Q4W (n = 386) • Etanercept (n = 382) • Placebo (n = 193)
Randomisation and masking	Computer-generated random sequence using an IVRS. Study site personnel, including outcomes assessor(s) and patients were blinded to study treatment until after all patients discontinued from treatment or completed week 60. Clinical trial material (syringes [and contents] containing either ixekizumab or placebo were visibly indistinguishable from each other).	Computer-generated random sequence using an IVRS. Study site personnel, including outcomes assessor(s) and patients were blinded to study treatment until after all patients discontinued from treatment or completed week 60. Clinical trial material (syringes [and contents] containing either [ixekizumab or placebo for ixekizumab] and [etanercept or placebo for etanercept] were visibly indistinguishable from each other).	Computer-generated random sequence using an IVRS. Study site personnel, including outcomes assessor(s) and patients were blinded to study treatment until after all patients discontinued from treatment or completed week 12. Clinical trial material (syringes [and contents] containing either [ixekizumab or placebo for ixekizumab] and [etanercept or placebo for etanercept] were visibly indistinguishable from each other).
Primary objectives (including scoring methods and timings of assessments)	Co-primary (gated) outcomes were to assess whether ixekizumab 80 mg (Q2W and Q4W) was superior to placebo at week 12 as measured by the proportions of patients achieving: • sPGA (0,1) with at least a 2-point improvement from baseline • PASI 75	Co-primary (gated) outcomes were to assess whether ixekizumab 80 mg (Q2W and Q4W) was superior to placebo and non-inferior and superior to etanercept at week 12 as measured by the proportions of patients achieving: • sPGA (0,1) with at least a 2-point improvement from baseline • PASI 75	Co-primary (gated) outcomes were to assess whether ixekizumab 80 mg (Q2W and Q4W) was superior to placebo and non-inferior and superior to etanercept at week 12 as measured by the proportions of patients achieving: • sPGA (0,1) with at least a 2-point improvement from baseline • PASI 75

Trial number (acronym)	UNCOVER- 1[15,21]	UNCOVER-2[16,22]	UNCOVER-3[16,23]
Major secondary outcomes (including scoring methods and timings of assessments)	Major secondary (gated) outcomes were assessed over 12-week or 48-week treatment periods with final assessments made at week 12 or week 60 and included: • Superiority of ixekizumab (Q2W and Q4W) to placebo at week 12 as measured by: ○ proportion of patients achieving sPGA (0), PASI 90, and PASI 100 ○ proportion of patients achieving Itch Numerical Rating Scale (NRS) ≥4-point reduction from baseline for patients who had baseline Itch NRS ≥4 ○ change from baseline in Dermatology life quality index (DLQI) total score and NAPSI score • Superiority of ixekizumab (Q4W and Q12W) to placebo in the proportion of patients maintaining: ○ sPGA (0,1) from week 12 to week 60	Major secondary (gated) outcomes were assessed over 12-week or 48-week treatment periods with final assessments made at week 12 or week 60 and included: • Superiority of ixekizumab (Q2W and Q4W) to placebo as measured by: ○ proportion of patients achieving sPGA (0), PASI 90, and PASI 100 at week 12 • Superiority of ixekizumab (Q4W and Q12W) to etanercept in the proportion of patients maintaining: ○ sPGA (0), PASI 90, and PASI 100 at week 12 • Superiority of ixekizumab (Q4W and Q12W) to placebo in the proportion of patients maintaining: ○ sPGA (0,1) from week 12 to week 60	Major secondary (gated) outcomes were assessed over a 12-week treatment period with final assessments made at week 12 and included: • Superiority of ixekizumab (Q2W and Q4W) to placebo as measured by: ○ proportion of patients achieving sPGA (0), PASI 90, and PASI 100 ○ proportions of patients achieving Itch NRS ≥4-point reduction from baseline for patients who had baseline Itch NRS ≥4 ○ change from baseline in DLQI total score and NAPSI score

Trial number (acronym)	UNCOVER- 1[15,21]	UNCOVER-2[16,22]	UNCOVER-3[16,23]
Other secondary outcomes presented in this submission	Other secondary outcomes were assessed over 12-week or 48-week treatment periods with final assessments made at week 12 or week 60 and included: • proportion of patients maintaining PASI 75, PASI 90 and PASI 100 from week 12 to week 60 • change from baseline in NAPSI score at week 60 • change from baseline in Psoriasis Scalp Severity Index (PSSI) score at week 12 and 60 • change from baseline in Palmoplantar Psoriasis Severity Index (PPASI) score at week 12 and 60	Other secondary outcomes were assessed over 12-week or 48-week treatment periods with final assessments made at week 12 or week 60 and included: • proportion of patients maintaining PASI 75, PASI 90 and PASI 100 from week 12 to week 60	Other secondary outcomes were assessed over 12-week treatment periods with final assessments made at week 12 and included: • change from baseline in PSSI score at week 12 • change from baseline in PPASI score at week 12
Selected subgroups	• Gender • Age • Geographic region • Disease severity • Weight • BMI • Specific psoriasis locations at baseline • Previous non-biologic systemic therapy • Previous biologic systemic therapy • TNF-α insufficient responders		

BMI = body mass index; DLQI = Dermatology Life Quality Index; ETV = early termination visit; IVRS = interactive voice response system; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI /75/90/100 = ≥75%/≥90%/100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = once every 12 weeks; sPGA = static Physician Global Assessment; TNF-α = tumour necrosis factor alpha

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

Efficacy and health outcome analyses for the Induction Dosing Period were conducted according to the treatment to which all randomised patients were assigned (intent-to-treat [ITT] population), even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Safety analyses were conducted on the safety population, defined as all randomised patients who received at least 1 dose of study treatment.

The co-primary efficacy and major secondary objectives were assessed using a gatekeeping testing strategy. An overview of the types of analyses of treatment comparisons of categorical and continuous efficacy and health outcomes variables that were conducted has been presented in can be seen in Table 15. A pre-specified Fisher's exact test was also used to analyse categorical data associated with non-gated secondary objectives of the Induction Dosing (all UNCOVER trials).

Table 15: Overview of analyses conducted of categorical and continuous efficacy and health outcomes variables[21-23]

Study periods	Trial number (acronym)	Efficacy and health outcomes variables	
		Categorical	Continuous
Induction dosing period	UNCOVER-1	Logistic regression with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category in the model	ANCOVA model which included treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline value
	UNCOVER-2	CMH test stratified by pooled centre	ANCOVA model which included treatment, pooled centre, and baseline value
	UNCOVER-3	CMH test stratified by pooled centre	ANCOVA model which included treatment, pooled centre, and baseline value
Maintenance dosing period	UNCOVER-1	Logistic regression model with treatment group and baseline weight category fitted as factors (explanatory variables)	ANCOVA model with treatment group and baseline weight category fitted as factors, and baseline result fitted as a covariate
	UNCOVER-2	Fisher's exact test	ANCOVA model with treatment group and baseline weight category fitted as factors, and baseline result fitted as a covariate

ANCOVA = analysis of covariance; CMH = Cochran Mantel Haenszel

A summary of the statistical analysis conducted for the primary endpoints can be seen in Table 16.

Table 16: Summary of statistical analyses in the UNCOVER trials (primary hypotheses)[21-23]

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
UNCOVER-1	The co-primary objectives of the study were to assess, after 12 weeks of treatment in the Induction Dosing Period, whether Ixe 80 mg Q2W or 80 mg Q4W was superior to placebo as measured by the proportions of patients achieving: • sPGA (0,1) with at least a 2-point improvement from baseline • achieving PASI 75	The co-primary objectives were compared using a logistic regression analysis (NRI) stratified by randomisation strata (geographical location, previous non-biologic systemic therapy and weight). The effect of study centre on the primary objectives at week 12 (NRI) was also investigated. Secondary analyses were conducted using a Fisher's exact test. The gatekeeping testing strategy for the primary and major secondary analyses was implemented to control the overall type I error rate at a 2-sided alpha level of 0.05 for the multiple comparisons. The endpoints were assessed at baseline (week 0), and Weeks 1, 2, 4, 8, and 12.	The total sample size for UNCOVER-1 was planned at 1,296 patients randomised at a 1:1:1 ratio in the blinded Induction Dosing Period to 80 mg Q2W, 80 mg Q4W, and placebo. In order to account for multiple testing for the two ixekizumab groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. This study had >99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (0,1) and for PASI 75 at week 12. The following assumptions were used for the power calculations for both sPGA and PASI 75 response rates at week 12: • 70% for each ixekizumab treatment group • 10% for the placebo group	All missing data were imputed using NRI in which patients were defined as a non-responder if they: • did not meet the clinical response criteria at week 12 • had missing clinical response data at week 12 • discontinued study treatment at any time prior to week 12 or for any reason • did not have at least 1 post-baseline observation
UNCOVER-2	The co-primary objectives of the study were to assess, after 12 weeks of treatment in the Induction Dosing Period, whether Ixe 80 mg Q2W or 80 mg Q4W was superior to placebo and non-inferior and superior to etanercept as measured by the proportion of patients achieving:	The co-primary objectives were compared using the pre-specified Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre (NRI) for missing data imputation. Secondary analyses were conducted using a Fisher's exact test. The gatekeeping testing strategy for the primary and major secondary analyses was implemented to control the overall type I error rate at a 2-sided	The total planned sample sizes for UNCOVER-2 was 1,224 patients, randomised at a 2:2:2:1 ratio in the blinded Induction Dosing Period to ixe 80 mg Q2W, ixe 80 mg Q4W, etanercept, and placebo, respectively. In order to account for multiple testing for the two ixe groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. This study had >93% power to test the superiority of each ixekizumab dose	All missing data were imputed using NRI in which patients were defined as a non-responder if they: • did not meet the clinical response criteria at week 12 • had missing clinical response data at week 12 • discontinued study treatment at any time prior to week 12 or for any reason • didn't have at least

	• sPGA (0,1) with at least a 2-point improvement from baseline • achieving PASI 75	alpha level of 0.05 for the multiple comparisons. Non-inferiority and superiority of ixe compared with etanercept for sPGA (0,1) and PASI 75 was analysed using the fixed-margin approach. The endpoints were assessed at baseline (week 0), and Weeks 1, 2, 4, 8, and 12.	regimen to etanercept and >99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (0,1) and for PASI 75 at week 12. The following assumptions were used for the power calculations for both sPGA and PASI 75 response rates at week 12: • 70% for each ixekizumab treatment group • 56% for the etanercept group • 10% for the placebo group	1 post-baseline observation
UNCOVER-3	The co-primary objectives of the study were to assess, after 12 weeks of treatment in the Induction Dosing Period, whether Ixe 80 mg Q2W or 80 mg Q4W was superior to placebo and non-inferior and superior to etanercept as measured by the proportion of patients achieving: • sPGA (0,1) with at least a 2-point improvement from baseline • achieving PASI 75	The co-primary objectives were compared using the pre-specified Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre (NRI) for missing data imputation. Secondary analyses were conducted using a Fisher's exact test. The gatekeeping testing strategy for the primary and major secondary analyses was implemented to control the overall type I error rate at a 2-sided alpha level of 0.05 for the multiple comparisons. Non-inferiority and superiority of ixe compared with etanercept for sPGA (0,1) and PASI 75 was analysed using the fixed-margin approach. The endpoints were assessed at baseline (week 0), and Weeks 1, 2, 4, 8, and 12.	The total planned sample sizes for UNCOVER-3 was 1,223 patients, randomised at a 2:2:2:1 ratio in the blinded Induction Dosing Period to ixe 80 mg Q2W, ixe 80 mg Q4W, etanercept, and placebo, respectively. In order to account for multiple testing for the 2 ixe groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. This study had >93% power to test the superiority of each ixekizumab dose regimen to etanercept and >99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (0,1) and for PASI 75 at week 12. The following assumptions were used for the power calculations at week 12: • 70% for each ixekizumab treatment group • 56% for the etanercept group • 10% for the placebo group	All missing data were imputed using non-responder imputation (NRI), in which patients were defined as a non-responder if they: • did not meet the clinical response criteria at week 12 • had missing clinical response data at week 12 • discontinued study treatment at any time prior to week 12 or for any reason • didn't have at least 1 post-baseline observation

ANCOVA = analysis of covariance; CMH = Cochran Mantel Haenszel; ixe = ixekizumab; NRI = non responder imputation; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physicians Global Assessment

4.5 *Participant flow in the relevant randomised controlled trials*

The participant flow and accompanying Consolidated Standards of Reporting Trials (CONSORT) diagrams for each of the UNCOVER studies can be seen in the following sections. The CONSORT diagrams illustrate the patient flow for the blinded Induction Treatment Period (ITT population) and also the Maintenance Dosing Period for the UNCOVER-1 and -2 studies.

4.5.1 UNCOVER-1

The CONSORT diagram illustrating patient disposition in UNCOVER-1 can be seen in Figure 10.

A total of 1,660 patients signed informed consent and were entered in to UNCOVER-1. Of these patients who entered the study, 364 patients were discontinued prior to randomisation (main reason for not randomising patients was screening failures). At the start of the Induction Dosing Period (week 0 to week 12), 1,296 patients were randomly assigned in a 1:1:1 ratio by centre to receive:[15]

- Placebo (n=431)
- Ixekizumab Q2W (n=433) single injection 80 mg after a 160-mg starting dose
- Ixekizumab Q4W (n=432) single injection 80 mg after a 160-mg starting dose

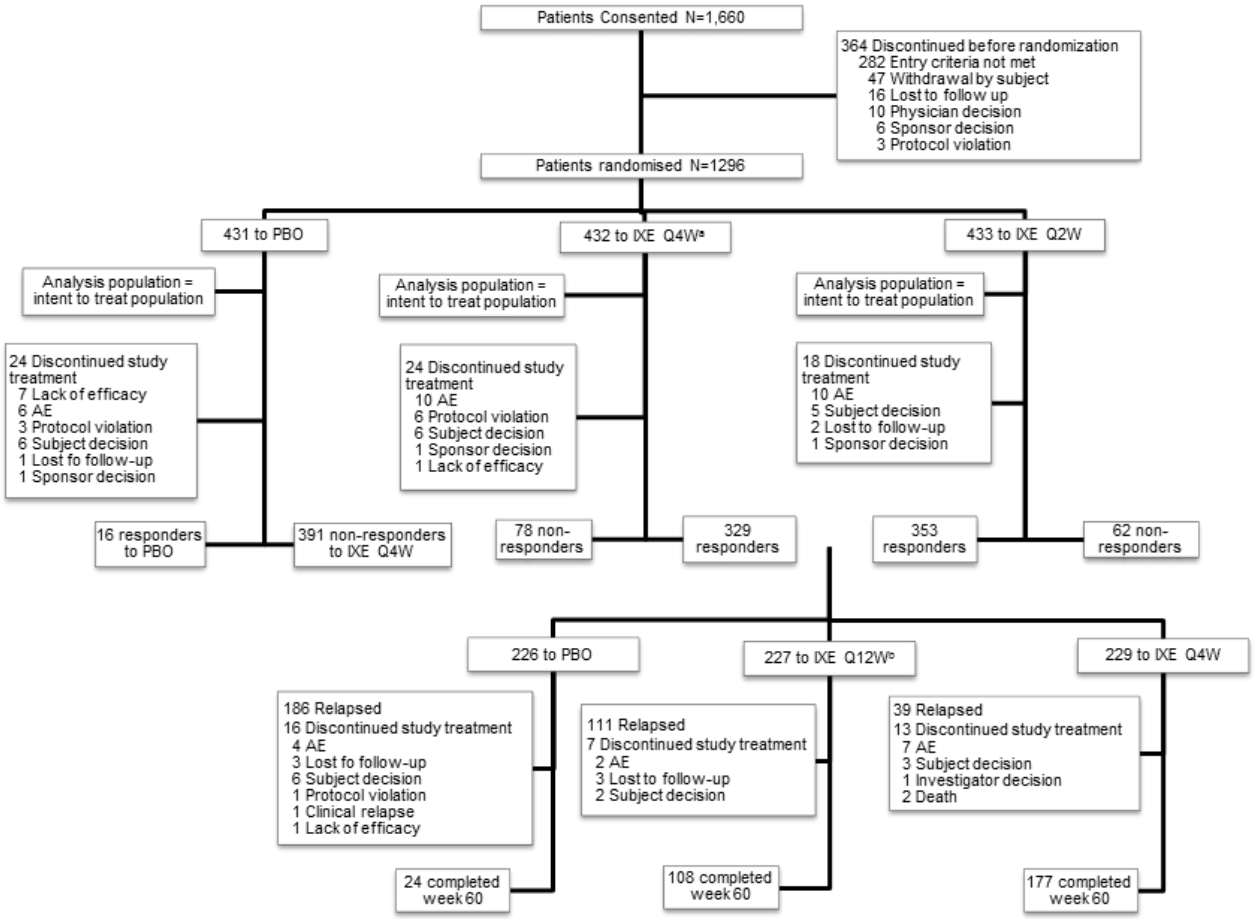
Approximately 95% of patients across all treatment groups completed the Induction Dosing Period, with 66 (5.1%) patients (18 in the ixekizumab 80 mg Q2W group and 24 each in the ixekizumab 80 mg Q4W and placebo groups) discontinuing from study treatment. There were no statistically significant differences between groups in the number of patients who discontinued. The most frequently reported reasons for discontinuation were AEs and subject decision.[78]

A statistically significant difference was observed in the number of patients who discontinued because of lack of efficacy (7 patients in the placebo group compared with 1 patient in the ixekizumab 80 mg Q4W group and 0 patients in the ixekizumab 80 mg Q2W group; $p<0.05$ for both comparisons.[78]

After week 12, patients entered the double-blind Maintenance Dosing Period (week 12 - week 60). Ixekizumab-treated patients who were classified as responders were re-randomised (1:1:1) to ixekizumab 80 mg Q4W (n=229), ixekizumab 80 mg Q12W (n=227), or placebo (n=226) and referred to as the Maintenance Dosing Period Primary Population. Placebo-responders (n=16) continued to receive placebo Q4W until relapse, while non-responders (from any treatment arm) received treatment with ixekizumab 80 mg Q4W maintaining the study blind.[78]

There were statistically significantly higher percentages of patients who completed the Maintenance Dosing Period in the ixekizumab 80 mg Q4W or Q12W groups than in the placebo group; when summarised by pooled dose, the completion rates were 77.3%, 47.6%, and 10.6%, respectively ($p<0.001$ for both comparisons). When comparing the patients who relapsed, there were statistically significantly lower percentages of patients who relapsed in the ixekizumab 80 mg Q4W or Q12W groups than in the placebo group; the relapse rates (relapse defined as a loss of response equal to a sPGA score of ≥3) were 17.0%, 48.9%, and 82.3%, respectively ($p<0.001$ for both comparisons). There was no statistically significant difference in the proportions of patients who discontinued across treatment groups.[78]

Figure 10: Patient disposition in UNCOVER-1[78]



[a] One patient completed the Induction Dosing Period and was re-randomised to the Maintenance Dosing Period at Visit 7 but discontinued at Visit 8 because of investigator decision and did not contribute data to the Maintenance Dosing Period

[b] One more patient was recorded as entered the Maintenance Dosing Period than completed the Induction Dosing Period because 1 patient discontinued at week 12 due to subject decision, but at the same visit on the same day was also re-randomised and took the first dose of Maintenance Dosing Period study drug. Per the statistical analysis plan (SAP) definition, the patient was qualified for the Maintenance Dosing Period Primary Population even though he/she discontinued at week 12

AE = adverse event; IXE = ixekizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12 = every 12 weeks

4.5.2 UNCOVER-2

The CONSORT diagram illustrating patient disposition in UNCOVER-2 can be seen in Figure 11.

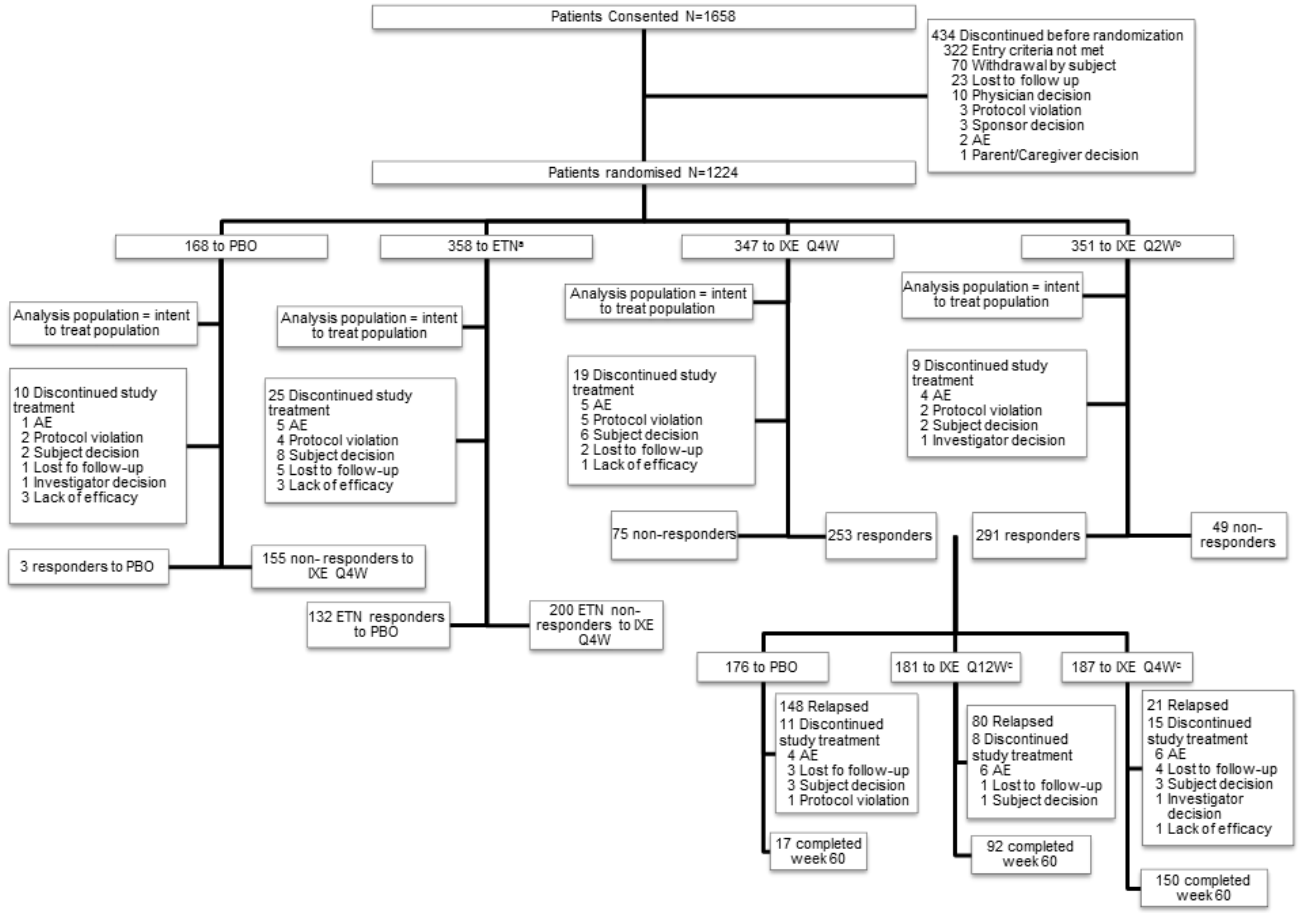
A total of 1,658 patients signed informed consent and were entered in to UNCOVER-2. Of these patients who entered the study, 434 were discontinued prior to randomisation (main reason for not randomising patients was screening failures). During the Induction Dosing Period (week 0 to week 12), 1,224 patients were randomly assigned in a 1:2:2:2 ratio by centre to receive:[16]

- Placebo (n=168)
- Etanercept (n=358) 50 mg twice weekly
- Ixekizumab Q2W (n=351) single injection 80 mg after a 160-mg starting dose
- Ixekizumab Q4W (n=347) single injection 80 mg after a 160-mg starting dose

Across the Induction Dosing Period treatment groups, at least 93% of patients completed the Induction Dosing Period with 63 (5.1%) patients discontinued from study treatment. A statistically significant difference was observed between ixekizumab 80 mg Q2W and etanercept, with more patients discontinuing from etanercept (25 patients and 9 patients, respectively). The most frequently reported reasons for discontinuation were AEs and subject decision.[16]

After week 12, patients entered the double-blind Maintenance Dosing Period (week 12 - week 60). Ixekizumab-treated patients who were classified as responders were re-randomised (1:1:1 ratio) to ixekizumab 80 mg Q4W (n=187), ixekizumab 80 mg Q12W (n=181), or placebo (n=176) and considered the Maintenance Dosing Period Primary Population. Placebo or etanercept responders received placebo Q4W until relapse (placebo: n=3; etanercept: n=132), at which point they were switched to ixekizumab 80 mg Q4W for the remainder of the trial. Non-responders from any treatment arm received treatment with ixekizumab 80 mg Q4W for the remainder of the study whilst maintaining study blind.[78]

Figure 11: Patient disposition in UNCOVER-2[78]



[a] One subject discontinued due to subject decision after completing week 12, assigned maintenance dosing period treatment but never took treatment in the Maintenance Dosing Period

[b] One subject discontinued due to AE after completing week 12, assigned with maintenance dosing period treatment but never took treatment in the Maintenance Dosing period; and 2) another subject discontinued after completing week 12, not assigned with maintenance dosing period treatment

[c] Two subjects are classified as ongoing in the analysis dataset; however, these patients discontinued the Maintenance Period

AE = adverse event; ETN = etanercept; IXE = ixekizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12 = every 12 weeks

4.5.3 UNCOVER-3

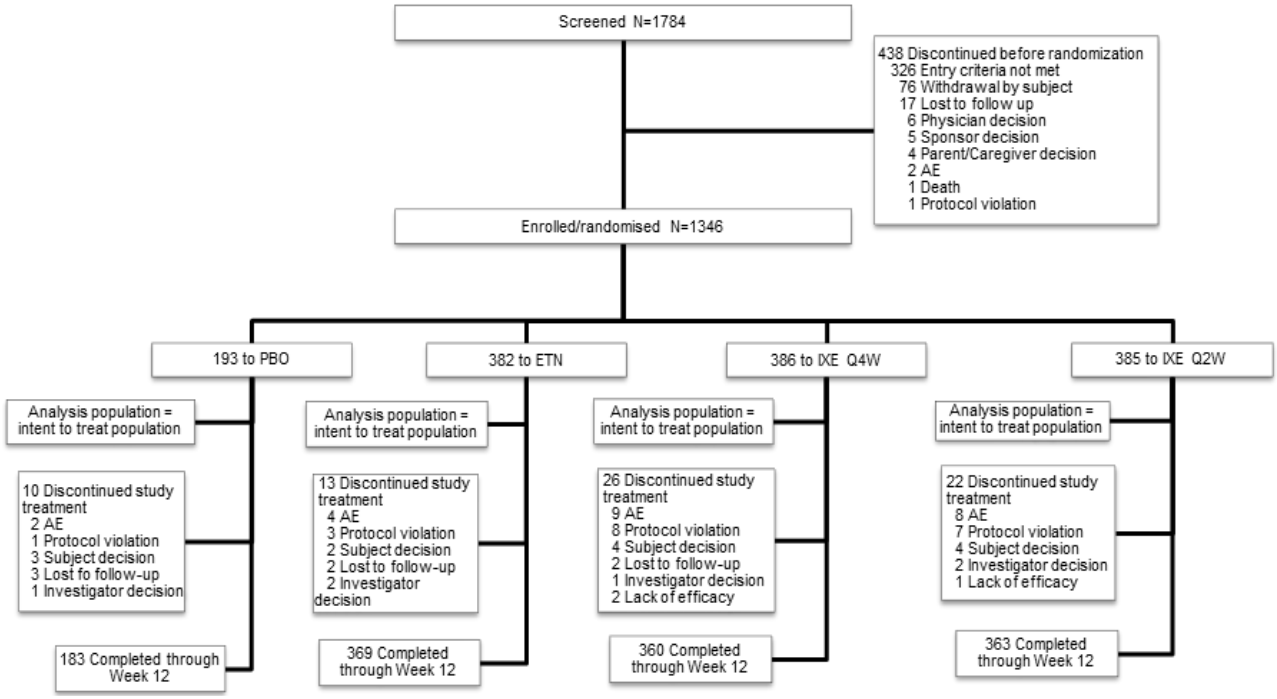
The CONSORT diagram illustrating patient disposition in UNCOVER-3 can be seen in Figure 12.

A total of 1,783 patients signed informed consent and were entered into UNCOVER-3. Of these patients who entered the study, 437 were discontinued prior to randomisation. During the blinded Induction Dosing Period (week 0 to week 12), 1,346 patients were randomly assigned in 1:2:2:2 ratio by centre to receive:[16]

- Placebo (n=193)
- Etanercept (n=382) 50 mg twice weekly
- Ixekizumab Q2W (n=385) single injection 80 mg after a 160-mg starting dose
- Ixekizumab Q4W (n=386) single injection 80 mg after a 160-mg starting dose

Approximately, 95% of patients across all treatment groups completed the Induction Dosing Period, with 71 (5.3%) patients discontinued from study treatment. The most frequently reported reasons for discontinuation were AE and protocol violation.[16]

Figure 12: Patient disposition in UNCOVER-3[78]



AE = adverse event; ETN = etanercept; IXE = ixekizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

4.5.4 Patient demographics and baseline characteristics in the UNCOVER studies

Patient demographics, baseline characteristics, or disease severity were consistent for all the ITT populations across the UNCOVER studies. Prior use of biologic therapy varied across studies; this difference may be related to the exclusion criteria regarding prior etanercept use in UNCOVER-2 and -3 to avoid bias since etanercept was a comparator treatment.

Mean age across the three studies ranged from 45.0 to 45.8 years, and the proportion of male patients ranged from 67.1% to 68.2%. The majority of patients were enrolled in North America (51.3%) and Europe (42.8%). The patient population included in the studies was reflective of a moderate to severe illness patient cohort as represented by the baseline sPGA scores and PASI scores (mean baseline range 19.6 to 20.9). Patients also reported moderate severity of itching with mean baseline values ranging from 6.3 to 7.1 across studies (for further details of the itch numeric rating scale [NRS] see Appendix 6). Approximately 43.5% of patients had received phototherapy prior to enrolment; 54.6% had received prior conventional non-biologic systemic therapy; 26.4% had received prior biologic therapy for the treatment of psoriasis[15,16]

Full patient demographic data and baseline disease characteristics for UNCOVER-1, -2 and -3 can be seen in Table 17, Table 18 and Table 19, respectively.

Table 17: Patient demographics and baseline characteristics in UNCOVER-1[15,21]

	Placebo (N=431)	**IXE 80 mg Q4W (N=432)**	**IXE 80 mg Q2W (N=433)**	**Total IXE (N=865)**	**Total (N=1,296)**
Patient demographics					
Age (years)					
Mean (SD)	46.4 (13.4)	45.6 (12.95)	45.1 (12.40)	45.3 (12.68)	45.7 (12.93)
Gender, n (%)					
Male	303 (70.3)	289 (66.9)	291 (67.2)	580 (67.1)	883 (68.1)
Female	128 (29.7)	143 (33.1)	142 (32.8)	285 (32.9)	413 (31.9)
Race, n (%)					
White	401 (93.0)	397 (91.9)	401 (92.6)	798 (92.3)	1199 (92.5)
Asian	21 (4.9)	23 (5.3)	18 (4.2)	41 (4.7)	62 (4.8)
Black	8 (1.9)	10 (2.3)	8 (1.8)	18 (2.1)	26 (2.0)
Other	1 (0.2)	2 (0.4)	6 (1.4)	8 (0.9)	9 (0.7)

	Placebo (N=431)	IXE 80 mg Q4W (N=432)	IXE 80 mg Q2W (N=433)	Total IXE (N=865)	Total (N=1,296)
Geographical region, n (%)					
North America	223 (51.7)	225 (52.1)	225 (52.0)	450 (52.0)	673 (51.9)
Europe	176 (40.8)	180 (41.7)	192 (44.3)	372 (43.0)	548 (42.3)
Asia	13 (3.0)	12 (2.8)	8 (1.8)	20 (2.3)	33 (2.5)
Australia	19 (4.4)	15 (3.5)	8 (1.8)	23 (2.7)	42 (3.2)
Weight (kg)					
Mean (SD)	91.82 (24.950)	92.49 (23.891)	92.43 (22.681)	92.46 (23.280)	92.25 (23.840)
Range	45.8-186.0	47.0-200.0	48.0-190.5	47.0-200.0	45.8-200.0
Weight Category, n (%)					
<80 kg	147 (34.1)	132 (30.6)	133 (30.7)	265 (30.6)	412 (31.8)
≥80 to <100 kg	142 (32.9)	158 (36.6)	155 (35.8)	313 (36.2)	455 (35.1)
≥100 kg	142 (32.9)	142 (32.9)	145 (33.5)	287 (33.2)	429 (33.1)
BMI (kg/m^2),					
Mean (SD)	30.43 (7.608)	30.69 (7.500)	30.82 (7.117)	30.75 (7.307)	30.65 (7.407)
Range	16.07-66.00	17.40-76.39	17.63-64.65	17.40-76.39	16.07-76.39
Baseline characteristics					
BSA (%),					
Mean (SD)	27.4 (17.77)	27.4 (16.20)	28.2 (17.83)	27.8 (17.03)	27.7 (17.27)
Range	10-95	10-92	10-95	10-95	10-95
Duration of psoriasis (years),					
Mean (SD)	19.50 (11.73)	19.49 (11.91)	19.89 (11.91)	19.69 (11.92)	19.63 (11.85)
Range	0.5-61.7	0.6-60.9	0.6-60.0	0.6-60.9	0.5-61.7
sPGA, n (%)					
3	204 (47.3)	197 (45.6)	231 (53.3)	428 (49.5)	632 (48.8)
4	193 (44.8)	205 (47.5)	179 (41.3)	384 (44.4)	577 (44.5)
5	34 (7.9)	30 (6.9)	23 (5.3)	53 (6.1)	87 (6.7)
PASI score,					
Mean (SD)	20.32 (8.64)	20.03 (7.30)	20.09 (7.99)	20.06 (7.65)	20.15 (7.99)
Range	12.0-69.2	12.0-61.2	12.0-60.0	12.0-61.2	12.0-69.2
NAPSI,					
Mean (SD)	26.09 (20.492)	24.12 (18.243)	24.64 (18.916)	24.38 (18.569)	24.95 (19.238)
Range	0.0-80.0	1.0-80.0	1.0-80.0	1.0-80.0	0.0-80.0
DLQI,					
Mean (SD)	12.8 (7.11)	13.2 (7.02)	13.4 (7.02)	13.3 (7.02)	13.1 (7.05)
Range	0-30	0-30	0-30	0-30	0-30
Itch NRS,					
Mean (SD)	7.0 (2.58)	7.0 (2.50)	7.2 (2.39)	7.1 (2.45)	7.1 (2.49)
Range	0-10	0-10	0-10	0-10	0-10
Patients with nail psoriasis, n (%)	283 (65.7)	283 (65.5)	284 (65.)	567 (65.5)	850 (65.6)

	Placebo (N=431)	IXE 80 mg Q4W (N=432)	IXE 80 mg Q2W (N=433)	Total IXE (N=865)	Total (N=1,296)
Previous systemic therapies, n (%)					
Never used	132 (30.6)	132 (30.6)	108 (24.9)	240 (27.7)	372 (28.7)
Biologics	57 (13.2)	62 (14.4)	49 (11.3)	111 (12.8)	168 (13.0)
Non-biologics	118 (27.4)	132 (30.6)	152 (35.1)	284 (32.8)	402 (31.0)
Biologics and non-biologics	124 (28.8)	106 (24.5)	124 (28.6)	230 (26.6)	354 (27.3)
Previous phototherapy, n (%)	185 (42.9)	205 (47.5)	201 (46.4)	406 (46.9)	591 (45.6)

Notes: For weight and baseline is defined as the safety baseline for each period. Previous nonbiologic systemic therapy includes the following: methotrexate, cyclosporine, retinoids, and PUVA.

BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; IXE80 = ixekizumab 80 mg; IXE = ixekizumab; kg = kilogram; m2 = meters squared; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; sPGA = static Physician Global Assessment.

Table 18: Patient demographics and baseline characteristics in UNCOVER-2[16,22]

	Placebo (N=168)	IXE 80 mg Q4W (N=347)	IXE 80 mg Q2W (N=351)	Total IXE (N=698)	Etanercept (N=358)	Total (N=1,224)
Patient demographics						
Age (years)						
Mean (SD)	45.3 (12.13)	45.0 (13.53)	44.5 (13.27)	44.7 (13.39)	45.3 (12.79)	45.0 (13.04)
Gender, n (%)						
Male	120 (71.4)	244 (70.3)	221 (63.0)	465 (66.6)	236 (65.9)	821 (67.1)
Female	48 (28.6)	103 (29.7)	130 (37.0)	233 (33.4)	122 (34.1)	403 (32.9)
Race, n (%)						
White	149 (88.7)	315 (91.8)	330 (94.3)	645 (93.1)	331 (93.5)	1125 (92.6)
Asian	6 (3.6)	11 (3.2)	12 (3.4)	23 (3.3)	8 (2.3)	37 (3.0)
Black	10 (6.0)	11 (3.2)	5 (1.4)	16 (2.3)	13 (3.7)	39 (3.2)
Other	3 (1.8)	6 (1.8)	3 (0.9)	9 (1.3)	2 (0.6)	14 (1.1)
Geographical region, n (%)						
North America	89 (53.0)	187 (53.9)	188 (53.6)	375 (53.7)	193 (53.9)	657 (53.7)
Europe	72 (42.9)	145 (41.8)	147 (41.9)	292 (41.8)	152 (42.5)	516 (42.2)
Australia	7 (4.2)	15 (4.3)	16 (4.6)	31 (4.4)	13 (3.6)	51 (4.2)
Weight (kg)						
Mean (SD)	91.83 (21.897)	92.51 (22.523)	89.17 (21.638)	90.83 (22.130)	92.85 (22.365)	91.56 (22.167)
Range	50.0-165.0	46.8-216.2	41.0-162.3	41.0-216.2	48.6-173.2	41.0-216.2
Weight Category, n (%)						
<80 kg	50 (30.1)	97 (28.0)	123 (35.0)	220 (31.6)	111 (31.1)	381 (31.2)
≥80 to <100kg	61 (36.7)	130 (37.6)	133 (37.9)	263 (37.7)	121 (33.9)	445 (36.5)
≥100 kg	55 (33.1)	119 (34.4)	95 (27.1)	214 (30.7)	125 (35.0)	394 (32.3)

	Placebo (N=168)	IXE 80 mg Q4W (N=347)	IXE 80 mg Q2W (N=351)	Total IXE (N=698)	Etanercept (N=358)	Total (N=1,224)
BMI (kg/m^2),						
Mean (SD)	30.85 (7.141)	30.62 (6.589)	30.08 (7.020)	30.35 (6.811)	31.25 (7.252)	30.68 (6.994)
Range	18.3-60.6	17.2-53.8	15.2-60.2	15.2-60.2	17.0-58.6	15.2-60.6
Baseline characteristics						
BSA (%),						
Mean (SD)	27.2 (18.12)	27.0 (17.23)	25.1 (15.82)	26.1 (16.55)	25.3 (15.50)	26.0 (16.47)
Range	10-92	10-85	10-95	10-95	10-90	10-95
Duration of psoriasis (years),						
Mean (SD)	19.05 (12.710)	18.52 (12.738)	18.33 (12.120)	18.43 (12.423)	18.89 (12.455)	18.65 (12.464)
Range	0.5-63.4	0.5-60.3	0.5-61.4	0.5-61.4	0.6-56.9	0.5-63.4
sPGA, n (%)						
3	86 (51.2)	166 (47.8)	178 (50.7)	344 (49.3)	186 (52.0)	616 (50.3)
4	70 (41.7)	164 (47.3)	151 (43.0)	315 (45.1)	156 (43.6)	541 (44.2)
5	12 (7.1)	17 (4.9)	22 (6.3)	39 (5.6)	16 (4.5)	67 (5.5)
PASI score,						
Mean (SD)	20.57 (8.366)	20.04 (6.962)	19.35 (7.339)	19.69 (7.157)	19.07 (6.701)	19.63 (7.216)
Range	12-54	12-46.8	12-57.5	12-57.5	12-61.2	12-61.2
NAPSI,						
Mean (SD)	27.62 (20.937)	23.70 (18.696)	26.27 (20.388)	24.96 (19.559)	30.44 (20.648)	26.97 (20.211)
Range	1-80	1-80	1-80	1-80	1-80	1-80
DLQI,						
Mean (SD)	12.8 (7.24)	11.6 (6.65)	12.4 (6.86)	12.0 (6.76)	12.7 (7.03)	12.3 (6.91)
Range	0-30		0-30	0-30	0-30	0-30
Itch NRS,						
Mean (SD)	6.4 (2.67)	6.5 (2.50)	6.7 (2.51)	6.6 (2.50)	6.6 (2.58)	6.6 (2.55)
Range	0-10	0-10	0-10	0-10	0-10	0-10
Patients with nail psoriasis, n (%)	113 (67.3)	219 (63.1)	209 (59.5)	428 (61.3)	229 (64.0)	770 (62.9)
Previous systemic therapies, n (%)						
Never used	64 (38.1)	115 (33.1)	126 (35.9)	241 (34.5)	133 (37.2)	438 (35.8)
Biologics	19 (11.3)	28 (8.1)	29 (8.3)	57 (8.2)	33 (9.2)	109 (8.9)
Non-biologics	61 (36.3)	147 (42.4)	141 (40.2)	288 (41.3)	149 (41.6)	498 (40.7)
Biologics and non-biologics	24 (14.3)	57 (16.4)	55 (15.7)	112 (16.0)	43.(12.0)	179 (14.6)
Previous phototherapy, n (%)	74 (44.0)	160 (46.1)	163 (46.4)	323 (46.3)	173 (48.3)	570 (46.6)

Notes: For weight and baseline is defined as the safety baseline for each period. Previous nonbiologic systemic therapy includes the following: methotrexate, cyclosporine, retinoids, and PUVA.

BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; IXE80 = ixekizumab 80 mg; IXE = ixekizumab; kg = kilogram; m2 = meters squared; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; sPGA = static Physician Global Assessment.

Table 19: Patient demographics and baseline characteristics in UNCOVER-3[16,23]

	Placebo (N=193)	IXE 80 mg Q4W (N=386)	IXE80 mg Q2W (N=385)	Total IXE (N=771)	Etanercept (N=382)	Total (N=1,346)
Age (years)						
Mean (SD)	46.4 (12.11)	45.6 (12.76)	45.6 (13.10)	45.6 (12.92)	45.8 (13.84)	45.8 (13.07)
Gender, n (%)						
Male	137 (71.0)	258 (66.8)	254 (66.0)	512 (66.4)	269 (70.4)	918 (68.2)
Female	56 (29.0)	128 (33.2)	131 (34.0)	259 (33.6)	113 (29.6)	428 (31.8)
Race, n (%)						
White	176 (91.21)	360 (93.3)	361 (93.8)	721 (93.5)	351 (91.9)	1248 (92.7)
Asian	7 (3.6)	11 (2.8)	12 (3.1)	23 (3.0)	11 (2.9)	41 (3.0)
Black	8 (4.1)	9 (2.3)	5 (1.3)	14 (1.8)	10 (2.6)	32 (2.4)
Other	2 (1.0)	6 (1.6)	7 (1.8)	13 (1.6)	10 (2.6)	25 (1.8)
Geographical region, n (%)						
North America	91 (47.2)	191 (49.5)	183 (47.5)	374 (48.5)	190 (49.7)	655 (48.7)
Europe	88 (45.6)	166 (43.0)	173 (44.9)	339 (44.0)	162 (42.4)	589 (43.8)
Australia	14 (7.3)	29 (7.5)	29 (7.5)	58 (7.5)	30 (7.9)	102 (7.6)
Weight (kg)						
Mean (SD)	90.97 (21.450)	91.23 (23.916)	90.35 (23.440)	90.79 (23.667)	92.15 (24.305)	91.20 (23.539)
Range	55.5-176.0	46.4-200.0	52.0-176.5	46.4-200.0	43.0-177.0	43.0-200.0
Weight Category, n (%)						
<80 kg	61 (31.8)	125 (32.8)	138 (35.9)	263 (34.4)	123 (32.2)	447 (33.4)
≥80 to <100 kg	77 (40.1)	149 (39.1)	137 (35.7)	286 (37.4)	133 (34.8)	496 (37.0)
≥100 kg	54 (28.1)	107 (28.1)	109 (28.4)	216 (28.2)	126 (33.0)	396 (29.6)
BMI (kg/m^2),						
Mean (SD)	30.24 (6.339)	30.67 (7.310)	30.21 (7.139)	30.44 (7.223)	30.73 (7.586)	30.49 (7.207)
Range	19.8-55.5	17.5-61.3	18.5-56.8	17.5-61.3	16.9-57.2	16.9-61.3
Baseline characteristics						
BSA (%),						
Mean (SD)	28.6 (17.45)	28.4 (16.49)	28.0 (17.30)	28.2 (16.89)	28.3 (17.43)	28.3 (17.11)
Range	10-90	10-94	10-90	10-94	10-95	10-95
Duration of psoriasis (years),						
Mean (SD)	18.24 (12.515)	18.45 (12.471)	17.80 (12.191)	18.12 (12.328)	18.12 (11.787)	18.14 (12.195)
Range	0.5-51.3	0.4-63.4	0.5-63.0	0.4-63.4	0.7-50.3	0.4-63.4
sPGA, n (%)						
3	92 (47.7)	206 (53.8)	207 (53.8)	413 (53.8)	190 (49.7)	695 (51.7)
4	91 (47.2)	159 (41.5)	157 (40.8)	316 (41.1)	174 (45.5)	581 (43.3)
5	10 (5.2)	18 (4.7)	21 (5.5)	39 (5.1)	18 (4.7)	67 (5.0)
PASI score,						
Mean (SD)	21.11 (8.388)	21.15 (8.142)	20.73 (8.176)	20.94 (8.157)	20.68 (8.167)	20.89 (8.188)
Range	12.0-49.1	12.0-60.0	12.0-63.0	12.0-63.0	12.0-57.0	12.0-63.0

	Placebo (N=193)	IXE 80 mg Q4W (N=386)	IXE80 mg Q2W (N=385)	Total IXE (N=771)	Etanercept (N=382)	Total (N=1,346)
NAPSI, *Mean (SD)* *Range*	25.47 (19.625) 1.0-80.0	26.19 (20.155) 1.0-80.0	26.14 (20.095) 1.0-80.0	26.17 (20.103 1.0-80.0	25.09 (20.021) 1.0-80.0	25.75 (19.993) 1.0-80.0
DLQI, *Mean (SD)* *Range*	12.7 (7.00) 0-29	11.9 (6.97) 0-30	12.4 (6.93) 0-30	12.1 (6.95) 0-30	11.5 (6.84) 0-30	12.0 (6.93) 0-30
Itch NRS, *Mean (SD)* *Range*	6.5 (2.63) 0-10	6.3 (2.60) 0-10	6.4 (2.59) 0-10	6.4 (2.60) 0-10	6.2 (2.63) 0-10	6.3 (2.61) 0-10
Patients with Nail Psoriasis, n (%)	116 (60.1)	228 (59.1)	229 (59.5)	457 (59.3)	236 (61.8)	809 (60.1)
Previous systemic therapies, n (%) *Never used* *Biologics* *Non-biologics* *Biologics and non-biologics*	88 (45.6) 16 (8.3) 72 (37.3) 17 (8.8)	162 (42.0) 23 (6.0) 166 (43.0) 35 (9.1)	170 (44.2) 25 (6.5) 157 (40.8) 33 (8.6)	332 (43.1) 48 (6.2) 323 (41.9) 68 (8.8)	160 (41.9) 26 (6.8) 162 (42.4) 34 (8.9)	580 (43.1) 90 (6.7) 557 (41.4) 119 (8.8)
Previous phototherapy, n (%)	60 (31.1)	154 (39.9)	151 (39.2)	305 (39.6)	157 (41.1)	522 (38.8)

Notes: For weight and baseline is defined as the safety baseline for each period. Previous non-biologic systemic therapy includes the following: methotrexate, cyclosporine, retinoids, and PUVA.

BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; IXE80 = ixekizumab 80 mg; IXE = ixekizumab; kg = kilogram; m2 = meters squared; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; sPGA = static Physician Global Assessment.

4.6 *Quality assessment of the relevant randomised controlled trials*

An overview of the quality assessment results for the UNCOVER studies can be seen in Table 20. Given the design of the UNCOVER studies, in addition to the patient demographics/baseline demographics listed above and the recruitment of study participants from multiple sites in the UK, it can be assumed that the UNCOVER studies are reflective of UK clinical practice.

Table 20: Quality assessment results for the UNCOVER studies

Trial number (acronym)	UNCOVER-1	UNCOVER-2	UNCOVER-3
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

The full quality assessment giving further details of the UNCOVER can be seen in Appendix 7.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

Summary of ixekizumab clinical effectiveness:

Ixekizumab is an IL-17A inhibitor which can achieve complete clearance (PASI 100), high-level responses (PASI 90) and relief from bothersome psoriasis symptoms (e.g. itch), thus improving the HRQoL of patients with moderate to severe psoriasis. Ixekizumab is also efficacious in difficult-to-treat areas, alleviating the burden of psoriasis symptoms in areas such as the nails, scalp and palmoplantar regions. Ixekizumab has a rapid onset of efficacy and is able to produce high-level responses in patients regardless of prior therapy.

- The efficacy and safety of ixekizumab has been evaluated in a comprehensive clinical development programme including three pivotal, double-blind, randomised, phase III studies in patients with moderate to severe psoriasis (UNCOVER-1, -2 and -3).
- All three UNCOVER studies compared ixekizumab with placebo. In addition, UNCOVER-2 and -3 compared ixekizumab with active comparator etanercept.
- The co-primary endpoints of the UNCOVER studies were sPGA (0, 1) and PASI 75 response rates at week 12.
- In all three UNCOVER studies significantly higher sPGA (0, 1) and PASI 75 response rates were achieved with ixekizumab compared with placebo at week 12 ($p<0.001$ for all comparisons).
- In UNCOVER-2 and -3 significantly higher sPGA (0, 1) and PASI 75 response rates were achieved with ixekizumab compared with active comparator etanercept at week 12 ($p<0.001$ for all comparisons).
- The proportion of patients achieving complete clearance (PASI 100) and high-level responses (PASI 90) were significantly greater with ixekizumab compared with etanercept (UNCOVER-2 and -3 only) and placebo at week 12 ($p<0.001$ for all comparisons).
- Ixekizumab demonstrated rapid onset of efficacy in the UNCOVER-2 and -3 studies, with significant differences in PASI 75 as early as week 2 compared with etanercept and placebo ($p<0.001$ for all comparisons).
- In the UNCOVER-1 and -2 studies, which included a maintenance dosing period (week 12-60), sPGA (0,1) and PASI responses (including PASI 100) were achieved or maintained in the maintenance dosing period with ixekizumab.

- Ixekizumab demonstrated superior efficacy to etanercept (UNCOVER-2 and -3 only) and placebo in difficult-to-treat areas, including psoriasis of the nail, scalp and palmoplantar areas at week 12 ($p<0.001$ for all comparisons).
- Treatment with ixekizumab significantly alleviated the bothersome symptom of itch compared to etanercept (UNCOVER-2 and -3 only) and placebo at week 12 ($p<0.001$ for all comparisons).
- HRQoL as measured by DLQI scores was significantly improved for patients treated with ixekizumab compared with etanercept (UNCOVER-2 and -3 only) and placebo at week 12 ($p<0.001$ for all comparisons).
- Data from the open-label extension period of UNCOVER-3 demonstrate that [redacted] between weeks 12 and 108.
- Ixekizumab was able to produce consistent PASI response rates across all pre-specified subgroups in the UNCOVER studies. Of particular note, ixekizumab demonstrated significant improvements in PASI 75 response rates compared with placebo in patients who had been previously treated with biologics, patients who had responded inadequately to TNF-α inhibitors and patients who are eligible for biologic therapy according to NICE criteria.

The co-primary objectives were met in all three UNCOVER trials with both ixekizumab treatment groups showing greater efficacy than placebo (UNCOVER-1, -2 and -3) and etanercept (UNCOVER-2 and -3 only) at 12 weeks as measured by the proportion of patients achieving PASI 75 and sPGA (0, 1) ($p<0.001$ for all comparisons).[15,16]

In addition, all major secondary objectives for the 12-week Induction Dosing Period (UNCOVER-1, -2 and -3) and for the Maintenance Dosing Period (week 12 though week 60 in UNCOVER-1 and -2) were met ($p<0.001$ for all comparisons).[15,16]

4.7.1 UNCOVER-1

Co-primary objectives: sPGA (0,1) and PASI 75 at week 12

The two co-primary objectives of the UNCOVER-1 study were both met. Both ixekizumab treatment groups (80 mg Q2W and 80 mg Q4W) were statistically significantly superior to placebo at week 12 as measured by the proportions of patients achieving sPGA (0,1) and PASI 75 (p<0.001 for all comparisons).

At week 12, the proportions of patients who achieved sPGA (0,1) with at least a 2-point improvement from baseline (80 mg Q2W group: 81.8% and 80 mg Q4W group : 76.4%) were significantly higher than the percentages of patients treated with placebo (3.2%). Similar results were also observed for PASI 75 at week 12. The proportions of patients who achieved PASI 75 at week 12 were 89.1% and 82.6% in the ixekizumab 80 mg Q2W and Q4W groups, respectively, compared with 3.9% in the placebo group (p<0.001 for all comparisons; Table 21 and Figure 13).[15]

Table 21: UNCOVER-1: sPGA (0,1) and PASI 75 response rates at week 12 – NRI (ITT population)[15,21]

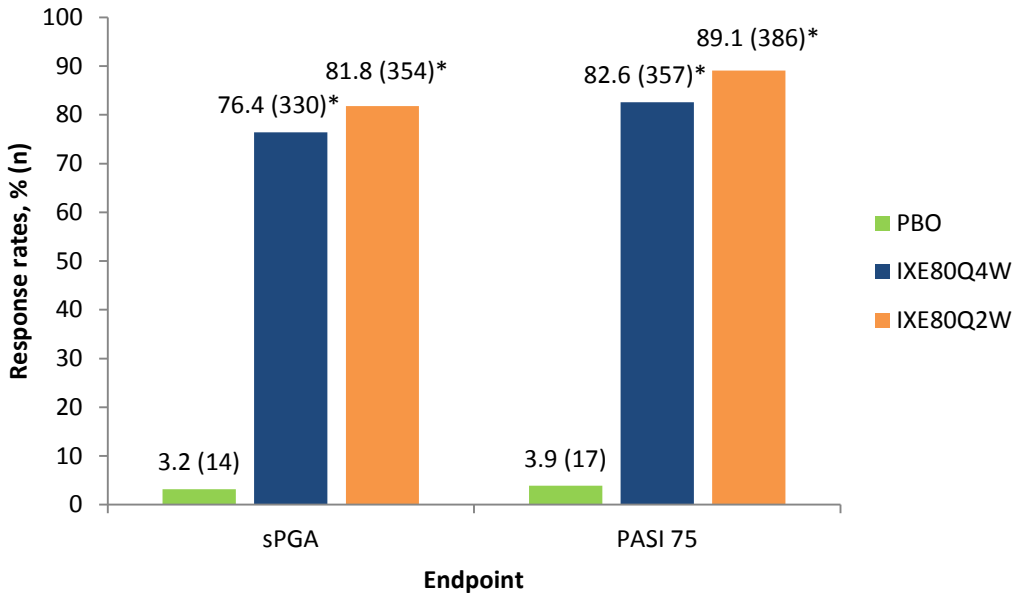
Endpoint	Placebo (N=431)	IXE80Q4W (N=432)	IXE80Q2W (N=433)	Total IXE (N=865)	Total (N=1,296)
sPGA (0,1), n (%)	14 (3.2)	330 (76.4)	354 (81.8)	684 (79.1)	698 (53.9)
OR 95% CI[1] p-value[1]	-	102.89 (57.52, 184.04) <0.001	146.51 (81.02, 264.92) <0.001	-	-
PASI 75, n (%)	17 (3.9)	357 (82.6)	386 (89.1)	743 (85.9)	760 (58.6)
OR 95% CI[1] p-value[1]	-	125.54 (72.26, 218.10) <0.001	223.94 (125.05, 401.03) <0.001	-	-

[1] A logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category as factors

CI = confidence interval; IXE = ixekizumab; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; sPGA = static Physician Global Assessment

Source: **sPGA (0,1)**: CSR RHAZ, Table RHAZ.11.3; **PASI 75**: CSR RHAZ; Table RHAZ 11.4

Figure 13: UNCOVER-1: sPGA and PASI 75 response rates at week 12 – NRI (ITT population)[15]



* p<0.001 versus placebo.

ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

Major secondary (gated) endpoints

All major secondary (gated) objectives for the analysis of the 12-week Induction Dosing Period and for the Maintenance Dosing Period (week 12 through week 60) were met (p<0.001 for all comparisons) and are summarised in the following section.

sPGA (0), PASI 90 and PASI 100 at week 12

At week 12, both ixekizumab treatment groups were statistically significantly superior to placebo as measured by the proportions of patients achieving sPGA (0), PASI 90, and PASI 100 (p<0.001 for all comparisons; Table 22 and Figure 14).[15]

Table 22: UNCOVER-1: sPGA 0, PASI 90, and PASI 100 results at week 12 – NRI (ITT population)[15,21]

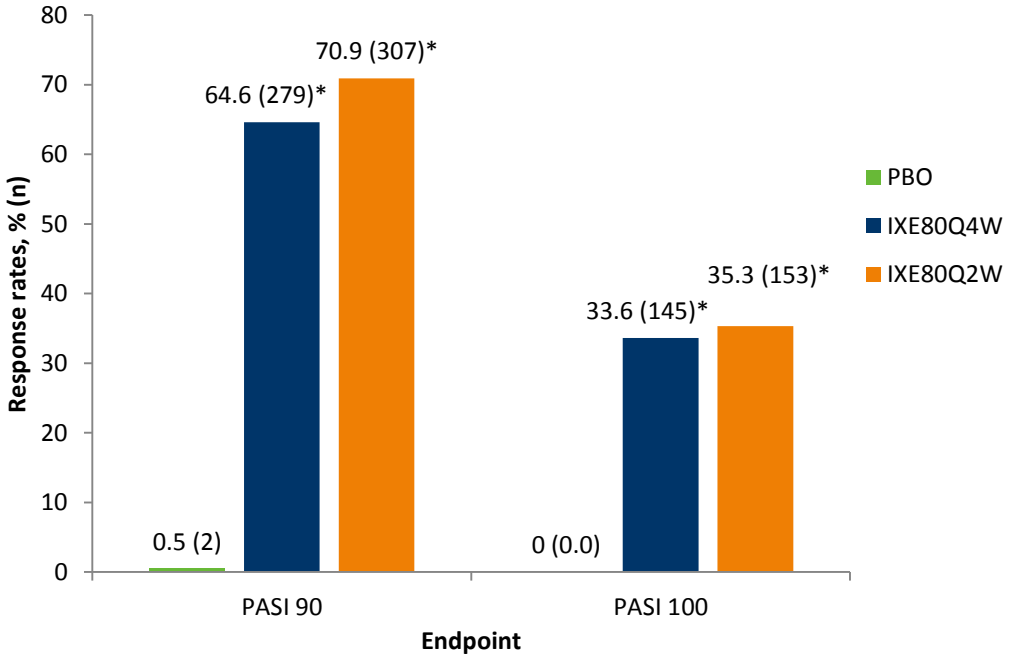
Endpoint	Placebo (N=431)	IXE80Q4W (N=432)	IXE80Q2W (N=433)	Total IXE (N=865)	Total (N=1,296)
sPGA (0), n (%)	0 (0.0)	149 (34.5)	160 (37.0)	309 (35.7)	309 (23.8)
OR (95% CI)[1] p-value[1]	-	N/A	N/A	N/A	-
PASI 90, n (%)	2 (0.5)	279 (64.6)	307 (70.9)	586 (67.7)	588 (45.4)
OR (95% CI)[1] p-value[1]		411.70 (101.09, 1,676.63) <0.001	562.34 (137.80, 2,294.78) <0.001	478.32 (118.23, 1,935.24) <0.001	
PASI 100, n (%)	0 (0.0)	145 (33.6)	153 (35.3)	298 (34.5)	298 (23.0)
OR (95% CI)[1] p-value[1]	-	N/A	N/A	N/A	-

[1] A logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category as factors

CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; N/A = not applicable; NRI = non-responder imputation; Q2W = every 2 weeks; Q4W = every 4 weeks; OR = odds ratio; sPGA = static Physician Global Assessment

Source: **sPGA (0)**: CSR RHAZ, Table RHAZ.11.6; **PASI 90**: CSR RHAZ; Table RHAZ 11.8; **PASI 100**: CSR RHAZ; Table RHAZ 11.9

Figure 14: UNCOVER-1: PASI 90 and PASI 100 response rates at week 12 – NRI (ITT population)[15]



* p<0.001 versus placebo.

ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

Itch NRS at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving patients' itch severity as measured by the Itch NRS (p<0.001; Table 23). The proportions of patients who had Itch NRS score ≥4 at baseline and achieved a ≥4-point reduction from baseline at week 12 were 85.9%, 80.5%, and 15.5% in the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo groups, respectively.[82]

Table 23: UNCOVER-1: Percentage of Patients with ≥4-Point Reduction from Baseline at week 12 – NRI (ITT population)[21,82]

Endpoint	Placebo N=431	IXE80Q4W N=432	IXE80Q2W N=433	Total IXE N=865	Total N=1,296
Itch Severity - Patients with ≥4 point reduction from baseline (NRI)					
Patients with Itch NRS Score ≥4 at Baseline	n=374	n=379	n=391	n=770	n=1,144
Patients with ≥4 point reduction from baseline (NRI), n (%)	58 (15.5%)	305 (80.5%)	336 (85.9%)	641 (83.2%)	699 (61.1%)
OR (95%CI)[1] p-value [1]	-	22.90 (15.65, 33.51) <0.001	34.39 (22.97, 51.49) <0.001	27.75 (19.73, 39.04) <0.001	-

[1] A logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category included as factors

CI = confidence interval; ITT = intent-to-treat; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category, NRI = non-responder imputation; NRS = numeric rating scale; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks

Source: CSR RHAZ, Table RHAZ.11.12 (Page 3 of 3)

DLQI at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving patients' HRQoL as measured by the DLQI (p<0.001; Table 24). The least squares mean (LSM) changes from baseline in the DLQI total scores at week 12 were -10.7, -10.3, and -0.7 in the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo groups, respectively (Table 24).[83]

Table 24: UNCOVER-1: DLQI Total Score Mean Change from Baseline (LOCF; ANCOVA) and Percentage of Patients Achieving a DLQI (0,1) or (0) at week 12 – NRI (ITT population)[21,83]

Endpoint	Placebo (N=431)	IXE80Q4W (N=432)	IXE80Q2W (N=433)	Total IXE (N=865)	Total (N=1,296)
Number of patients	431	431	432	863	1,294
Baseline Mean (SD)	12.8 (7.11)	13.2 (7.02)	13.4 (7.02)	13.3 (7.02)	13.1 (7.05)

Endpoint	Placebo (N=431)	IXE80Q4W (N=432)	IXE80Q2W (N=433)	Total IXE (N=865)	Total (N=1,296)
Observed Mean at week 12 (SD)	11.6 (7.53)	2.3 (3.87)	2.0 (3.33)	2.1 (3.61)	5.3 (6.88)
Endpoint (LSM) Change (SE)	-0.7 (0.29)	-10.3 (0.29)	-10.7 (0.28)	-	-
LSM Difference (95% CI)	-	-9.6 (-10.3, -9.0)	-10.0 (-10.6 – 9.3)	-	-
p-value[1]	-	<0.001	<0.001	-	-
Effect Size	-	-1.6	-1.7	-	-
Patients with DLQI (0,1) (NRI)					
n (%)	20 (4.6)	258 (59.7)	287 (66.3)	545 (63.0)	565 (43.6)
OR (95%CI) p-value[2]	-	31.16 (19.09, 50.85) <0.001	41.54 (25.37, 68.02) <0.001	-	-
Patients with DLQI (0) (NRI)					
n (%)	2 (0.5)	174 (40.3)	181 (41.8)	355 (41.0)	357 (27.5)
OR (95%CI)[2] p-value[2]	-	147.46 (36.26, 599.74) <0.001	157.15 (38.64, 639.08) <0.001	-	-

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus placebo comparison at each visit and use an ANCOVA model including treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline DLQI value in the model

[2] A logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category included as factors

ANCOVA = analysis of covariance; CI = confidence interval; DLQI = Dermatology Life Quality Index; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source: **DLQI total score:** CSR RHAZ, Table RHAZ.14.185 (Page 1&4 of 28); **DLQI (0,1):** CSR RHAZ, Table RHAZ 14.191 (Page 2 of 4); **DLQI (0):** CSR RHAZ, Table RHAZ 14.191 (Page 4 of 4)

Nail psoriasis at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving fingernail psoriasis as measured by Nail Psoriasis Severity Index (NAPSI) scores (p<0.001; Table 25). The LSM changes from baseline in the NAPSI scores at week 12 among patients who had fingernail involvement at baseline were -7.12, -7.14, and 2.30 for the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo groups, respectively (Table 25). In addition, nail clearance rates (NAPSI=0) at week 12 were significantly greater for the ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W groups compared with placebo (p<0.001).[21]

Table 25: UNCOVER-1: NAPSI score mean change from baseline at week 12 and nail clearance rates (NAPSI=0) - LOCF; ANCOVA (ITT population with baseline fingernail involvement)[21]

Endpoint	Placebo (N=431)	IXE80Q4W (N=432)	IXE80Q2W (N=433)	Total IXE (N=865)	Total (N=1,296)
Number of patients	283	281	283	564	847
Baseline Mean (SD)	26.09 (20.492)	24.12 (18.243)	24.64 (18.916)	24.38 (18.569)	24.95 (19.238)
Observed Mean at week 12 (SD)	28.14 (20.457)	16.91 (16.453)	17.61 (17.974)	17.26 (17.229)	20.84 (19.041)
Endpoint (LSM) Change (SE)	2.30 (0.736)	-7.14 (0.733)	-7.12 (0.696)	-	-
LSM Difference (95% CI)	-	-9.43 (-11.12, -7.75)	-9.42 (-11.11, -7.74)	-	-
p-value[1]	-	<0.001	<0.001	-	-
Effect Size	-	-0.61	-0.55	-	-
Patients with NAPSI (0) (NRI)					
n (%)	10 (3.5)	36 (12.7)	48 (16.9)	84 (14.8)	94 (11.1)
OR (95%CI) p-value[2]	-	3.99 (1.94, 8.21) <0.001	5.74 (2.84, 11.63) <0.001	-	-

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus placebo comparison at each visit and use an ANCOVA model including treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline NAPSI value in the model

ANCOVA = analysis of covariance; CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; NAPSI = Nail Psoriasis Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source: **NAPSI total score:** CSR RHAZ, Table RHAZ.14.101 (Page 1&9 of 9); **NAPSI (0):** CSR RHAZ, Table RHAZ.14.102 (Page 3 of 3)

Maintenance of sPGA (0,1) to week 60

At week 60, maintenance treatment with ixekizumab Q4W was statistically significantly superior to placebo in the proportion of patients who achieved or maintained sPGA (0,1) (p<0.001; Table 26). At week 60, 74.8% and 7.7% of patients from the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups, respectively, maintained sPGA (0,1) (Table 26).[15,21]

Table 26: UNCOVER-1: Maintenance of Response, results of sPGA (0,1) response at week 60 - NRI (Maintenance Dosing Period Primary Population)[15,21]

Endpoint	IXE80Q4W /PBO (N=109)	IXE80Q4W/ IXE80Q4W (N=110)	IXE80Q2W/ PBO (N=117)	IXE80Q2W/ IXE80Q4W (N=119)	IXE/PBO (N=226)	IXE/ IXE80Q4W (N=229)
sPGA (0,1), n (%)	8 (7.3%)	78 (70.9%)	9 (7.7%)	89 (74.8%)	17 (7.5%)	167 (72.9%)
OR (95% CI)[1] p-value[1]	-	33.10 (14.33, 76.45) <0.001		38.82 (17.35, 86.87) <0.001	-	35.84 (20.01, 64.20) <0.001

[1] A logistic regression analysis with treatment and baseline weight category as factors

CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the Maintenance Dosing Period Primary Population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment.

Source**:** CSR RHAZ, Table RHAZ.11.11

Other secondary outcomes

PASI 75, PASI 90 and PASI 100 at week 60

At week 60, maintenance treatment with ixekizumab Q4W was statistically significantly superior to placebo in the proportion of patients who achieved or maintained PASI 75, PASI 90 and PASI 100 (p<0.001; Table 27) . At week 60, 52.1% and 3.4% of patients from the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups, respectively, achieved or maintained PASI 100 (Table 27). PASI 100 responses were shown to improve over time. In addition, a significant proportion of patients achieved or maintained high-level responses (PASI 90) during the maintenance period. At week 60, 72.3% and 5.1% of patients from the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups, respectively, achieved or maintained PASI 90 (Table 27).[21]

Table 27: UNCOVER-1: Maintenance of Response, results of PASI 75, 90 and 100 response at week 60 - NRI (Maintenance Dosing Period Primary Population)[21]

Endpoint	IXE80Q4W /PBO (N=109)	IXE80Q4W/ IXE80Q4W (N=110)	IXE80Q2W/ PBO (N=117)	IXE80Q2W/ IXE80Q4W (N=119)	IXE/PBO (N=226)	IXE/ IXE80Q4W (N=229)
PASI 75, n (%)	9 (8.3)	85 (77.3)	11 (9.4)	93 (78.2)	20 (8.8)	178 (77.7)
OR[1] (95% CI)[1] p-value[1]	-	41.33 (18.12, 94.31) <0.001	-	38.09 (17.64, 82.23) <0.001	-	39.53 (22.45, 68.63) <0.001
PASI 90, n (%)	4 (3.7)	76 (69.1)	6 (5.1)	86 (72.3)	10 (4.4)	162 (70.7)
OR[1] (95% CI)[1] p-value[1]	-	63.29 (21.42, 187.04) <0.001	-	52.64 (20.92, 132.45) <0.001	-	56.65 (28.06, 114.37) <0.001
PASI 100, n (%)	2 (1.8)	57 (51.8)	4 (3.4)	62 (52.1)	6 (2.7)	119 (52.0)
OR[1] (95% CI)[1] p-value[1]	-	59.55 (13.97, 253.88) <0.001	-	31.96 (11.03, 92.55) <0.001	-	41.16 (17.52, 96.70) <0.001

[1] A logistic regression analysis with treatment and baseline weight category as factors
CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the Maintenance Dosing Period Primary Population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

Source**: PASI 75**: CSR RHAZ, Table RHAZ.14.121 (Page 14&42 of 56); **PASI 90:** CSR RHAZ, Table RHAZ.14.121 (Page 21&49 of 56); **PASI 100:** CSR RHAZ, Table RHAZ.14.121 (Page 28&56 of 56)

Nail psoriasis at week 60

At week 60 statistically significant improvements were observed in NAPSI scores for patients in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W treatment group compared with the ixekizumab 80 mg Q2W/placebo group (p<0.001; Table 28). The LSM changes from baseline in NAPSI scores at week 60 were -19.49 in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W treatment group compared with -8.77 in the ixekizumab 80 mg Q2W/placebo group (Table 28).[21]

Table 28: UNCOVER-1: NAPSI score mean change from baseline at week 60 and nail clearance rates (NAPSI=0) - LOCF; ANCOVA (Maintenance Dosing Period Primary Population with Baseline Fingernail Involvement)[21]

Endpoint	IXE80Q4W /PBO (N=79)	IXE80Q4W/ IXE80Q4W (N=74)	IXE80Q2W/ PBO (N=77)	IXE80Q2W/ IXE80Q4W (N=76)	IXE/PBO (N=156)	IXE/ IXE80Q4W (N=150)
Number of patients	79	73	77	76	156	149
Baseline Mean (SD)	21.92 (16.43)	23.56 (17.459)	27.30 (19.20)	22.08 (16.65)	24.57 (17.99)	22.81 (17.01)
Observed Mean at week 60 (SD)	9.57 (11.52)	4.07 (9.40)	5.00 (3.58)	2.37 (4.77)	7.46 (8.79)	3.23 (7.49)
Endpoint (LSM) Change (SE)	-9.32 (1.26)	-18.34 (1.32)	-8.77 (1.28)	-19.49 (1.28)	-9.06 (0.90)	-18.93 (0.92)
LSM Difference (95% CI)	-	-9.02 (-12.56, -5.48)	-	-10.72 (-14.26, -7.19)	-	-9.88 (-12.37, -7.39)
p-value[1]	-	<0.001	-	<0.001	-	<0.001
Effect Size	-	-0.57		-0.56	-	-0.56
Patients with NAPSI (0) (NRI)						
n (%)	3 (3.8)	33 (44.6)	0 (0)	38 (50.0)	3 (1.9)	71 (47.3)
OR[2] (95%CI)[2] p-value[2]	-	20.12 (5.80, 69.75) <0.001	-	N/A N/A <0.001	-	46.72 (14.24, 153.30) <0.001

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus placebo comparison at each visit and use an ANCOVA model including treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline NAPSI value in the model

[2] A logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category included as factors

ANCOVA = analysis of covariance; CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; IXE80Q4W = ixekizumab 80 mg every 4 weeks; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; NAPSI = Nail Psoriasis Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source**: NAPSI total score**: CSR RHAZ, Table RHAZ.14.141 (Page 1, 24 ,25, 26, 49 and 50 of 50); **NAPSI (0):** CSR RHAZ, Table RHAZ.14.142 (Page 6 and 12 of 12)

Psoriasis with scalp involvement at week 12 and 60

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving scalp psoriasis as measured by Psoriasis Scalp Severity Index (PSSI) scores (p<0.001; Table 29). The LSM changes from baseline in the PSSI scores at week 12 among patients who had scalp involvement at baseline were -19.0, -18.3, and -1.5 for the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo groups, respectively. In addition, scalp clearance rates (PSSI=0) at week 12 were significantly greater for the ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W groups compared with the placebo group (p<0.001) (Table 29).[21]

Table 29: UNCOVER-1: PSSI score mean change from baseline at week 12 and scalp clearance rates (PSSI=0) - LOCF; ANCOVA (ITT population with baseline scalp involvement)[21]

Endpoint	Placebo (N=393)	IXE80Q4W (N=413)	IXE80Q2W (N=393)	Total IXE (N=806)	Total (N=1,199)
Number of patients	393	413	393	806	1,199
Baseline Mean (SD)	21.8 (15.70)	19.9 (14.83)	21.1 (14.69)	20.5 (14.76)	20.9 (15.08)
Observed Mean at week 12 (SD)	19.1 (15.78)	1.8 (5.09)	1.6 (5.21)	1.7 (5.15)	7.3 (12.85)
Endpoint (LSM) Change (SE)	-1.5 (0.55)	-18.3 (0.54)	-19.0 (0.54)	-	-
LSM Difference (95% CI)	-	-16.8 (-18.0, -15.6)	-17.5 (-18.8, -16.3)	-	-
p-value[1]	-	<0.001	<0.001	-	-
Patients with PSSI (0) (NRI)					
n (%)	21 (5.3)	287 (69.5)	290 (73.8)	577 (71.6)	598 (49.9)
OR[2] (95%CI)[2] p-value[2]	-	42.24 (25.86, 69.02) <0.001	53.11 (32.25, 87.49) <0.001	-	-

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus placebo comparison at each visit and use an ANCOVA model including treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline PSSI value in the model

[2] A logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category included as factors

ANCOVA = analysis of covariance; CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; PSSI = Psoriasis Scalp Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source**: PSSI total score**: CSR RHAZ, Table RHAZ.14.106 (Page 1, 8 and 9 of 9); **PSSI (0):** CSR RHAZ, Table RHAZ.14.107 (Page 3 of 3)

At week 60 statistically significant improvements were observed in PSSI scores for patients in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W treatment group compared with the ixekizumab 80 mg Q2W/placebo group (p<0.001; Table 30). The LSM changes from baseline in PSSI scores at week 60 were -19.5 in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W treatment group compared with -8.9 in the ixekizumab 80 mg Q2W/placebo group (Table 30).[21]

Table 30: UNCOVER-1: PSSI score mean change from baseline at week 60 and scalp clearance rates (PSSI=0) - LOCF; ANCOVA (Maintenance Dosing Period Primary Population with baseline scalp Involvement)[21]

Endpoint	IXE80Q4W /PBO (N=107)	IXE80Q4W/ IXE80Q4W (N=104)	IXE80Q2W/ PBO (N=102)	IXE80Q2W/ IXE80Q4W (N=110)	IXE/PBO (N=209)	IXE/ IXE80Q4W (N=214)
Number of patients	107	104	102	110	209	214
Baseline Mean (SD)	18.9 (13.07)	19.4 (15.45)	21.7 (15.61)	21.5 (14.12)	20.3 (14.40)	20.5 (14.78)
Observed Mean at week 60 (SD)	9.1 (12.31)	0.6 (2.14)	2.2 (3.42)	0.5 (1.45)	5.5 (9.35)	0.6 (1.81)
Endpoint (LSM) Change (SE)	-12.2 (0.80)	-19.0 (0.81)	-8.9 (0.81)	-19.5 (0.78)	-10.6 (0.58)	-19.2 (0.57)
LSM Difference (95% CI)	-	-6.8 (-9.0, -4.6)	-	-10.6 (-12.8, -8.4)	-	-8.7 (-10.2, -7.1)
p-value[1]	-	<0.001	-	<0.001	-	<0.001
Patients with PSSI (0) (NRI)						
n (%)	5 (4.7)	73 (70.2)	7 (6.9)	75 (68.2)	12 (5.7)	148 (69.2)
OR (95%CI) p-value[2]	-	48.97 (18.14, 132.17) <0.001	-	29.60 (12.42, 70.51) <0.001	-	37.49 (19.52, 72.01) <0.001

[1] The LS Mean, SE, 95% CI and p-values are presented for each treatment comparison at each visit and use an analysis of covariance model including baseline as a covariate, treatment group and baseline weight category as factors in the model

[2] A logistic regression analysis with treatment and baseline weight category as factors.

ANCOVA = analysis of covariance; CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; PSSI = Psoriasis Scalp Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source**: PSSI total score**: CSR RHAZ, Table RHAZ.14.151 (Page 1, 24, 25, 26, 49 and 50 of 50); **PSSI (0):** CSR RHAZ, Table RHAZ.14.154 (Page 6 and 12 of 12)

Psoriasis with palmoplantar involvement at week 12 and 60

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving palmoplantar psoriasis as measured by Palmoplantar Psoriasis Severity Index (PPASI) scores (p<0.001; Table 31). The LSM changes from baseline in the PPASI scores at week 12 among patients who had palmoplantar involvement at baseline were -5.39, -5.34, and 0.57 for the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, and placebo groups, respectively. In addition, palmoplantar clearance rates (PPASI 100) at week 12 were significantly greater for the ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W groups compared with the placebo group (p<0.001) (Table 31).[21]

Table 31: UNCOVER-1: PPASI score mean change from baseline at week 12 and palmoplantar clearance rates (PPASI=100) - LOCF; ANCOVA (ITT population with baseline palmoplantar involvement)[21]

Endpoint	Placebo (N=133)	IXE80Q4W (N=131)	IXE80Q2W (N=140)	Total IXE (N=271)	Total (N=404)
Number of patients	133	131	140	271	404
Baseline Mean (SD)	9.65 (11.54)	8.49 (11.80)	7.93 (10.29)	8.20 (11.03)	8.68 (11.21)
Observed Mean at week 12 (SD)	-1.66 (7.92)	-6.68 (8.36)	-5.94 (8.56)	-6.29 (8.46)	-4.77 (8.56)
Endpoint (LSM) Change (SE)	0.57 (0.64)	-5.34 (0.63)	-5.39 (0.59)	-	-
LSM Difference (95% CI)	-	-5.91 (-7.38, -4.44)	-5.96 (-7.41, -4.51)	-	-
p-value[1]	-	<0.001	<0.001	-	-
Patients with PPASI 100 (NRI)					
n (%)	27 (20.3)	86 (65.6)	98 (70.0)	184 (67.9)	211 (52.2)
OR[2] (95%CI)[2] p-value[2]	-	7.68 (4.39, 13.43) <0.001	9.72 (5.52, 17.11) <0.001	-	-

[1] The LS Mean, SE, 95% CI and p-values are presented for each treatment versus placebo comparison at each visit and use an analysis of covariance model including treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline PPASI value in the model

[2] A logistic regression analysis with treatment, geographic region, previous non-biologic systemic therapy, and baseline weight category included as factors

ANCOVA = analysis of covariance; CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; PPASI = Palmoplantar Psoriasis Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source**: PPASI total score**: CSR RHAZ, Table RHAZ.14.113 (Page 1, 12 and 13 of 13); **PPASI (100):** CSR RHAZ, Table RHAZ.14.109 (Page 9 of 9)

At week 60 statistically significant improvements were observed in PPASI scores for patients in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W treatment group compared with the ixekizumab 80 mg Q2W/placebo group (p=0.015; Table 32). The LSM changes from baseline in PPASI scores at week 60 were -6.20 in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W treatment group compared with -2.58 in the ixekizumab 80 mg Q2W/placebo group (Table 32).

Table 32: UNCOVER-1: PPASI score mean change from baseline at week 60 and palmoplantar clearance rates (PPASI=100) - LOCF; ANCOVA (Maintenance Dosing Period Primary Population with baseline scalp Involvement)[21]

Endpoint	IXE80Q4W /PBO (N=35)	IXE80Q4W/ IXE80Q4W (N=31)	IXE80Q2W/ PBO (N=37)	IXE80Q2W/ IXE80Q4W (N=33)	IXE/PBO (N=72)	IXE/ IXE80Q4W (N=64)
Number of patients	35	31	37	33	72	64
Baseline Mean (SD)	9.45 (12.12)	7.53 (11.42)	7.82 (11.79)	4.71 (4.69)	8.61 (11.90)	6.08 (8.68)
Observed Mean at week 60 (SD)	0.00 (0.00)	1.33 (6.04)	0.13 (0.23)	0.14 (0.64)	0.05 (0.14)	0.76 (4.38)
Endpoint (LSM) Change (SE)	-5.81 (1.07)	-5.88 (1.15)	-2.58 (1.05)	-6.20 (1.09)	-4.17 (0.77)	-6.07 (0.81)
LSM Difference (95% CI)	-	-0.06 (-3.06, 2.93)	-	-3.62 (-6.54, -0.71)	-	-1.90 (-4.00, 0.20)
p-value[1]	-	0.967	-	0.015	-	0.076
Patients with PPASI 100 (NRI)						
n (%)	5 (14.3)	22 (71.0)	2 (5.4)	21 (63.6)	7 (9.7)	43 (67.2)
OR (95%CI) p-value[2]	-	15.09 (4.30, 52.94) <0.001	-	42.96 (8.36, 220.77) <0.001	-	23.06 (8.70, 61.12) <0.001

[1] The LS Mean, SE, 95% CI and p-values are presented for each treatment comparison at each visit and use an analysis of covariance model including baseline as a covariate, treatment group and baseline weight category as factors in the model

[2] A logistic regression analysis with treatment and baseline weight category as factors

ANCOVA = analysis of covariance; CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; PPASI = Palmoplantar Psoriasis Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source**: PPASI total score**: CSR RHAZ, Table RHAZ.14.164 (Page 1, 29, 30, 32, 60 and 61 of 62); **PPASI (100):** CSR RHAZ, Table RHAZ.14.160 (Page 24 and 48 of 48)

4.7.2 UNCOVER-2

Co-primary objectives: sPGA (0,1) and PASI 75 at week 12

The two co-primary objectives of the UNCOVER-2 study were both met. Both ixekizumab treatment groups (80 mg Q2W and 80 mg Q4W) were statistically significantly superior to placebo at week 12 as measured by the proportions of patients achieving sPGA (0,1) and PASI 75 ($p<0.001$ for all comparisons).[16]

At week 12, the proportions of patients who achieved sPGA (0,1) with at least a 2-point improvement from baseline (80 mg Q2W: 83.2% and 80 mg Q4W: 72.9%) were significantly higher than the percentages of patients treated with etanercept or placebo (36.0% and 2.4%, respectively). Similar results were also observed for PASI 75 at week 12. The proportions of patients who achieved PASI 75 at week 12 were 89.7% and 77.5% in the ixekizumab 80 mg Q2W and Q4W groups, respectively, compared with 41.6% in the etanercept group and 2.4% from the placebo group (p<0.001 for all comparisons; Table 33 and Figure 15).[16]

Table 33: UNCOVER-2: sPGA (0,1) and PASI 75 response rates at week 12 – NRI (ITT population)[16,84]

Endpoint	PBO (N=168)	ETN (N=358)	IXE80Q4W (N=347)	IXE80Q2W (N=351)	Total IXE (N=698)	Total (N=1,224)
sPGA (0,1), n (%)	4 (2.4)	129 (36.0)	253 (72.9)	292 (83.2)	545 (78.1)	678 (55.4)
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	27.58 (9.40, 80.98) <0.001	120.29 (39.95, 362.22) <0.001	282.24 (76.03, 1047.71) <0.001	174.63 (57.78, 527.84) <0.001	
OR vs ETN[2] (95% CI) p-value[1]	-	-	5.37 (3.82, 7.56) <0.001	10.70 (7.23, 15.85) <0.001	7.37 (5.44, 9.97) <0.001	
PASI 75, n (%)	4 (2.4)	149 (41.6)	269 (77.5)	315 (89.7)	584 (83.7)	737 (60.2)
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	30.73 (10.83, 87.16) <0.001	160.50 (51.33, 501.87) <0.001	997.29 (173.11, 5,745.5) <0.001	289.78 (88.85, 945.09) <0.001	
OR vs ETN[2] (95% CI) p-value[1]	-	-	5.05 (3.60, 7.09) <0.001	13.28 (8.66, 20.34) <0.001	7.63 (5.64, 10.31) <0.001	

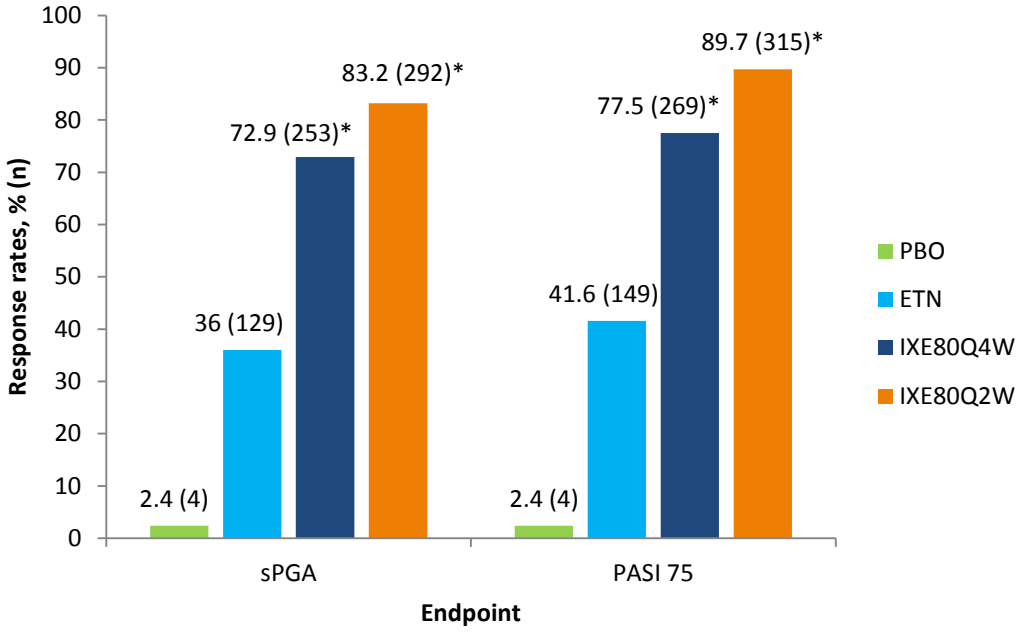
[1] p-value from CMH test stratified by pooled centre

[2] OR from the Mantel-Haenszel estimate adjusted by pooled centre

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ETN = etanercept; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; NNT = number needed to treat; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

Source: RHBA Clinical HTA toolkit, Table 3.3

Figure 15: UNCOVER-2: sPGA and PASI 75 response rates at week 12 – NRI (ITT population)[16]



*p<0.001 versus etanercept and placebo.

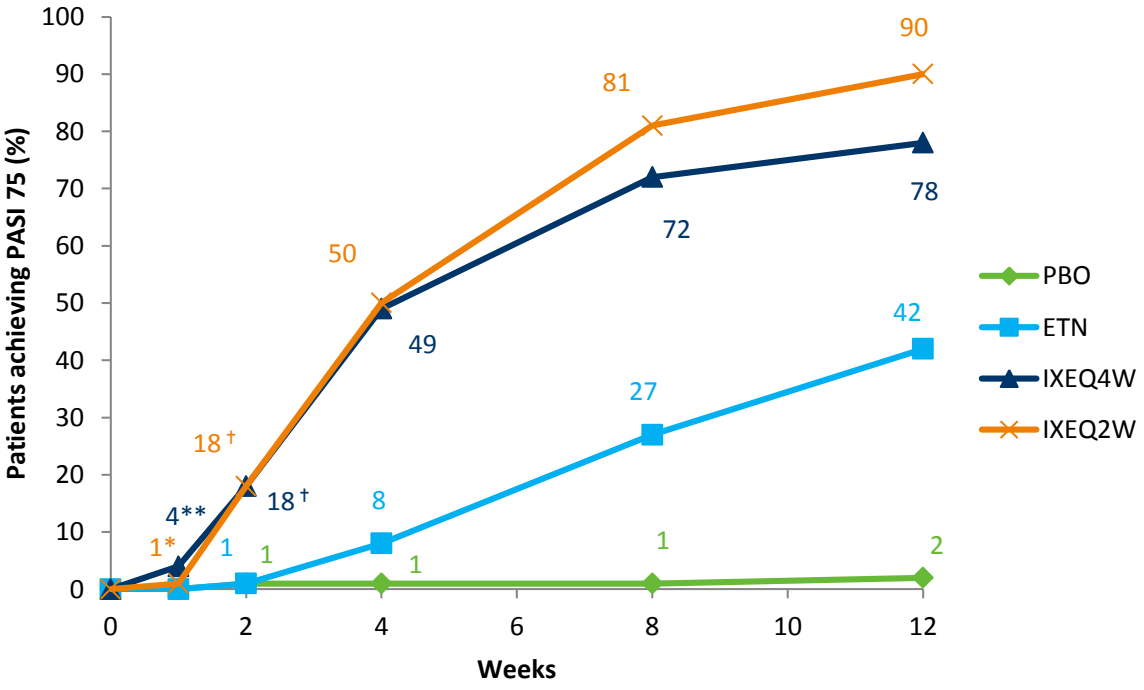
ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

At week 12 (using the fixed-margin approach for the ITT population), ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W were shown to be:[16]

- non-inferior to etanercept in terms of the percentages of patients who achieved sPGA (0,1) and PASI 75 at week 12 (lower bounds of the 97.5% CI for the difference in percentages of responders on 80 mg Q2W minus etanercept and 80 mg Q4W minus etanercept were greater than the pre-specified non-inferiority margin of -12.0%).
- superior to etanercept, in terms of the percentages of patients who achieved sPGA (0,1) and PASI 75 at week 12 (lower bounds of the 97.5% CI for the difference in percentages of responders on 80 mg Q2W minus etanercept and 80 mg Q4W minus etanercept were greater than the pre-specified superiority threshold of 0%).

Greater proportions of patients achieved PASI 75 as early as week 1 for both ixekizumab groups compared with etanercept (p=0.001 [IXE80Q4W] and p=0.022 [IXE80Q2W]) and by week 2 for both ixekizumab groups compared with placebo and etanercept (p<0.0001). By week 4, approximately 50% of all patients given ixekizumab achieved PASI 75 (Figure 16).[16]

Figure 16: UNCOVER-2: Proportion of patients achieving PASI 75 from baseline through to week 12 – NRI (ITT population)[16]



*p<0.05 versus etanercept.

** p<0.001 versus etanercept

† p<0.0001 versus etanercept and placebo

ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks;

Major secondary endpoints

sPGA (0), PASI 90 and PASI 100 at week 12

At week 12, both ixekizumab treatment groups were statistically significantly superior to placebo as measured by the proportions of patients achieving sPGA (0), PASI 90, and PASI 100 (p<0.001 for all comparisons; Table 34 and Figure 17).[16]

Table 34: UNCOVER-2: sPGA 0, PASI 90, and PASI 100 results at week 12 – NRI (ITT population)[16,84]

Endpoint	PBO (N=168)	ETN (N=358)	IXE80Q4W (N=347)	IXE80Q2W (N=351)	Total IXE (N=698)	Total (N=1,224)
sPGA (0), n (%)	1 (0.6)	21 (5.9)	112 (32.3)	147 (41.9)	259 (37.1)	281 (23.0)
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	10.87 (1.42, 83.08) 0.005	86.49 (11.60, 644.87) <0.001	118.34 (17.18, 815.05) <0.001	101.76 (14.37, 720.78) <0.001	
OR vs ETN[2] (95% CI) p-value[1]	-	-	8.28 (4.95, 13.85) <0.001	14.72 (8.57, 25.29) <0.001	11.03 (6.73, 18.08) <0.001	
PASI 90, n (%)	1 (0.6)	67 (18.7)	207 (59.7)	248 (70.7)	455 (65.2)	523 (42.7)
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	40.31 (5.59, 290.89) <0.001	223.76 (31.67,1,581.01) <0.001	434.42 (56.60, 3,334.3) <0.001	310.70 (43.07,2,241.41) <0.001	
OR vs ETN[2] (95% CI) p-value[1]	-	-	6.55 (4.61, 9.31) <0.001	12.18 (8,28, 17.91) <0.001	8.78 (6.36, 12.12) <0.001	
PASI 100, n (%)	1 (0.6)	19 (5.3)	107 (30.8)	142 (40.5)	249 (35.7)	269 (22.0)
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	9.89 (1.28, 76.15) 0.008	75.44 (10.49, 542.60) <0.001	113.79 (16.20, 799.34) <0.001	93.49 (13.28, 658.20)	
OR vs ETN[2] (95% CI) p-value[1]	-	-	8.46 (4.97, 14.42) <0.001	14.27 (8.25, 24.68) <0.001	11.06 (6.65, 18.40) <0.001	

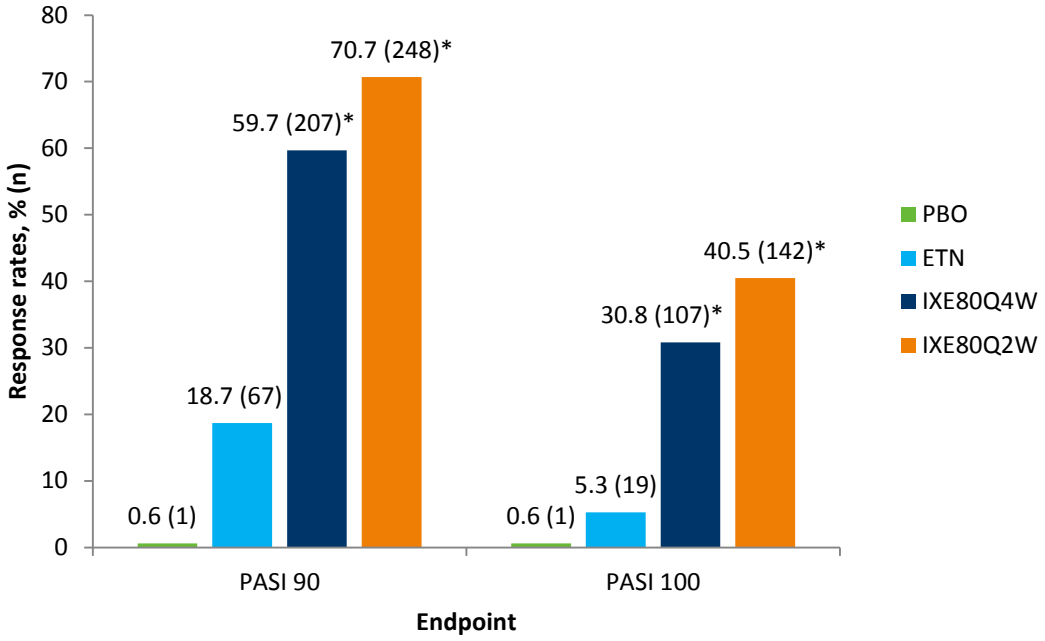
[1] p-value from CMH test stratified by pooled centre

[2] OR from the Mantel-Haenszel estimate adjusted by pooled centre

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ETN = etanercept; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

Source: RHBA Clinical HTA toolkit, Table 3.4

Figure 17: UNCOVER-2: PASI 90 and PASI 100 response rates at week 12 – NRI (ITT population)[16]



*p<0.001 versus etanercept and placebo.

ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

Maintenance of sPGA (0,1) to week 60

At week 60, maintenance treatment with ixekizumab Q4W was statistically significantly superior to placebo in the proportion of patients who achieved or maintained sPGA (0,1) (p<0.001; Table 35). At week 60, 82.4% and 7.4% of patients from the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups, respectively, maintained sPGA (0,1) (Table 35).[22,84]

Table 35: UNCOVER-2: Maintenance of Response, Results of sPGA (0,1) response at week 60 - NRI (Maintenance Dosing Period Primary Population)[22,84]

	IXE80Q4W /PBO (N=82)	IXE80Q4W/ IXE80Q4W (N=85)	IXE80Q2W/ PBO (N=94)	IXE80Q2W/ IXE80Q4W (N=102)	IXE/PBO (N=176)	IXE/ IXE80Q4W (N=187)
sPGA (0,1), n (%)	4 (4.9)	56 (65.9)	7 (7.4)	84 (82.4)	11 (6.3)	140 (74.9)
OR[1] (95% CI)[1] p-value[1]	-	37.66 (12.53, 113.16) <0.001	-	58.00 (23.04, 145.99) <0.001	-	44.67 (22.32, 89.41) <0.001

[1] OR and p-value from logistic regression analysis with treatment in the model

; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = Placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

Source: RHBA Clinical HTA toolkit, Table 3.12

Other secondary outcomes

PASI 75, PASI 90 and PASI 100 at week 60

At week 60, maintenance treatment with ixekizumab Q4W was statistically significantly superior to placebo in the proportion of patients who achieved or maintained PASI 75, PASI 90 and PASI 100 (p<0.001; Table 36). At week 60, 63.7% and 2.1% of patients from the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups, respectively, achieved or maintained PASI 100 (Table 36). PASI 100 responses were shown to improve over time. In addition, significant proportion of patients achieved or maintained high-level responses (PASI 90) during maintenance period. At week 60, 81.4% and 4.3% of patients from the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups, respectively, achieved or maintained PASI 90 (Table 36).[84]

Table 36: UNCOVER-2: Maintenance of Response, results of PASI 75, 90 and 100 response at week 60 - NRI (Maintenance Dosing Period Primary Population)[84]

Endpoint	IXE80Q4W /PBO (N=109)	IXE80Q4W/ IXE80Q4W (N=110)	IXE80Q2W/ PBO (N=117)	IXE80Q2W/ IXE80Q4W (N=119)	IXE/PBO (N=226)	IXE/ IXE80Q4W (N=229)
PASI 75, n (%)	6 (7.3)	60 (70.6)	8 (8.5)	91 (89.2)	14 (8.0)	151 (80.7)
OR[1] (95% CI)[1] p-value[1]	-	30.40 (11.72, 78.84) <0.001	-	88.93 (34.14, 231.61) <0.001	-	48.53 (25.19, 93.52) <0.001
PASI 90, n (%)	5 (6.1)	54 (63.5)	4 (4.3)	83 (81.4)	9 (5.1)	137 (73.3)
OR[1] (95% CI)[1] p-value[1]	-	26.83 (9.80, 73.40) <0.001	-	98.29 (32.11, 300.85) <0.001	-	50.84 (24.14, 107.07) <0.001
PASI 100, n (%)	1 (1.2)	40 (47.1)	2 (2.1)	65 (63.7)	3 (1.7)	105 (56.1)
OR[1] (95% CI)[1] p-value[2]	-	72.00 (9.58, 541.40) <0.001	-	80.81 (18.81, 347.23) <0.001	-	73.81 (22.75, 239.49) <0.001

[1] OR and p-value from logistic regression analysis with treatment in the model

CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the Maintenance Dosing Period Primary Population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

Source: RHBA Clinical HTA toolkit, Table 3.12

4.7.3 UNCOVER-3

Co-primary objectives: sPGA (0,1) and PASI 75 at week 12

The two co-primary objectives of the UNCOVER-3 study were both met. Both ixekizumab treatment groups (80 mg Q2W and 80 mg Q4W) were statistically significantly superior to placebo at week 12 as measured by the proportions of patients achieving sPGA (0,1) and PASI 75 ($p<0.001$ for all comparisons).[16]

At week 12, the proportions of patients who achieved sPGA (0,1) with at least a 2-point improvement from baseline (80 mg Q2W: 80.5% and 80 mg Q4W: 75.4%) were significantly higher than the percentages of patients treated with etanercept or placebo (41.6% and 6.7%, respectively). Similar results were also observed for PASI 75 at week 12. The proportions of patients who achieved PASI 75 at week 12 were 87.3% and 84.2% in the ixekizumab 80 mg Q2W and Q4W groups, respectively, compared with 53.4% in the etanercept group and 7.3% from the placebo group ($p<0.001$ for all comparisons) (Table 37 and Figure 18).[16]

Table 37: UNCOVER-3: sPGA (0,1) and PASI 75 results at week 12 – NRI (ITT population)[16,85]

Endpoint	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (N=771)	Total (N=1,346)
sPGA (0,1), n (%)	13 (6.7)	159 (41.6)	291 (75.4)	310 (80.5)	601 (78.0)	773 (57.4)
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	11.30 (6.01, 21.25) <0.001	40.84 (21.10, 79.03) <0.001	50.47 (26.54, 95.98) <0.001	45.53 (24.75, 83.75) <0.001	
OR vs ETN[2] (95% CI) p-value[1]	-	-	4.80 (3.46, 6.67) <0.001	6.47 (4.55, 9.20) <0.001	5.55 (4.17, 7.38) <0.001	
PASI 75, n (%)	14 (7.3)	204 (53.4)	325 (84.2)	336 (87.3)	661 (85.7)	879 (65.3)
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	13.71 (7.61, 24.72) <0.001	68.95 (34.53, 137.68) <0.001	72.29 (36.11, 144.73) <0.001	70.51 (37.83, 131.44) <0.001	

Endpoint	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (N=771)	Total (N=1,346)
OR vs ETN[2] (95% CI) p-value[1]	-	-	4.91 (3.46, 6.98) <0.001	6.46 (4.42, 9.45) <0.001	5.59 (4.15, 7.52) <0.001	

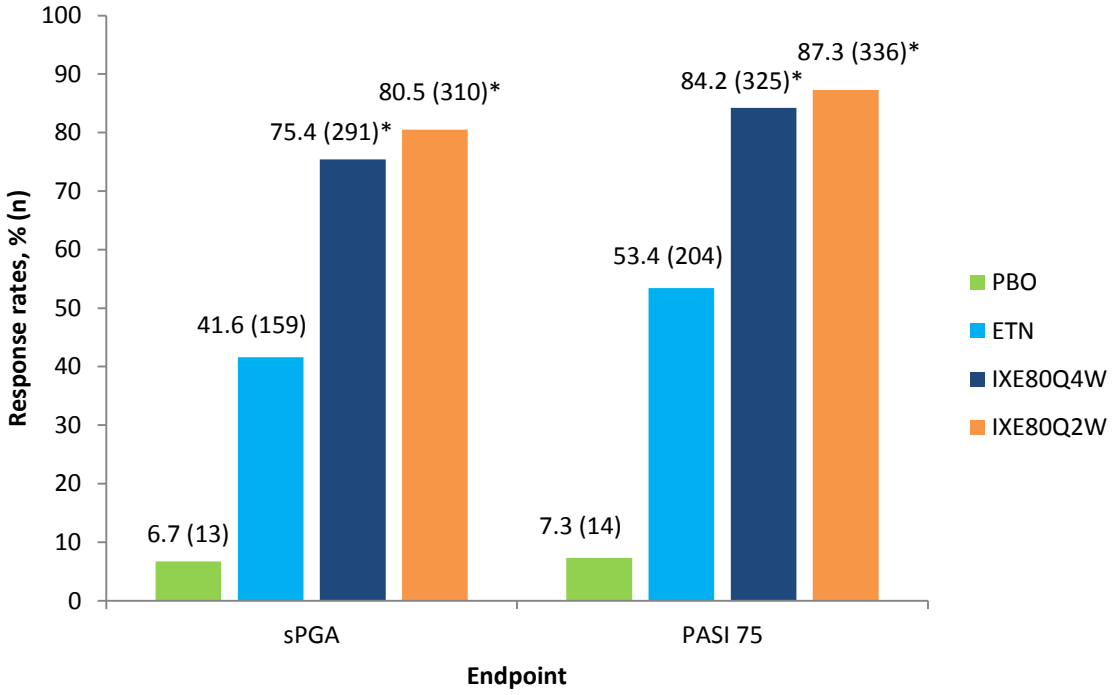
[1] p-value from CMH test stratified by pooled centre

[2] OR from the Mantel-Haenszel estimate adjusted by pooled centre

CI = confidence interval; CMH = Chochran-Mantel-Haenszel; ETN = etanercept; IXE = ixekizumab; IXE80= ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

Source: RHBC Clinical HTA toolkit, Table 3.3

Figure 18: UNCOVER-3: sPGA and PASI 75 response rates at week 12 – NRI (ITT population)[16]



*p<0.001 versus etanercept and placebo.

ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

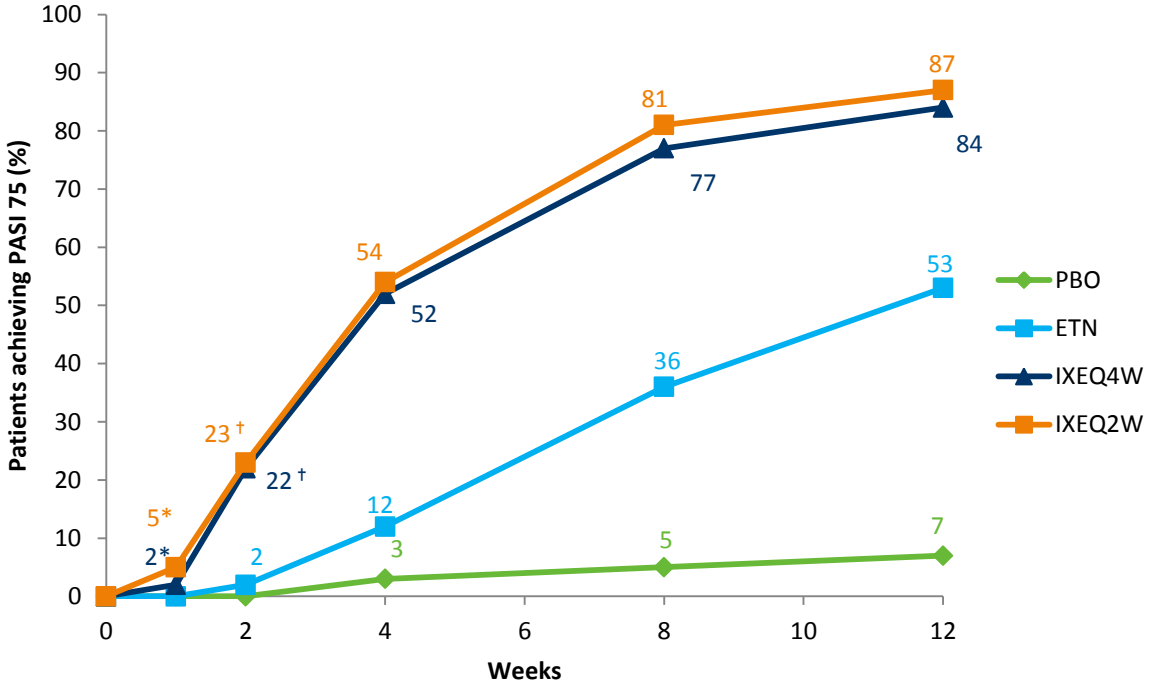
At week 12 (using the fixed-margin approach for the ITT population), ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W were shown to be:[16]

- non-inferior to etanercept in terms of the percentages of patients who achieved sPGA (0,1) and PASI 75 at week 12 (lower bounds of the 97.5% CI for the difference in percentages of responders on 80 mg Q2W minus etanercept and 80 mg Q4W minus etanercept were greater than the pre-specified non-inferiority margin of -12.0%).

- superior to etanercept, in terms of the percentages of patients who achieved sPGA (0,1) and PASI 75 at week 12 (lower bounds of the 97.5% CI for the difference in percentages of responders on 80 mg Q2W minus etanercept and 80 mg Q4W minus etanercept were greater than the pre-specified superiority threshold of 0%).

Greater proportions of patients achieved PASI 75 as early as week 1 for both ixekizumab groups compared with patients receiving placebo or etanercept (p<0.05). By week 4, approximately 50% of all patients given ixekizumab achieved PASI 75 (Figure 19).[16]

Figure 19: UNCOVER-3: Proportion of patients achieving PASI 75 from baseline through to week 12 (ITT population)[16]



*p<0.05 versus etanercept.

† p<0.0001 versus etanercept and placebo.

ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

Major secondary endpoints

Secondary endpoints: sPGA (0), PASI 90 and PASI 100

At week 12, both ixekizumab treatment groups were statistically significantly superior to placebo as measured by the proportions of patients achieving sPGA (0), PASI 90, and PASI 100 (p<0.001 for all comparisons; Table 38 and Figure 20).[16]

Table 38: UNCOVER-3: sPGA 0, PASI 90, and PASI 100 results at week 12 – NRI (ITT population)[16,85]

Endpoint	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (N=771)	Total (N=1,346)
sPGA (0), n (%)	0 (0.0)	33 (8.6)	139 (36.0)	155 (40.3)	294 (38.1)	327 (24.3)
p-value vs PBO[1] p-value vs ETN[1]	- -	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[2] (95% CI) p-value[1]	-	N/A	N/A	N/A	N/A	-
OR vs ETN[2] (95% CI) p-value[1]	-	-	6.23 (4.08, 9.52) <0.001	7.98 (5.16, 12.33) <0.001	7.05 (4.73, 10.50 <0.001)	-
PASI 90, n (%)	6 (3.1)	98 (25.7)	252 (65.3)	262 (68.1)	514 (66.7)	618 (45.9)
p-value vs PBO[1] p-value vs ETN[1]	- -	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	-
OR vs PBO[2] (95% CI) p-value[1]	-	12.25 (5.07, 29.61) <0.001	81.81 (29.56, 226.42) <0.001	72.49 (28.39, 185.09) <0.001	77.75 (30.80, 196.23) <0.001	-
OR vs ETN[2] (95% CI) p-value[1]	-	-	5.68 (4.11, 7.86) <0.001	6.56 (4.70, 9.14) <0.001	6.13 (4.60, 8.17) <0.001	-
PASI 100, n (%)	0 (0.0)	28 (7.3)	135 (35.0)	145 (37.7)	280 (36.3)	308 (22.9)
p-value vs PBO[1] p-value vs ETN[1]	- -	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	-
OR vs PBO[2] (95% CI) p-value[1]	-	N/A	N/A	N/A	N/A	-
OR vs ETN[2] (95% CI) p-value[1]	-	-	6.96 (4.46, 10.87) <0.001	8.48 (5.35, 13.45) <0.001	7.67 (5.02, 11.72) <0.001	-

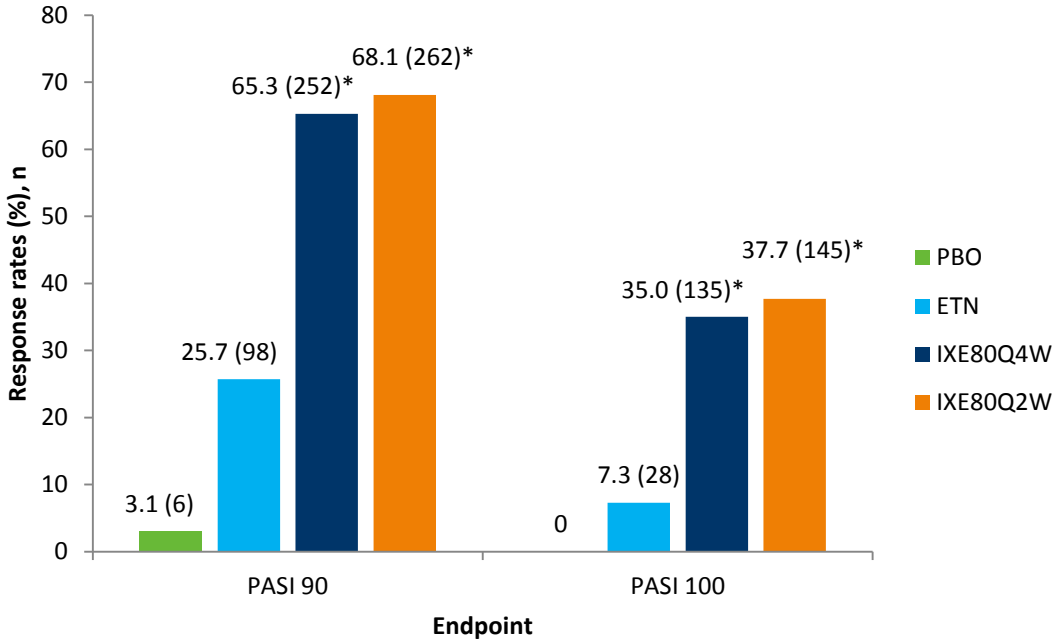
[1] p-value from CMH test stratified by pooled centre

[2] OR from the Mantel-Haenszel estimate adjusted by pooled centre

CI = confidence interval; CMH = Chochran-Mantel-Haenszel; ETN = etanercept; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

Source: RHBC Clinical HTA toolkit, Table 3.4

Figure 20: UNCOVER-3: PASI 90 and PASI 100 response rates at week 12 – NRI (ITT population)[16]



*p<0.001 *p<0.001 versus etanercept and placebo.

ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

Itch NRS at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving patients' itch severity as measured by the Itch NRS (Table 39). The proportions of patients who had Itch NRS score ≥4 at baseline and achieved a ≥4-point reduction from baseline at week 12 were 82.5% for the ixekizumab 80 mg Q2W group, 79.9% for the ixekizumab 80 mg Q4W group, 64.1% for the etanercept group and 20.9% for the placebo group.[16]

Table 39: UNCOVER-3: Percentage of Patients with ≥4 Point Reduction from Baseline at week 12 – NRI (ITT population)[16,85]

Endpoint	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (N=771)	Total (N=1,346)
Itch Severity – Patients with >4 point reduction from baseline (NRI)						
Patients with Itch NRS Score ≥4 at Baseline	N=158	N=312	N=313	N=320	N=633	N=1,103
Patients with ≥4 point reduction from baseline (NRI), n (%)	33 (20.9)	200 (64.1)	250 (79.9)	264 (82.5)	514 (81.2)	747 (67.7)
p-value vs PBO[2] p-value vs ETN[2]	- -	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	
OR vs PBO[3] (95% CI) p-value[2]	-	7.15 (4.47, 11.44) <0.001	14.58 (8.89, 23.91) <0.001	16.70 (10.04, 27.80) <0.001	15.39 (9.87, 23.99) <0.001	
OR vs ETN[3] (95% CI) p-value[2]	-	-	2.27 (1.58, 3.28) <0.001	2.72 (1.86, 3.97) <0.001		

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus PBO comparison at each visit and use an ANCOVA model including treatment, pooled centre, and baseline Itch NRS value in the model

[2] p-value from CMH test stratified by pooled centre

[3] OR from the Mantel-Haenszel estimate adjusted by pooled centre

ANCOVA = analysis of covariance; CI = confidence interval; CMH = Chochran-Mantel-Haenszel; ETN = etanercept; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source: RHBC Clinical HTA toolkit, Table 3.5

DLQI at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo and etanercept at improving patients' HRQoL as measured by the DLQI (Table 40). The least squares mean (LSM) changes from baseline in the DLQI total scores at week 12 were -10.0, -9.6, -8.1 and -1.5 in the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, etanercept and placebo groups, respectively (Table 40).[16,23,85]

Table 40: UNCOVER-3: DLQI Total Score Mean Change from Baseline (LOCF; ANCOVA) and Percentage of Patients Achieving a DLQI (0,1) or (0) at week 12 – NRI (ITT population)[16,23,85]

Endpoint	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (n=771)	Total (N=1,346)
Number of patients	193	382	382	383	765	1,340
Baseline Mean (SD)	12.7 (7.00)	11.5 (6.84)	11.9 (6.97)	12.4 (6.93)	12.1 (6.95)	12.0 (6.93)
Observed Mean at week 12 (SD)	10.5 (7.23)	3.8 (4.75)	2.4 (4.25)	2.0 (3.30)	2.2 (3.81)	3.8 (5.48)
Endpoint (LSM) Change (SE)	-1.5 (0.32)	-8.1 (0.23)	-9.6 (0.23)	-10.0 (0.23)	-	-
LSM Difference (95% CI)	-	-6.5 (-7.3, -5.8)	-8.0 (-8.8, -7.3)	-8.5 (-9.2, -7.7)	-	-
p-value vs PBO[1]	-	<0.001	<0.001	<0.001	-	-
p-value vs ETN[1]	-	-	<0.001	<0.001		
Patients with DLQI (0,1) (NRI)						
n (%)	15 (7.8)	167 (43.7)	246 (63.7)	249 (64.7)	495 (64.2)	677 (50.3)
p-value vs PBO[2]	-	<0.001	<0.001	<0.001	-	-
p-value vs ETN[2]	-	-	<0.001	<0.001		
OR vs PBO[3] (95% CI) p-value[2]	-	10.51 (5.75, 19.20) <0.001	21.05 (11.58, 38.27) <0.001	21.00 (14.1, 27.9) <0.001	21.28 (12.11, 37.40) <0.001	-
OR vs ETN[3] (95% CI) p-value[2]	-	-	2.32 (1.72, 3.12) <0.001	2.38 (1.77, 3.20) <0.001	2.36 (1.83, 3.04) <0.001	-
Patients with DLQI (0) (NRI)						
n (%)	5 (2.6)	79 (20.7)	157 (40.7)	163 (42.3)	320 (41.5)	404 (30.0)
p-value vs PBO[2]	-	<0.001	<0.001	<0.001	-	
p-value vs ETN[2]	-	-	<0.001	<0.001		
OR vs PBO[3] (95% CI) p-value[2]	-	10.04 (4.03, 25.03) <0.001	25.60 (10.21, 64.20) <0.001	35.76 (13.21, 96.82) <0.001	29.88 (11.71, 76.21) <0.001	

Endpoint	PBO (N=193)	ETN (N=382)	IXE80Q4W (N=386)	IXE80Q2W (N=385)	Total IXE (n=771)	Total (N=1,346)
OR vs ETN[3] (95% CI) p-value[2]	-	-	2.78 (1.99, 3.88) <0.001	2.83 (2.04, 3.92) <0.001	2.82 (2.10, 3.78) <0.001	

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus placebo comparison at each visit and use an ANCOVA model including treatment, pooled centre, and baseline DLQI value in the model

[2] p-value from CMH test stratified by pooled centre

[3] OR from the Mantel-Haenszel estimate adjusted by pooled centre

ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source: RHBC Clinical HTA toolkit, Table 3.6

Nail psoriasis at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving fingernail psoriasis as measured by NAPSI scores. The LSM changes from baseline in the NAPSI scores at week 12 among patients who had fingernail involvement at baseline were -10.41, -9.84, -6.64 and 2.30 for the ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, etanercept and placebo groups, respectively (Table 41).[23] In addition, nail clearance rates (NAPSI=0) at week 12 were significantly greater for ixekizumab treatments 80 mg Q2W and ixekizumab 80 mg Q4W, than placebo (p<0.001).[23]

Table 41: UNCOVER-3: NAPSI score mean change from baseline at week 12 and nail clearance rates (NAPSI=0) - LOCF; ANCOVA (ITT population with baseline fingernail involvement)[23]

Endpoint	PBO (N=116)	ETN (N=236)	IXE80Q4W (N=228)	IXE80Q2W (N=229)	Total IXE (N=457)	Total (N=809)
Number of patients	115	236	227	229	456	807
Baseline Mean (SD)	25.47 (19.63)	25.09 (20.02)	26.19 (20.16)	26.14 (20.09)	26.17 (20.10)	25.75 (19.99)
Observed Mean at week 12 (SD)	27.19 (21.08)	19.00 (17.89)	16.48 (16.74)	15.98 (15.43)	16.23 (16.08)	18.62 (17.79)
Endpoint (LSM) Change (SE)	1.12 (0.98)	-6.64 (0.68)	-9.84 (0.70)	-10.41 (0.70)	-	-
LSM Difference (95% CI)[1]	-	-7.76 (-10.06, -5.45)	-10.96 (-13.28, -8.64)	-11.53 (-13.84, -9.21)	-	-
p-value vs PBO[1] p-value vs ETN[1]	-	<0.001 -	<0.001 <0.0001	<0.001 <0.001	-	-

Endpoint	PBO (N=116)	ETN (N=236)	IXE80Q4W (N=228)	IXE80Q2W (N=229)	Total IXE (N=457)	Total (N=809)
Patients with NAPSI (0) (NRI)						
n (%)	5 (4.3)	24 (10.2)	45 (19.7)	40 (17.5)	85 (18.6)	114 (14.1)
p-value vs PBO[2]	-	0.099	<0.001	<0.001	-	-
p-value vs ETN[2]	-	-	0.004	0.009	-	-

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus placebo comparison at each visit and use an ANCOVA model including treatment, pooled centre, and baseline NAPSI value in the model

[2] Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre

ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; NAPSI = Nail Psoriasis Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source**: NAPSI total score**: CSR RHBC, Table RHBC.14.60 (Page 1, 9 and 10 of 11); **NAPSI (0):** CSR RHBC, Table RHBC.14.62 (Page 3 of 3)

Other secondary outcomes

Psoriasis with scalp involvement at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to etanercept and placebo at improving scalp psoriasis as measured by PSSI scores (p<0.001; Table 42). The LSM changes from baseline in the PSSI scores at week 12 among patients who had scalp involvement at baseline were -18.1, -18.6, -15.6 and -5.0 for patients who received treatment with ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, etanercept and placebo, respectively (Table 42). In addition, scalp clearance rates (PSSI=0) at week 12 were significantly greater for ixekizumab treatments 80 mg Q2W and ixekizumab 80 mg Q4W groups compared with the etanercept and placebo groups (p<0.001) (Table 42).[23]

Table 42: UNCOVER-3: PSSI score mean change from baseline at week 12 and scalp clearance rates (PSSI=0) - LOCF; ANCOVA (ITT population with baseline scalp involvement)[23]

Endpoint	Placebo (N=176)	ETN (N=348)	IXE80Q4W (N=349)	IXE80Q2W (N=349)	Total IXE (N=698)	Total (N=1,222)
Number of patients	176	348	349	349	698	1,222
Baseline Mean (SD)	18.4 (12.85)	19.8 (13.49)	19.5 (14.40)	20.0 (13.64)	19.8 (14.02)	19.6 (13.70)
Observed Mean at week 12 (SD)	14.1 (12.13)	3.8 (7.35)	1.5 (4.23)	0.9 (3.38)	1.2 (3.84)	3.8 (7.98)
Endpoint (LSM) Change (SE)	-5.0 (0.51)	-15.6 (0.37)	-18.1 (0.37)	-18.6 (0.36)	-	-
LSM Difference (95% CI)	-	-10.6 (-11.8, -9.4)	-13.1 (-14.3, -11.9)	-13.6 (-14.9, -12.4)	-	-
p-value vs PBO[1]	-	<0.001	<0.001	<0.001	-	-

Endpoint	Placebo (N=176)	ETN (N=348)	IXE80Q4W (N=349)	IXE80Q2W (N=349)	Total IXE (N=698)	Total (N=1,222)
p-value vs ETN[1]		-	<0.001	<0.001		
Patients with PSSI (0) (NRI)						
n (%)	16 (9.1)	178 (51.1)	253 (72.5)	264 (75.6)	517 (74.1)	711 (58.2)
p-value vs PBO[2] p-value vs ETN[2]	-	<0.001 -	<0.001 <0.001	<0.001 <0.001	-	-

[1] The LSM, SE, 95% CI, and p-values are presented for each treatment versus placebo comparison at each visit and use an ANCOVA model including treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline PSSI value in the model

[2] Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre

ANCOVA = analysis of covariance; CI = confidence interval; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; PSSI = Psoriasis Scalp Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source: **PSSI total score**: CSR RHBC, Table RHBC.14.67 (Page 1, 9 and 10 of 11); **PSSI (0):** CSR RHBC, Table RHBC.14.69 (Page 3 of 3)

Psoriasis with palmoplantar involvement at week 12

At week 12, both dose regimens of ixekizumab were statistically significantly superior to placebo at improving palmoplantar psoriasis as measured by PPASI scores (p<0.001; Table 43). In addition, numerical improvements in PPASI score were observed at week 12 for both ixekizumab groups compared with etanercept, however these differences were non-significant (Table 43).[23]

Table 43: UNCOVER-3: PPASI score mean change from baseline at week 12 and palmoplantar clearance rates (PPASI=100) - LOCF; ANCOVA (ITT population with baseline palmoplantar involvement)[23]

Endpoint	Placebo (N=54)	ETN (N=95)	IXE80Q4W (N=87)	IXE80Q2W (N=96)	Total IXE (N=183)	Total (N=332)
Number of patients	54	95	87	96	183	331
Baseline Mean (SD)	10.99 (13.39)	7.35 (9.83)	10.21 (12.88)	9.90 (11.34)	10.05 (12.06)	9.43 (11.75)
Observed Mean at week 12 (SD)	7.90 (14.02)	3.24 (8.16)	2.01 (5.24)	2.03 (5.29)	2.02 (5.25)	3.32 (8.34)
Endpoint (LSM) Change (SE)	-2.55 (1.02)	-6.13 (0.78)	-7.65 (0.84)	-7.64 (0.80)	-	-
LSM Difference (95% CI)	-	-3.58 (-6.10, -1.05)	-5.10 (-7.63, -2.57)	-5.09 (-7.61, -2.57)	-	-
p-value vs PBO[1] p-value vs ETN[1]	-	0.006 -	<0.001 0.177	<0.001 0.166	-	-

Endpoint	Placebo (N=54)	ETN (N=95)	IXE80Q4W (N=87)	IXE80Q2W (N=96)	Total IXE (N=183)	Total (N=332)
Patients with PPASI 100 (NRI)						
n (%)	15 (27.8)	57 (60.0)	54 (62.1)	61 (63.5)	115 (62.8)	187 (56.3)
p-value vs PBO[1]	-	<0.001	<0.001	<0.001	-	-
p-value vs ETN[1]		-	0.466	0.236		

[1] The LS Mean, SE, 95% CI and p-values are presented for each treatment versus placebo comparison at each visit and use an analysis of covariance model including treatment, geographic region, previous non-biologic systemic therapy, baseline weight category, and baseline PPASI value in the model

[2] Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre

ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the analysis population; PBO = placebo; PPASI = Palmoplantar Psoriasis Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; SE = standard error

Source: **PPASI total score**: CSR RHBC, Table RHBC.14.74 (Page 1, 9 and 10 of 11); **PPASI (100):** CSR RHBC, Table RHBC.14.71 (Page 9 of 9)

Open-label long-term extension period data (up to week 108)

In the UNCOVER-3 study, all patients received fixed, open-label dosing of ixekizumab 80 mg Q4W, from week 12 onward (patients were not re-randomised at the start of the open-label extension phase), for the duration of the five-year long-term extension period, thus reflecting real world practice more closely. [redacted]

Figure 21: [redacted]

Figure 22: [redacted]

Figure 23: [redacted]

Pre-specified subgroups from the three pivotal phase 3 trials (UNCOVER-1, UNCOVER-2 and UNCOVER-3) were examined to determine if there were differences in the rates of achievement of treatment goals. The integrated analysis set was used to investigate the effects of subgroup variables such as patient demographics (geographic region, weight), disease-related variables (disease severity, presence of nails or scalp involvement, concomitant psoriatic arthritis [PsA]), previous therapies, on the PASI 75 endpoint at week 12. The integrated analysis sets included:

- The Primary Psoriasis Placebo-Controlled Integrated Analysis Set – included the ixekizumab and placebo arms from the induction periods of UNCOVER-1, -2 and -3.
- The Psoriasis Placebo- and Active-Controlled Integrated Analysis Set – included all treatment arms from the induction period of the pivotal studies, plus an etanercept arm from studies UNCOVER-2 and UNCOVER-3.

In Primary Psoriasis Placebo-Controlled Integrated Analysis Set, the efficacy and safety of ixekizumab was demonstrated regardless of age, gender, race, body weight, PASI baseline severity, plaques location, concurrent psoriatic arthritis, and previous treatment with systemic biologic and non-biologics systemic therapy (Table 44). Ixekizumab was also consistently efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-α-exposed and biologic/anti-TNF-α-failure patients (Section 4.7.4, Section 4.7.5 and Section 4.7.6).

Table 44: Proportion of patients achieving PASI 75 at week 12 (NRI). Primary Psoriasis Placebo-controlled Integrated Analysis Set. ITT population – UNCOVER-1, UNCOVER-2 and UNCOVER-3[86]

Subgroup	p-value (interaction)[a]	PBO N=792 n (%)	IXE80 Q4W N=1,165 n (%)	IXE80 Q2W N=1,169 n (%)	All IXE N=2,334 n (%)
Gender					
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female		[redacted]	[redacted]	[redacted]	[redacted]
Age					
<40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥40 years		[redacted]	[redacted]	[redacted]	[redacted]
Geographic region					
Europe[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease severity					
PASI <20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI ≥ 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight					
<80 kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	p-value (interaction)[a]	PBO N=792 n (%)	IXE80 Q4W N=1,165 n (%)	IXE80 Q2W N=1,169 n (%)	All IXE N=2,334 n (%)
≥80 to <100 kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥100 kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI					
Underweight (<18.5 kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal (≥18.5 and <25 kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overweight (≥25 and <30 kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obese (≥30 and <40/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extreme obese (≥40 kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specific psoriasis locations at baseline					
Baseline scalp psoriasis Yes No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline palmoplantar psoriasis Yes No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline nail psoriasis Yes No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline psoriatic arthritis Yes No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous non-biologic systemic therapy (NBST): inadequate response, intolerance or contraindication					
<3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] A logistic regression analysis with treatment, subgroup and the interaction of treatment by subgroup included as factors, and the treatment by subgroup interaction is tested at the 10% significance level

[b] p<0.001 versus PBO

[c] p<0.001 versus 80 mg Q4W

[d] p≤0.05 versus 80 mg Q4W

[e] Europe's geographic region includes patients from European Union member states (1576 patients, 95.3% across all treatment arms [including etanercept], in Austria, France, Netherlands, Spain, United Kingdom, Germany, Italy, Denmark, Poland, Romania, Czech Republic, Hungary, and Bulgaria), and from Russia (77 patients, 4.7% across all treatment arms [including etanercept]), for the purpose of this report, due to the small number of Russian patients and the preponderance of investigative sites in the west of Russia

[f] p≤0.05 versus PBO

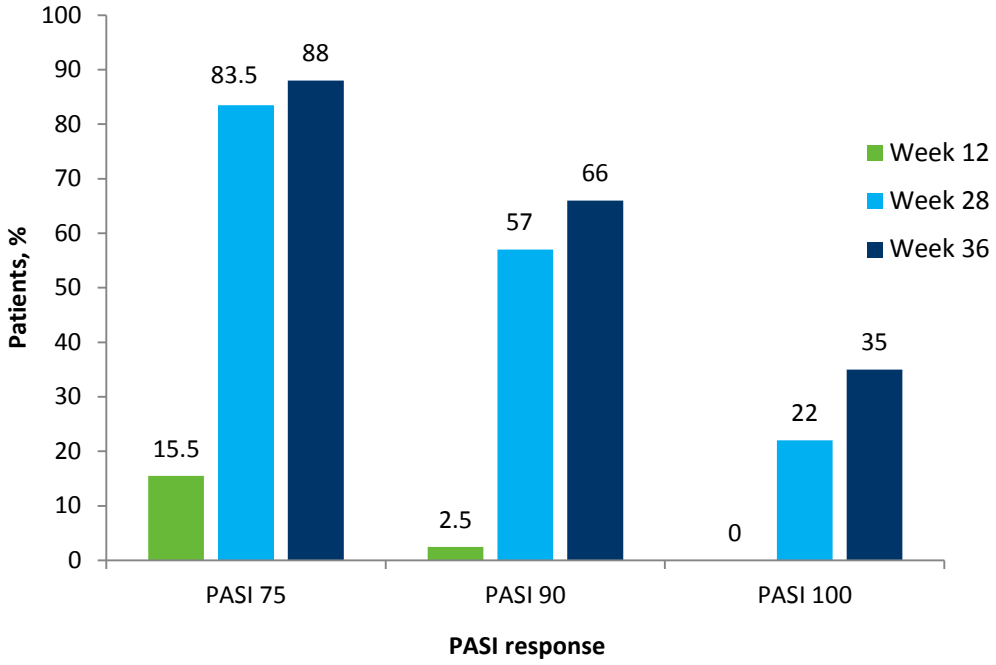
ITT = intent-to-treat, PASI = psoriasis area and severity index, PBO = placebo, IXE = ixekizumab, IXE80 = ixekizumab 80 mg; N/A = not available; NBST = Non-biologic systemic therapies; NRI = non-responder imputation; Q2W = every 2 weeks; Q4W = every 4 weeks

4.7.4 Efficacy of ixekizumab in etanercept inadequate responders (pre-specified analysis)

Ixekizumab is able to achieve significant PASI responses in patients with previous inadequate response to etanercept treatment (i.e. inadequate response, as defined as PGA≥2 at week 12). In the UNCOVER-2 study, 358 patients were randomised to treatment with twice weekly etanercept. At week 12, 200 (56%) of these patients were classified as inadequate responders, with only 15.5% of these patients having achieved PASI 75.[87] Following a 4-week washout period, etanercept inadequate-responders were treated with ixekizumab 80 mg Q4W. After 12 weeks of ixekizumab treatment (week 28) 83.5% of patients achieved PASI 75, 57.0% achieved PASI 90 and 22.0% achieved PASI 100.[87]

These proportions increased to 88.0% for PASI 75, 66.0% for PASI 90 and 35.0% for PASI 100 following 20 weeks (week 36) of treatment with ixekizumab 80 mg Q4W (Figure 24). Following 44 weeks (week 60) of treatment with ixekizumab 82.5% of etanercept inadequate-responders achieved PASI 75, 68.5% achieved PASI 90 and 43.5% achieved PASI 100.[87] It should be noted that these patients did not receive the ixekizumab 160 mg loading dose nor the 12 week Q2W induction regimen. The PASI responses observed in these patients were consistent with those observed in patients who received ixekizumab 80mg Q4W during the induction period of the UNCOVER studies.

Figure 24: PASI response rates in etanercept inadequate-responders before starting (week 12), and after 12 weeks (week 28) and 20 weeks (week 36) of ixekizumab 80 mg Q4W treatment[87]



Note: Etanercept inadequate-responders at week 12 had a 4 week washout period before receiving ixekizumab 80 mg Q4W from week 16. Therefore, week 12, week 28 and week 36 data presented above are the equivalent of 0, 12 and 20 weeks of ixekizumab treatment, respectively

PASI = Psoriasis Area and Severity Index

4.7.5 Efficacy of ixekizumab in patients who have previously been treated with biologics (pre-specified analysis)

Ixekizumab provides a high-level of efficacy regardless of previous treatment with biologic therapy. In the UNCOVER-2 study, a total of 288 patients had received prior biologic therapy and 936 patients were biologic-naive.[88] For patients who had received prior biologic therapy and patients who were biologic-naive, PASI 75 response rates were significantly greater for ixekizumab 80 mg Q2W (92.9% and 88.8%, respectively) and ixekizumab 80 mg Q4W (74.1% and 78.6%, respectively) compared with those for placebo (0 and 3.2%, respectively [p<0.05]) and etanercept (30.3% and 44.3%, respectively [p<0.05]).[88] Furthermore, the proportion of patients who achieved complete clearance of their symptoms (PASI 100) in the biologic experienced and biologic-naïve patients populations was significantly greater for ixekizumab 80 mg Q2W (48.8% and 37.8%, respectively) and ixekizumab Q4W (22.4% and 33.6%, respectively) compared with those for placebo (0 and 0.8%, respectively [p<0.05]) and etanercept (5.3% and 5.3%, respectively [p<0.05]).[88] In addition, response rates were similar regardless of whether patients had received prior biologic therapy or not.

In the Psoriasis Placebo- and Active-controlled Integrated Analysis Set (UNCOVER-2 and UNCOVER-3), a total of [redacted] patients had previously discontinued biologic therapy due to inadequate response. Following treatment with ixekizumab 80 mg Q2W, [redacted] of these patients were able to achieve complete clearance of their symptoms (PASI 100) at week 12. The proportion of patients achieving PASI 100 at week 12 was significantly greater for patients treated with ixekizumab compared to those treated with etanercept (ixekizumab 80 mg Q2W [redacted] vs etanercept [redacted] p<0.001).[89]

In the Primary Psoriasis Placebo-controlled Integrated Analysis Set (UNCOVER-1, UNCOVER-2 and UNCOVER-3), significant proportions of patients achieved complete clearance (PASI 100) and high-level responses (PASI 75 and PASI 90) regardless of whether they had discontinued previous biologic treatment due to inadequate response or other reasons (Figure 25 and Figure 26).[90]

Figure 25: [redacted]

These results were also consistent with patients who had discontinued previous biologic therapy for reasons other than insufficient response (e.g. intolerance (Figure 26).[90]

Figure 26: [redacted]

Significant improvements in PASI 75 response were achieved regardless of the number of previous exposures to biologic therapy (Table 45).[90]

Table 45: Proportion of patients achieving PASI 75 at week 12 (NRI). Primary Psoriasis Placebo-controlled Integrated Analysis Set. ITT population – UNCOVER-1, UNCOVER-2 and UNCOVER-3[90]

Previous biologic exposure	p-value (interaction)*	PBO N=792 n (%)	IXE80 Q4W N=1,165 n (%)	IXE80 Q2W N=1,169 n (%)	All IXE N=2,334 n (%)
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used		[redacted]	[redacted]	[redacted]	[redacted]
Number of previous exposures	[redacted]				
Never used		[redacted]	[redacted]	[redacted]	[redacted]
Used 1		[redacted]	[redacted]	[redacted]	[redacted]
Used 2		[redacted]	[redacted]	[redacted]	[redacted]
Used ≥3		[redacted]	[redacted]	[redacted]	[redacted]

[a] p<0.001 versus PBO

[b] p<0.001 versus 80 mg Q4W

[c] p≤0.05 versus 80 mg Q4W

*A logistic regression analysis with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors, and the treatment-by-subgroup interaction is tested at the 10% significance level.

ITT = intent-to-treat, PASI = psoriasis area and severity index, PBO = placebo, IXE = ixekizumab, IXE80 = ixekizumab 80 mg; N/A = not available; NRI = non-responder imputation; Q2W = every 2 weeks; Q4W = every 4 weeks.

4.7.6 Efficacy of ixekizumab in patients eligible for biologic therapy under current NICE criteria (post-hoc analysis)

Treatment with ixekizumab has demonstrated efficacy in patient populations who would be eligible for treatment with biologics according to NICE criteria based on previous treatments and disease severity, demonstrating the efficacy of ixekizumab in a NICE-defined biologic eligible population (Table 46). The results illustrate the consistently high PASI 75 response rates observed in patients treated with ixekizumab regardless of previous exposure to systemic non-biologic and biologic therapies.[91]

Table 46: Proportion of patients achieving PASI 75 at week 12 (NRI). Primary Psoriasis Placebo-controlled Integrated Analysis Set, selected subgroups – NICE Specific Reimbursement Criteria; ITT population – UNCOVER-1, UNCOVER-2 and UNCOVER-3[91]

NICE Criteria	p-value (interaction)[a]	PBO N=792 n (%)	IXE80Q4W N=1,165 n (%)	IXE80Q2W N=1,169 n (%)
Prior exposure to ≥2 NBST and /or PUVA				
Yes (with PUVA)	[redacted]	[redacted]	[redacted]	[redacted]
No (without PUVA)		[redacted]	[redacted]	[redacted]
Prior exposure to ≥2 NBST/PUVA and baseline DLQI>10				
Yes (with DLQI>10)	[redacted]	[redacted]	[redacted]	[redacted]
No (without DLQI>10)		[redacted]	[redacted]	[redacted]
Prior exposure to ≥2 NBST/PUVA and baseline DLQI>10 and no prior biologic use				
Yes (with no prior biologic use)	[redacted]	[redacted]	[redacted]	[redacted]
No (with prior biologic use)		[redacted]	[redacted]	[redacted]
Prior exposure to methotrexate and baseline DLQI >10 and no prior biologic use				
Yes (with no prior biologic use)	[redacted]	[redacted]	[redacted]	[redacted]
No (with prior biologic use)		[redacted]	[redacted]	[redacted]
Prior failure to methotrexate and baseline DLQI>10 and no prior biologic use				
Yes (with no prior biologic use)	[redacted]	[redacted]	[redacted]	[redacted]
No (with prior biologic use)		[redacted]	[redacted]	[redacted]
Prior exposure to ≥1 NBST/PUVA and baseline DLQI>10 and no prior biologic use				
Yes (with no prior biologic use)	[redacted]	[redacted]	[redacted]	[redacted]
No (with prior biologic use)		[redacted]	[redacted]	[redacted]
Prior failure to ≥1 NBST/PUVA and baseline DLQI>10 and no prior biologic use				
Yes (with no prior biologic use)	[redacted]	[redacted]	[redacted]	[redacted]
No (with prior biologic use)		[redacted]	[redacted]	[redacted]

[a] A logistic regression analysis with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors, and the treatment-by-subgroup interaction is tested at the 10% significance level

Note: DLQI>10 was not an eligibility criterion for the UNCOVER studies, however DLQI>10 is used as part of the assessment of patient eligibility for biologics according to NICE guidance

DLQI>10 and PASI≥10 are used as the measures for disease severity

DLQI = Dermatology Life Quality Index, PUVA = psoralen combined with ultraviolet A, NBST = non-biologic systemic therapies, N = number of patients, n = number of patients in the specified category; N/A = not applicable; NRI = non-responders imputed

4.8 *Meta-analysis*

Head-to-head RCTs between all comparators specified in the NICE scope have not been conducted; therefore an NMA was conducted to estimate the comparative efficacy between these treatments as described in Section 4.9. NMA can provide relative measures of effect for all relevant comparators in the absence of direct evidence and is most suitable when there are multiple-arm trials included within networks. Use of an NMA in preference to pairwise meta-analysis allowed all available and relevant evidence to be included, allowing more precise treatment effects to be calculated. In addition, the results from the NMA will feed into the economic model to provide the relevant cost-effectiveness of ixekizumab against relevant comparators. This approach has been used in previous NICE STA submissions for biologics in psoriasis (for example ustekinumab[69] and secukinumab[68]).

4.9 *Indirect and mixed treatment comparisons*

4.9.1 Identification of studies

The SLR described in Section 4.1 was used to identify all potential studies that may have been relevant for indirect comparison with ixekizumab. The search was broad in order to capture studies that may have been appropriate once the license for ixekizumab was granted and the decision problem was confirmed.

4.9.2 Treatments to be compared

The interventions and doses of interest in the base case analysis are presented in Table 47. For each of the interventions included in the NMA, only licensed doses were taken forward in the analysis. As the different dosing schedules of etanercept with 25 mg BIW and 50 mg QW were assumed to be of identical clinical efficacy the two dosages were pooled in the base case results (etanercept 25mg BIW and etanercept 50mg QW as one etanercept treatment arm). In addition the base case network did not include the etanercept 50 mg BIW dosing regimen as the base case analysis used only the biologics at doses approved by NICE in the decision set. An additional scenario analysis included etanercept 50mg twice weekly (BIW) - a licensed dose that has not been approved by NICE. This scenario expanded the decision set and allowed inclusion of a number of studies that included an active head to head comparison with etanercept 50mg BIW. An additional scenario analysis compared ixekizumab with the available evidence on standard systemic treatments.

Table 47: Approved dosing schedules and included studies for the treatments included in the base case analysis

Drug name	Induction phase dose	Maintenance phase dose	Included studies
Adalimumab	80 mg at week 1	40 mg every two weeks starting one week after the initial dose	Gordon *et al.* 2006[92] CHAMPION (NCT00235820), Saurat *et al.* 2008[51] REVEAL (NCT00237887), Menter *et al.* 2008[93] Asahina *et al.* 2010[94] NCT01483599, Gordon *et al.* 2015[95] NCT00940862, Bissonette *et al.* 2013[96]
Etanercept	25 mg administered twice weekly or 50 mg administered once weekly	25 mg administered twice weekly or 50 mg administered once weekly	Leonardi *et al.* 2003[97] Papp *et al.* 2005[98] Van de Kerkhof *et al.* 2008[99] Gottlieb *et al.* 2003[100]
Infliximab	5 mg/kg at week 1, 2 and 6.	5 mg/kg every 8 weeks	EXPRESS, Reich *et al.* 2005[101] SPIRIT, Gottlieb *et al.* 2004[102] Torii *et al.* 2010[103] EXPRESS II, Menter *et al.* 2007[104] Chaudhari *et al.* 2001[105] Yang *et al.* 2012[106]
Ixekizumab	80 mg every 2 weeks or every 4 weeks		UNCOVER 1 (NCT01474512), Eli Lilly CSR 2015[21] UNCOVER 2 (NCT01597245), Griffiths *et al.* 2015 and Eli Lilly CSR 2015[16,22] UNCOVER 3 (NCT01646177), Griffiths *et al.* 2015 and Eli Lilly CSR 2015[16,23]
Secukinumab	300 mg at Weeks 0, 1, 2, 3 and 4	300 mg monthly maintenance starting at week 4	ERASURE (NCT01365455), Langely *et al.* 2014[107] FIXTURE (NCT01358578), Langely *et al.* 2014[107] FEATURE (NCT01555125), Blauvelt *et al.* 2015[108] JUNCTURE (NCT01636687), Paul *et al.* 2015[109] CLEAR (NCT02074982), Thaci *et al.* 2015[110]

Drug name	Induction phase dose	Maintenance phase dose	Included studies
Ustekinumab	45 mg or 90 mg at week 1 and 4	45 mg or 90 mg every 12 weeks	PEARL, Tsai *et al.* 2011[111] PHOENIX 1 (NCT00267969), Leonardi *et al.* 2008[112] PHOENIX 2 (NCT00307437), Papp *et al.* 2008[113] LOTUS, Zhu *et al.* 2013[114] ACCEPT (NCT00454584), Griffiths *et al.* 2010[115] Igarashi *et al.* 2012[116] AMAGINE-2 (NCT01708603), Lebwohl *et al.* 2015[117] AMAGINE-3 (NCT01708629), Lebwohl *et al.* 2015[117] CLEAR (NCT02074982), Thaci *et al.* 2015[110]
Etanercept 50mg BIW †	50 mg twice weekly		PRISTINE (NCT00663052), Strohal *et al*. 2013[118] UNCOVER 2 (NCT01597245), Griffiths *et al.* 2015 and Eli Lilly CSR 2015[16,22] UNCOVER 3 (NCT01646177), Griffiths *et al.* 2015 and Eli Lilly CSR 2015[16,23] Tyring *et al*. 2006[119] NCT01241591, Bachelez *et al*. 2015[120] Bagel et al. 2012[121] Gottlieb *et al.* 2003[100] NCT00710580, Strober *et al.* 2011[122] NCT00691964, Gottlieb *et al*. 2011[123] ACCEPT (NCT00454584), Griffiths *et al.* 2010[115] FIXTURE (NCT01358578), Langely *et al.* 2014[107]
Cyclosporin	For inducing remission, the recommended initial dose is 2.5 mg/kg/day orally given in 2 divided doses. If there is no improvement after 1 month, the daily dose may be gradually increased, but should not exceed 5 mg/kg.		Meffert *et al*. 1997[124]
Methotrexate	10-25 mg orally, once a week is recommended	1. Weekly single oral. IM or IV dosage schedule: 10 to 25 mg per week until adequate response is achieved. 2. Divided oral dose schedule 2.5 mg at 12 hour intervals for three doses	RESTORE 1 (NCT00251641), Barker *et al*. 2011[125]

† Etanercept 50mg BIW is a licensed dose that has not been approved by NICE

BIW = twice weekly;IM = intramuscular; IV = intravenous

4.9.3 Inclusion/exclusion criteria for studies included in the NMA

As highlighted in Section 4.9.2, broad inclusion/exclusion criteria were used to identify potential relevant studies for the NMA. Further criteria specific to the decision problem were then applied to determine which studies populated the base-case analysis network which were as follows:

- European Medicines Agency (EMA) licensed dose.
- Dosage regimen approved as cost-effective by NICE.
- Data aligned with assessment point defined by NICE (primary study endpoint).

All of the above criteria had to apply for data from a study to be used to populate the base-case analysis network. The following clarifications should also be noted:

- Ixekizumab Q4W regimen was included due to uncertainty with the final approved label.
- Ustekinumab- although the NICE assessment point for response to treatment is 16 weeks, this guidance was based on 12 week data and 12 week data was used in the base-case NMA. Additionally, limited data was available regarding the weight-based dosing regimen therefore published 45 mg and 90 mg data was used.
- In studies with multiple treatment arms, an active treatment arm that met the above criteria was included in the analysis.

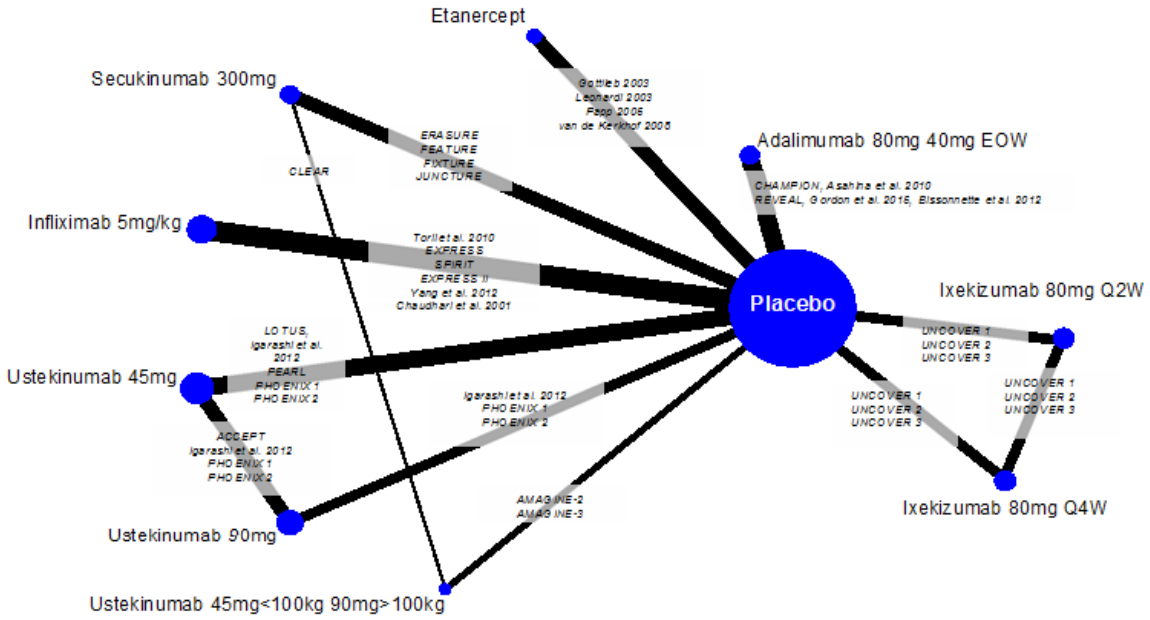
As noted in Section 4.9.2, the above criteria were relaxed to allow inclusion of etanercept 50 mg BIW treatment groups for a sensitivity analysis and an additional network compared ixekizumab with the available date on standard systemic therapies. It was not feasible to construct a network that included fumarates, acitretin or phototherapy.

4.9.4 Summary of trials included in the NMA

Network diagrams for the base-case NMA analysis and the two scenario analyses presented in the submission can be seen in Figure 27, Figure 28 and Figure 29, respectively.

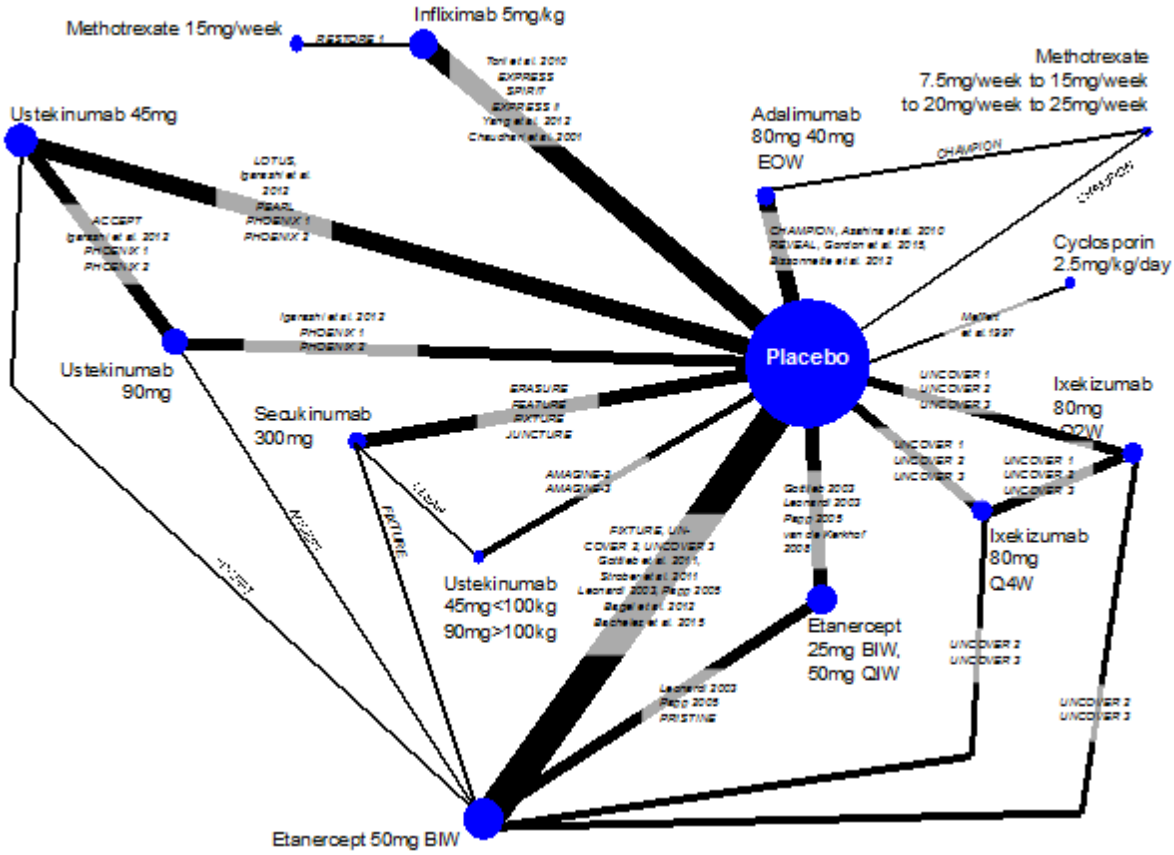
A summary of each of the trials which were included in the base-case and scenario analyses can be seen in Table 48.

Figure 27: Network diagram for the NMA base case analysis



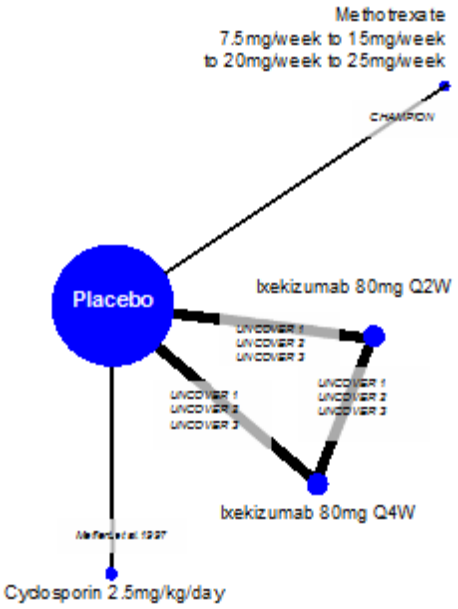
EOW = every other week; Q2W = every 2 weeks; Q4W = every 4 weeks

Figure 28: Network diagram for scenario analysis including 50 mg BIW treatment groups at week 12



BID = twice daily; BIW= twice weekly; EOW = every other week; PASI = Psoriasis Area and Severity Index; QIW = once weekly; Q2W = every two weeks; Q4W = every four weeks.

Figure 29: Network diagram for scenario analysis of ixekizumab and conventional systemic treatments at week 12



Q2W = every two weeks; Q4W = every four weeks

Table 48: Summary of trials used to conduct the base case NMA

Author	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion
FEATURE (NCT01555125), Blauvelt *et al.* 2015[108]	2015	Secukinumab administration by pre-filled syringe: Efficacy, safety and usability results from a randomised controlled trial in psoriasis (FEATURE)	Secukinumab 300 mg Secukinumab 150 mg Placebo	PASI 75 IGA 0,1 Adverse events Infections Serious adverse events Withdrawals	This study (FEATURE) was included as it contained comparators of interest. Data for the NMA was extracted from the EMA 2015 secukinumab report rather than the primary publication.
NCT01483599, Gordon *et al.* 2015[95]	2015	A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis	Guselkumab 50 mg Guselkumab 100 mg Guselkumab 200 mg Adalimumab 40 mg EOW Placebo	PGA 0,1 PASI 75 PASI 90 PASI 100 DLQI	Although guselkumab was excluded, the adalimumab treatment arm was on-label. The study was included, but the guselkumab arms were excluded.
UNCOVER 2 and 3 (NCT01597245), Griffiths *et al*. 2015 and Eli Lilly CSR 2015[16]	2015	Comparison of ixekizumab with etanercept or placebo in moderate to severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials	Ixekizumab 80 mg Q2W Ixekizumab 80 mg Q4W Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PASI 100 DLQI sPGA Itch NRS Safety	This publication was included, although most data were gathered from the ixekizumab CSR.
UNCOVER-1 (NCT01474512), Eli Lilly CSR 2015[21]	2015	A multicentre study with a randomised, double-blind, placebo-controlled induction dosing period followed by a randomised maintenance dosing period and a long-term extension period to evaluate the efficacy of LY2439821 in patients with moderate to severe plaque psoriasis. IF-MC-RHAZ Clinical Study Report (UNCOVER 1)	Placebo Ixekizumab 80 mg Q2W Ixekizumab 80 mg Q4W	PASI 50 PASI 75 PASI 90 PASI 100 DLQI sPGA Itch NRS Safety	This study met all the inclusion criteria

ERASURE (NCT01365455), Langely *et al.* 2014 FIXTURE (NCT01358578), Langely *et al.* 2014	**2014**	**Secukinumab in plaque psoriasis - Results of two phase 3 trials**	**Etanercept** **Secukinumab 300 mg** **Secukinumab 150 mg** **Placebo**	**PASI 75** **PASI 90** **PASI 100** **DLQI** **PGA 0,1**	**Data from ERASURE and FIXTURE were included, although all data were gathered from the secukinumab EMA report as it was more comprehensively reported.**
AMAGINE-2 (NCT01708603), Lebwohl *et al*. 2015[117] AMAGINE-3 (NCT01708629), Lebwohl *et al*. 2015[117]	2015	Phase 3 studies comparing brodalumab with ustekinumab in psoriasis	Ustekinumab 45 mg Ustekinumab 90 mg Brodalumab 140 mg Brodalumab 210 mg Placebo	PASI 75 PASI 90 PASI 100 sPGA PSI	Ustekinumab data only included
JUNCTURE (NCT01636687), Paul *et al.* 2015[109]	2014	Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomised, controlled trial (JUNCTURE)	Secukinumab 300 mg Secukinumab 150 mg Placebo	PASI 75 IGA Adverse events Serious adverse events Infections	This study was included as it includes comparators of interest. Data was also sourced from the EMA 2015 report for secukinumab where not available in the publication.
CLEAR (NCT02074982), Thaci *et al.* 2015[110]	2015	Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomised controlled trial	Secukinumab 300 mg Ustekinumab 45 mg Ustekinumab 90 mg	PASI 75 PASI 90 PASI 100 IGA DLQI Itch NRS Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
NCT00940862, Bissonette *et al.* 2013[96]	2013	Effects of the Tumour Necrosis Factor-α Antagonist Adalimumab on Arterial Inflammation Assessed by Positron Emission Tomography in Patients With Psoriasis Results of a Randomised Controlled Trial	Adalimumab 40 mg EOW Control (no treatment, topical psoriasis treatments or PUVA)	Carotid artery and ascending aorta inflammation PASI change from baseline	This study met all inclusion criteria.

EXPRESS II, Menter *et al*. 2007[104]	2007	A randomised comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate to severe plaque psoriasis	Infliximab 3 mg/kg (continuous) Infliximab 5 mg/kg (continuous) Infliximab 3 mg/kg (as needed) Infliximab 5 mg/kg (as needed) Placebo	PASI 75 PASI 90	Only 5mg/kg continuous arm included.
Chaudhari *et al.* 2001[105]	2001	Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: A randomised trial	Infliximab 5 mg/kg Placebo	PASI 75 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
Gordon *et al*. 2006[92]	2006	Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomised controlled trial and open-label extension study	Adalimumab 40 mg EOW Adalimumab 40 mg QW Placebo	PASI 75 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria. Adalimumab 40 mg QW was not included.
Yang *et al.* 2012[106]	2012	Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomised, double-blind, placebo-controlled multicenter trial	Infliximab 5 mg/kg Placebo	PASI 75 PGA DLQI Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
Torii *et al.* 2010[103]	2010	Infliximab monotherapy in Japanese patients with moderate to severe plaque psoriasis and psoriatic arthritis. A randomised, double-blind, placebo-controlled multicenter trial.	Infliximab 5 mg/kg Placebo	PASI 50 PASI 75 PASI 90 PGA DLQI Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.

ACCEPT Griffiths *et al.* 2010[115]	2010	Comparison of Ustekinumab and Etanercept for Moderate to severe Psoriasis	Ustekinumab 45 mg Ustekinumab 90 mg Etanercept BIW 50 mg	PASI 75 PASI 90 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
Saurat *et al.* 2008[51]	2008	Efficacy and safety results from the randomised controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION)	Adalimumab 40 mg EOW Methotrexate 7.5 mg Placebo	PASI change from baseline PGA BSA PASI 50 PASI 75 PASI 90 PASI 100	This study met all inclusion criteria.
Secukinumab EMA report[126]	2015	ERASURE study	Secukinumab 300 mg Secukinumab 150 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria. Secukinumab 150 mg was excluded.
EXPRESS, Reich *et al.* 2005[101]	2005	Infliximab induction and maintenance therapy for moderate to severe psoriasis: a phase III, multicentre, double-blind trial	Infliximab 5 mg/kg Placebo	PASI 50 PASI 75 PASI 90	This study met all inclusion criteria.
Secukinumab EMA report[126]	2015	FEATURE study	Secukinumab 300 mg Secukinumab 150 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.

Secukinumab EMA report[126]	2015	FIXTURE study	Secukinumab 300 mg Secukinumab 150 mg Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PASI 100 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
Secukinumab EMA report[126]	2015	JUNCTURE study	Secukinumab 300 mg Secukinumab 150 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
LOTUS, Zhu *et al.* 2013[114]	2013	Efficacy and Safety of Ustekinumab in Chinese Patients with Moderate to severe Plaque-type Psoriasis: Results from a Phase 3 Clinical Trial (LOTUS)	Ustekinumab 45 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
Gottlieb *et al.* 2003[100]	2003	A Randomised Trial of Etanercept as Monotherapy for Psoriasis	Etanercept 25 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PGA DLQI Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.

Leonardi *et al.* 2003[97]	2003	Etanercept as Monotherapy in Patients with Psoriasis	Etanercept 25 mg QW Etanercept 25 mg BIW Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PGA DLQI Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria. Etanercept 25 mg QW was excluded.
Papp *et al.* 2005[98]	2005	A global phase III randomised controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction.	Etanercept 25 mg BIW Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 sPGA Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.
Van de Kerkhof *et al.* 2008[99]	2008	Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate to severe plaque psoriasis: a randomised controlled trial with open-label extension	Etanercept 50 mg QW Placebo	PASI 50 PASI 75 PASI 90 PGA Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.
Asahina *et al.* 2010[94]	2010	Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomised controlled study	Adalimumab 40 mg EOW (with loading dose) Adalimumab 40 mg EOW (without loading dose) Adalimumab 80 mg EOW Placebo	PASI 50 PASI 75 PASI 90 PGA Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria. Adalimumab 40 mg without loading dose and adalimumab 80 mg were excluded.

Igarashi *et al.* 2012[116]	2012	Efficacy and safety of ustekinumab in Japanese patients with moderate to severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial	Ustekinumab 45 mg Ustekinumab 90 mg Placebo	PASI 50 PASI 75 PASI 90 PASI change from baseline PGA VAS DLQI PDI SF-36	This study met all inclusion criteria.
PEARL, Tsai *et al.* 2011[111]	2011	Efficacy and safety of ustekinumab for the treatment of moderate to severe psoriasis: a phase III, randomised, placebo-controlled trial in Taiwanese and Korean patients (PEARL)	Ustekinumab 45 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 PASI change from baseline PGA DLQI Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.
PHOENIX 1 (NCT00267969), Leonardi *et al.* 2008[112]	2008	Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised double-blind, placebo-controlled trial (PHOENIX 1)	Ustekinumab 45 mg Ustekinumab 90 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 PASI change from baseline PGA DLQI	This study met all inclusion criteria.

PHOENIX 2 (NCT00307437), Papp *et al.* 2008[113]	2008	Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)	Ustekinumab 45 mg Ustekinumab 90 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 PASI change from baseline Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.
REVEAL (NCT00237887), Menter *et al.* 2008[93]	2008	Adalimumab therapy for moderate to severe psoriasis: a randomised, controlled phase III trial	Adalimumab 40 mg EOW Placebo	PASI 90 PASI 100 PASI change from baseline PGA Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.
SPIRIT, Gottlieb *et al.* 2004[102]	2004	Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomised, double-blind, placebo-controlled trial	Infliximab 3 mg/kg Infliximab 5 mg/kg Placebo	PASI 50 PASI 75 PASI 90 PGA Adverse events Infections Serious adverse events Withdrawals	Only the 5mg/kg arm included.

PRISTINE trial Strohal *et al* 2013[118]	2013	The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial)	Etanercept 50 mg QW Etanercept 50 mg BIW	PASI 50 PASI 75 PASI 90 PASI change from baseline PGA DLQI Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
Tyring *et al.* 2006[119]	2006	Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial	Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 HAM-D FACIT Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.
Bachelez *et al.* 2015[120]	2015	Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PASI change from baseline PGA 0 DLQI	Whilst this study included tofacitinib which was excluded in the PICOS, the etanercept and placebo treatment arms could be used.
Bagel *et al.* 2012[121]	2012	Moderate-to-severe plaque psoriasis with scalp involvement: a randomised, double-blind, placebo-controlled study of etanercept	Etanercept 50 mg BIW Placebo	PASI PSSI Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.
Gottlieb *et al.* 2011[123]	2011	Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate-to-severe chronic plaque psoriasis	Briakinumab 200 mg/kg Etanercept 50 mg BIW Placebo	PASI 75 PGA Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria. Briakinumab was not included.

Strober *et al.* 2011[122]	2011	Efficacy and safety results from a phase III, randomised controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate-to-severe chronic plaque psoriasis	Briakinumab 200 mg/kg Etanercept 50 mg BIW Placebo	PASI 75 PGA Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria. Briakinumab was not included.
Meffert *et al.* 1997[124]	1997	Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile.	Cyclosporin 1.25 mg/kg Cyclosporin 2.5 mg/kg Placebo	PASI 50 PASI 75 Blood lipids	This study met all inclusion criteria. Cyclosporin 1.25 mg/kg was excluded.
RESTORE (Barker *et al.*2011)[125]	2011	Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomised trial (RESTORE1)	Infliximab 5 mg/kg Methotrexate 15 mg QW	PASI 50 PASI 75 PASI 90 PGA DLQI SF-36	This study met all inclusion criteria.

BID = twice daily; BIW = twice weekly; BSA = body surface area; DLQI = Dermatology Life Quality Index; EMA = European Medicines Agency; EOW = every other week; HAM-D = Hamilton Rating Scale for Depression; NMA = network meta-analysis; PASI = Psoriasis Area And Severity Index; PASI 50 = ≥50% improvement psoriasis area and severity index score; PASI70 = ≥70% improvement psoriasis area and severity index score; PASI 75 = ≥75% improvement psoriasis area and severity index score; PASI 90 = ≥90% improvement psoriasis area and severity index score; PASI 100 = 100% improvement psoriasis area and severity index score; PDI = Psoriasis Disability Index; PGA = physician's global assessment; PSI = psoriasis symptom inventory; QW = once weekly; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static physician global assessment score; VAS = visual analogue scale

4.9.5 Excluded studies

Studies which were excluded from the NMA and the justification for their exclusion can be seen in Appendix 8.

4.9.6 Outcomes assessed in the NMA

The NMA results presented in this submission focus on the most relevant efficacy parameter in the moderate to severe psoriasis therapy area, namely PASI response rates. PASI response rates were consistently reported across all studies and are the key efficacy parameter in the economic analysis. Other outcomes were either poorly or inconsistently reported across studies (e.g. definition of adverse events) and are therefore not reported further in this section. The PASI response rates which have been included are as follows:

- PASI 50 defined as a minimum of 50% improvement of PASI score from baseline
- PASI 75 defined as a minimum of 75% improvement of PASI score from baseline
- PASI 90 defined as a minimum of 90% improvement of PASI score from baseline
- PASI 100 defined as complete resolution of all disease.

The use of PASI response rates as the primary outcome measure is consistent with previous NICE STA submissions for biologics in psoriasis and, as stated, also aligns with the efficacy inputs used to inform the cost-effectiveness model.

4.9.7 Patient populations of trials included in the NMA

The NMA base-case analysis included the ITT patient populations as reported in the final publications/sources. No sub-groups are reported - as noted below the sub-group of patients that were inadequate responders to TNF-α inhibitors was considered but this analysis could not be progressed. Entry criteria for the included studies were largely consistent with patients requiring a baseline PASI of 10-12 or greater. Exposure to prior treatment varied across studies, as noted, i.e. not all patients in the included study were documented inadequate responders/contra-indicated to standard systemic therapies. However as a large proportion of the included studies have informed prior NICE technology appraisals, it can was assumed that the overall populations were relevant to the NICE scope. The patient demographics and baseline characteristics of studies included in the base case NMA can be seen in Table 49. In addition, the PASI outcome responses from the trials can be seen in Table 50.

Table 49: Patient demographics and baseline characteristics of studies included in the base-case NMA

Study	Treatment	Trial duration/1° endpoint (weeks)	N	Age (years)	±SD (range)	Male (%)	Weight (kg)	±SD	White (%)	Psoriasis duration (years)	±SD	Previous systemic and/or PUVA (%)	Prior biologic (%)	PASI score	±SD (range)
UNCOVER 1 Lilly CSR 2015	IXE 80mg Q2W	264/12	433	45.1	12.4	67.2	92.4	22.7	92.6	19.9	19.9	63.7/NR	40	20.1	8
	IXE 80mg Q4W		432	45.6	13	66.9	92.5	23.9	91.9	19.5	11.9	55.1/NR	38.9	20	7.3
	PBO		431	46.4	13.4	70.3	91.8	25	93	19.5	11.7	56.1/NR	42	20.3	8.6
UNCOVER 2 Griffiths 2015	IXE 80mg Q2W	264/12	351	45.0	13	63	89	22	94	18	12	51/46	24	19	7
	IXE 80mg Q4W		347	45.0	14	70	93	23	92	19	13	51/46	25	20	7
	PBO		168	45.0	12	71	92	22	89	19	13	48/44	26	21	8
UNCOVER 3 Griffiths 2015	IXE 80mg Q2W	264/12	385	46.0	13	66	90	23	94	18	12	44/39	15	21	8
	IXE 80mg Q4W		386	46.0	13	67	91	24	93	18	12	47/40	15	21	8
	PBO		193	46.0	12	70	91	21	91	18	13	43/31	17	21	8
CHAMPION Saurat 2007	ADA 40mg EOW	16	108	42.9	12.6	64.8	81.7	20	95.4	17.9	10.1	82.2	NR	20.2	7.5
	PBO		53	40.7	11.4	66	82.6	19.9	92.5	18.8	8.7	90.4	NR	19.2	6.9
NCT01483599 Gordon 2015	ADA 40mg EOW	52/16	43	50.0		70	91.6	19.9	91	19.3	12.8	40/27.5	60	20.2	7.6
	PBO		42	46.5		67	93.6	22.6	93	18	13.3	50/21.4	36	21.8	10
NCT00940862 Bissonette 2012	ADA 40mg EOW	16	20	56.1	11	85	95.1	11.5	100	NR		NR	NR	11.6	5.3
	PBO		10	57.4	7.6	60	94.8	17.6	100	NR		NR	NR	13.1	5.7
REVEAL Menter 2008	ADA 40mg EOW	52/16	814	44.1	13.2	67.1	92.3	23	91.2	18.8	11.9	23.1/17.0	11.9	19	7.1

Study	Treatment	Trial duration/1° endpoint (weeks)	N	Age (years)	±SD (range)	Male (%)	Weight (kg)	±SD	White (%)	Psoriasis duration (years)	±SD	Previous systemic and/or PUVA (%)	Prior biologic (%)	PASI score	±SD (range)
	PBO		398	45.4	13.4	64.6	94.1	23	90.2	18.4	11.9	22.1/14.8	13.3	18.8	7.1
Asahina 2010	ADA 40mg EOW	24/16	43	44.2	14.3	81.4	67.4	9.9	0	14	7.4	41.9/23.3	NR	30.2	10.9
	PBO		46	43.9	10.8	89.1	71.3	15.3	0	15.5	8.8	37.0/41.3	NR	29.1	11.8
Gottlieb 2003	ETN 25mg BIW	24/12	57	48.2	(25-72)	58	91.8		89	23	(SE±1.6)	MTX 39/37	NR	17.8	(SE±1.1)
	PBO		55	46.5	(18 to77)	67	90.7		95	20	(SE±1.7)	MTX 36/42	NR	19.5	(SE±1.3)
Leonardi 2003	ETN 25mg BIW	24/12	162	45.4	(SE±1.0)	67	NR		85	18.5	(SE±0.9)	NR	NR	18.5	(SE±0.7)
	PBO		166	45.6	(SE±1.0)	63	NR		90	18.4	(SE±0.9)	NR	NR	18.3	(SE±0.6)
Papp 2005	ETN 25mg BIW	24/12	196	46.0	(20-87)	65	NR		92	21.5	(0.8-64.6)	MTX 35/35	NR	16.9	(4.0-51.2)
	PBO		193	44.0	(18-80)	64	NR		91	17.5	(1.4-51.2)	MTX 39/34	NR	16	(7.0-62.4)
van de Kerkhof 2008	ETN 50mg QW	24/12	96	45.9	12.8	61.5	83.4	16	NR	19.3	11.3	49.0/69.8	NR	21.4	9.3
	PBO		46	43.6	12.6	54.4	79.1	20.2	NR	17.3	8.2	47.8/69.6	NR	21	8.7
ERASURE Langley 2014 (EMA 2015)	SEC 300mg	52/12	245	44.9	13.5	69	88.8	24	69.8	17.4	11.1	52.2/NR	28.6	22.5	9.2
	PBO		248	45.4	12.6	69.4	89.7	25	71	17.3		43.5/NR	29.4	21.4	9.1
FEATURE Blauvelt 2015 (EMA 2015)	SEC 300mg	208/12	59	45.1	12.6	64.4	92.6	25.9	91.5	18	11.9	33.9/NR	39	20.7	8
	PBO		59	46.5	14.1	66.1	88.4	21.6	96.6	20.2	14.2	49.2/NR	44.1	21.1	8.5
FIXTURE Langley 2014 (EMA 2015)	SEC 300mg	52/12	327	44.5	13.2	68.5	83	21.6	68.5	15.8	-	59.6/NR	11.6	23.9	9.9
	PBO		326	44.1	12.6	72.7	82	20.4	66.9	16.6	-	61.0/NR	10.7	24.1	10.5
JUNCTURE	SEC	N/A/12	60	46.6	14.2	76.7	91	23.1	93.3	21	-	50.0/NR	25	18.9	6.4

Study	Treatment	Trial duration/1° endpoint (weeks)	N	Age (years)	±SD (range)	Male (%)	Weight (kg)	±SD	White (%)	Psoriasis duration (years)	±SD	Previous systemic and/or PUVA (%)	Prior biologic (%)	PASI score	±SD (range)
Paul *et al* 2015 (EMA 2015)	300mg														
	PBO		61	43.7	12.7	62.3	90.2	21.2	96.7	19.9	-	47.5/NR	21.3	19.4	6.7
CLEAR Thaci 2015	SEC 300mg	52/16	337	45.2	13.96	68	87.4	19.95	88.7	19.6	-	64.7	14.2	21.7	8.5
	UST 45mg		339	44.6	13.67	74.3	87.2	22.11	85	16.1	-	65.8	13	21.5	8.07
EXPRESS Reich 2005	INF 5mg	50/10	301	42.6	11.7	68.8	NR		NR	19.1	-	MTX 41.9 /42.5	NR	22.9	9.3
	PBO		77	43.8	12.6	79.2	NR		NR	17.3	-	MTX 45.5/45.5	NR	22.8	8.7
EXPRESS 2 Menter 2007	INF 5mg	50/10	314	44.5	13	65	92.2	23.2	93.3	19.1	-	34.7/27.4	14.3	20.4	7.5
	PBO		208	44.4	12.5	69.2	91.1	22.6	90.9	17.8	-	33.7/29.8	13	19.8	7.7
Chaudhari 2001	INF 5mg	16/10	11	51	14	63.6	87	20	NR	NR	-	NR	NR	22.1	11.5
	PBO		11	45	12	72.7	85	19	NR	NR	-	NR	NR	20.3	5.5
SPIRIT Gottlieb 2004	INF 5mg	30/10	99	44†		73.7	NR		NR	16†	-	88.9/68.7	33.3	20†	
	PBO		51	45†		60.8	NR		NR	16†	-	82.4/66.7	31.4	18†	
Torii *et al* 2010	INF 5mg	78/10	35	46.9	13	62.9	68.5	13.4	0	14.2	8.9	94.3/34.3	NR	31.9	12.8
	PBO		19	43.3	12.3	73.7	69.7	8.9	0	11.1	6.5	94.7/36.8	NR	33.1	15.6
Yang 2012	INF 5mg	26/10	84	39.4	12.3	71.4	68.2	9.2	0	16	10.8	NR	NR	23.9	10.7
	PBO		45	40.1	11.1	77.8	67.4	9.9	0	16	8.9	NR	NR	25.3	12.7
ACCEPT Griffiths 2010	UST 45mg	64/12	209	45.1	12.6	63.6	90.4	21.1	92.3	18.9	11.8	61.7/66.0	12.4	20.5	9.2
	UST 90mg		347	44.8	12.3	67.4	91	22.8	89	18.7	11.8	52.4/66.3	10.4	19.9	8.4

Study	Treatment	Trial duration/1° endpoint (weeks)	N	Age (years)	±SD (range)	Male (%)	Weight (kg)	±SD	White (%)	Psoriasis duration (years)	±SD	Previous systemic and/or PUVA (%)	Prior biologic (%)	PASI score	±SD (range)
Igarashi 2012	UST 45mg	72/12	64	45.0†		82.8	73.2	15.4	0	15.8	8.2	73.4/56.3	1.6	30.1	12.9
	UST 90mg		62	44.0†		75.8	71.1	14	0	17.3	10.7	83.9/82.3	0	28.7	11.2
	PBO		32	49.0†		83.9	71.2	10.9	0	16	11.2	65.6/62.5	0	30.3	11.8
LOTUS Zhu 2013	UST 45mg	36/12	160	40.1	12.4	78.1	69.9	11.9	0	14.6	8.9	39.4/37.5	11.9	23.2	9.5
	PBO		162	39.2	12.2	75.9	70	12.6	0	14.2	8.6	42.6/37.0	6.8	22.7	9.5
PEARL Tsai 2011	UST 45mg	36/12	61	40.9	12.7	82	73.1	12.7	0	11.9	7.5	70.5/80.3	21.3	25.2	11.9
	PBO		60	40.4	10.1	88.3	74.6	13	0	13.9	7.3	71.7/86.7	15	22.9	8.6
PHOENIX 1 Leonardi 2008	UST 45mg	76/12	255	44.8	12.5	68.6	93.7	23.8	NR	19.7	11.7	55.3/67.8	52.5	20.5	8.6
	UST 90mg		256	46.2	11.3	67.6	93.8	23.9	NR	19.6	11.1	55.1/66.0	50.8	19.7	7.6
	PBO		255	44.8	11.3	71.8	94.2	23.5	NR	20.4	11.7	55.7/58.8	50.2	20.4	8.6
PHOENIX 2 Papp 2008	UST 45mg	52/12	409	45.1	12.1	69.2	90.3	21	NR	19.3	11.7	54.5/69.9	38.4	19.4	6.8
	UST 90mg		411	46.6	12.1	66.7	91.5	21.3	NR	20.3	12.3	54.5/65.0	36.5	20.1	7.5
	PBO		410	47	12.5	69	91.1	21.6	NR	20.8	12.2	58.8/67.3	38.8	19.4	7.5
AMAGINE 2 Lebwohl 2014	UST 45mg, 90mg	52/12	300	45	13	68.3	91	24	90.3	19	13	75	28	20	8.4
	PBO		309	44	13	70.9	92	23	88.3	18	12	74.4	29.1	20.4	8.2
AMAGINE 3 Lebwohl 2014	UST 45mg, 90mg	52/12	313	45	13	67.7	90	22	89.5	18	12	70.3	24	20.1	8.4
	PBO		315	44	13	66	89	22	93.3	18	12	65.4	24.1	20.1	8.7

ADA = Adalimumab; BIW = twice weekly; CSR = Clinical Study Report; EOW = every other week; ETN = Etanercept; INF = Infliximab; IXE = Ixekizumab; MTX = Methotrexate; NR = not reported; PASI = Psoriasis Area and Severity Index; PBO = placebo; PUVA = Psoralen plus ultraviolet light; QW = once weekly; Q2W = every 2 weeks; Q4W = every 4 weeks; UST = Ustekinumab; SEC = Secukinumab; SD = Standard deviation; SE = Standard error

Table 50: PASI outcome responses as reported by all included RCTs

Trial	Author	Treatment	Time point, weeks	N	PASI 50		PASI 75		PASI 90		PASI 100		12 weeks (NICE endpoint)	12 week	16 week (NICE endpoint)
					(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)			
ACCEPT	Griffiths 2010	Ustekinumab 45mg	12	209	-	-	141	67.46	76	36.36	-	-	Yes	Yes	Yes
ACCEPT	Griffiths 2010	Ustekinumab 90mg	12	347	-	-	256	73.78	155	44.67	-	-	Yes	Yes	Yes
AMAGINE-2	Lebwohl 2015	Ustekinumab 45mg<100kg, 90mg>100kg	12	300	-	-	210	70.00	141	47.00	65	21.67	Yes	Yes	Yes
AMAGINE-2	Lebwohl 2015	Placebo	12	309	-	-	25	8.09	9	2.91	2	0.65	Yes	Yes	Yes
AMAGINE-3	Lebwohl 2015	Ustekinumab 45mg<100kg, 90mg>100kg	12	313	-	-	217	69.33	150	47.92	58	18.53	Yes	Yes	Yes
AMAGINE-3	Lebwohl 2015	Placebo	12	315	-	-	19	6.03	6	1.90	1	0.32	Yes	Yes	Yes
CHAMPION	Saurat 2008	Adalimumab 80mg/40mg EOW	16	108	95	87.96	86	79.63	56	51.85	18	16.67	-	-	Yes
CHAMPION	Saurat 2008	Placebo	16	53	16	30.19	10	18.87	6	11.32	1	1.89	-	-	Yes
CLEAR	Thaci 2015	Secukinumab 300mg	12	334	-	-	304	91.02	243	72.75	130	38.92	Yes	Yes	-
CLEAR	Thaci 2015	Ustekinumab 45mg<100kg, 90mg>100kg	12	335	-	-	265	79.10	179	53.43	86	25.67	Yes	Yes	-
ERASURE	EMA 2015	Secukinumab 300mg	12	245	222	90.61	200	81.63	145	59.18	70	28.57	Yes	Yes	-
ERASURE	EMA 2015	Placebo	12	246	22	8.94	11	4.47	3	1.22	2	0.81	Yes	Yes	-
EXPRESS	Reich 2005	Infliximab 5mg/kg	10	301	274	91.03	242	80.40	172	57.14	-	-	Yes	-	Yes
EXPRESS	Reich 2005	Placebo	10	77	6	7.79	2	2.60	1	1.30	-	-	Yes	-	Yes
EXPRESS II	Menter 2007	Infliximab 5mg/kg	10	314			237	75.48	142	45.22	-	-	Yes	-	Yes
EXPRESS II	Menter 2007	Placebo	10	208	-	-	4	1.92	1	0.48	-	-	Yes	-	Yes

Trial	Author	Treatment	Time point, weeks	N	PASI 50		PASI 75		PASI 90		PASI 100		12 weeks (NICE endpoint)	12 week	16 week (NICE endpoint)
					(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)			
FEATURE	EMA 2015	Secukinumab 300mg	12	58	51	87.93	44	75.86	35	60.34	25	43.10	Yes	Yes	-
FEATURE	EMA 2015	Placebo	12	59	3	5.08	0	0.00	0	0.00	0	0.00	Yes	Yes	-
FIXTURE	EMA 2015	Secukinumab 300mg	12	323	296	91.64	249	77.09	175	54.18	78	24.15	Yes	Yes	-
FIXTURE	EMA 2015	Placebo	12	324	49	15.12	16	4.94	5	1.54	0	0.00	Yes	Yes	-
JUNCTURE	EMA 2015	Secukinumab 300mg	12	60	58	96.67	52	86.67	33	55.00	16	26.67	Yes	Yes	-
JUNCTURE	EMA 2015	Placebo	12	61	5	8.20	2	3.28	0	0.00	0	0.00	Yes	Yes	-
LOTUS	Zhu 2013	Ustekinumab 45mg	12	160	146	91.25	132	82.50	107	66.88	38	23.75	Yes	Yes	Yes
LOTUS	Zhu 2013	Placebo	12	162	32	19.75	18	11.11	5	3.09	1	0.62	Yes	Yes	Yes
PEARL	Tsai 2011	Ustekinumab 45mg	12	61	51	83.61	41	67.21	30	49.18	5	8.20	Yes	Yes	Yes
PEARL	Tsai 2011	Placebo	12	60	8	13.33	3	5.00	1	1.67	0	0.00	Yes	Yes	Yes
PHOENIX 1	Leonardi 2008	Ustekinumab 45mg	12	255	213	83.53	171	67.06	106	41.57	32	12.55	Yes	Yes	Yes
PHOENIX 1	Leonardi 2008	Ustekinumab 90mg	12	256	220	85.94	170	66.41	94	36.72	28	10.94	Yes	Yes	Yes
PHOENIX 1	Leonardi 2008	Placebo	12	255	26	10.20	8	3.14	5	1.96	0	0.00	Yes	Yes	Yes
PHOENIX 2	Papp 2008	Ustekinumab 45mg	12	409	342	83.62	273	66.75	173	42.30	74	18.09	Yes	Yes	Yes
PHOENIX 2	Papp 2008	Ustekinumab 90mg	12	411	367	89.29	311	75.67	209	50.85	75	18.25	Yes	Yes	Yes
PHOENIX 2	Papp 2008	Placebo	12	410	41	10.00	15	3.66	3	0.73	0	0.00	Yes	Yes	Yes
REVEAL	Menter 2008	Adalimumab 80mg/40mg EOW	16	814	-	-	578	71.01	-	-	-	-	-	-	Yes
REVEAL	Menter 2008	Placebo	16	398	-	-	26	6.53	-	-	-	-	-	-	Yes
SPIRIT	Gottlieb 2004	Infliximab 5mg/kg	10	99	96	96.97	87	87.88	57	57.58	-	-	Yes	Yes	-
SPIRIT	Gottlieb 2004	Placebo	10	51	11	21.57	3	5.88	1	1.96	-	-	Yes	Yes	-

Trial	Author	Treatment	Time point, weeks	N	PASI 50		PASI 75		PASI 90		PASI 100		12 weeks (NICE endpoint)	12 week	16 week (NICE endpoint)
					(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)			
UNCOVER 1	CSR	Ixekizumab 80mg Q4W	12	432	389	90.05	357	82.64	279	64.58	145	33.56	-	-	-
UNCOVER 1	CSR	Ixekizumab 80mg Q2W	12	433	406	93.76	386	89.15	307	70.90	153	35.33	-	-	-
UNCOVER 1	CSR	Placebo	12	431	50	11.60	17	3.94	2	0.46	0	0.00	-	-	-
UNCOVER 2	Griffiths 2015	Ixekizumab 80mg Q4W	12	347	303	87.32	269	77.52	207	59.65	107	30.84	-	-	-
UNCOVER 2	Griffiths 2015	Ixekizumab 80mg Q2W	12	351	333	94.87	315	89.74	248	70.66	142	40.46	-	-	-
UNCOVER 2	Griffiths 2015	Placebo	12	168	11	6.55	4	2.38	1	0.60	1	0.60	-	-	-
UNCOVER 3	Griffiths 2015	Ixekizumab 80mg Q4W	12	386	347	89.90	325	84.20	252	65.28	135	34.97	-	-	-
UNCOVER 3	Griffiths 2015	Ixekizumab 80mg Q2W	12	385	361	93.77	336	87.27	262	68.05	145	37.66	-	-	-
UNCOVER 3	Griffiths 2015	Placebo	12	193	30	15.54	14	7.25	6	3.11	0	0.00	-	-	-
Asahina	Asahina 2010	Adalimumab 80mg/40mg EOW	16	43	35	81.40	27	62.79	17	39.53	-	-	-	-	Yes
Asahina	Asahina 2010	Placebo	16	46	9	19.57	2	4.35	0	0.00	-	-	-	-	Yes
Bissonnette	Bissonnette 2012	Adalimumab 80mg/40mg EOW	16	20	-	-	14	70.00	-	-	-	-	-	-	Yes
Bissonnette	Bissonnette 2012	Placebo	16	10	-	-	2	20.00	-	-	-	-	-	-	Yes
Chaudhari	Chaudhari 2001	Infliximab 5mg/kg	10	11	-	-	9	81.82	-	-	-	-	Yes		Yes
Chaudhari	Chaudhari 2001	Placebo	10	11	-	-	2	18.18	-	-	-	-	Yes		Yes

Trial	Author	Treatment	Time point, weeks	N	PASI 50		PASI 75		PASI 90		PASI 100		12 weeks (NICE endpoint)	12 week	16 week (NICE endpoint)
					(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)			
Gordon	Gordon 2015	Adalimumab 80mg/40mg EOW	16	43	-	-	30	69.77	19	44.19	11	25.58	-	-	Yes
Gordon	Gordon 2015	Placebo	16	42	-	-	2	4.76	1	2.38	0	0.00	-	-	Yes
Gottlieb	Gottlieb 2003	Etanercept 25mg BIW	12	57	40	70.18	17	29.82	6	10.53	-	-	Yes	Yes	Yes
Gottlieb	Gottlieb 2003	Placebo	12	55	6	10.91	1	1.82	0	0.00	-	-	Yes	Yes	Yes
Igarashi	Igarashi 2012	Ustekinumab 45mg	12	64	53	82.81	38	59.38	21	32.81	-	-	Yes	Yes	Yes
Igarashi	Igarashi 2012	Ustekinumab 90mg	12	62	52	83.87	42	67.74	27	43.55	-	-	Yes	Yes	Yes
Igarashi	Igarashi 2012	Placebo	12	31	4	12.90	2	6.45	1	3.23	-	-	Yes	Yes	Yes
Leonardi	Leonardi 2003	Etanercept 25mg BIW	12	162	94	58.02	55	33.95	19	11.73	-	-	Yes	Yes	Yes
Leonardi	Leonardi 2003	Placebo	12	166	24	14.46	6	3.61	1	0.60	-	-	Yes	Yes	Yes
Papp	Papp 2005	Etanercept 25mg BIW	12	196	126	64.29	67	34.18	21	10.71	-	-	Yes	Yes	Yes
Papp	Papp 2005	Placebo	12	193	18	9.33	6	3.11	1	0.52	-	-	Yes	Yes	Yes
Torii	Torii 2010	Infliximab 5mg/kg	10	35	29	82.86	24	68.57	19	54.29	-	-	Yes		Yes
Torii	Torii 2010	Placebo	10	19	2	10.53	0	0.00	0	0.00	-	-	Yes		Yes
van de Kerkhof	van de Kerkhof 2008	Etanercept 50mg QIW	12	96	66	68.75	36	37.50	13	13.54	-	-	Yes	Yes	Yes
van de Kerkhof	van de Kerkhof 2008	Placebo	12	46	4	8.70	1	2.17	1	2.17	-	-	Yes	Yes	Yes
Yang	Yang 2012	Infliximab 5mg/kg	10	84	79	94.05	68	80.95	48	57.14	-	-	Yes		Yes
Yang	Yang 2012	Placebo	10	45	6	13.33	1	2.22	0	0.00	-	-	Yes		Yes

BIW=Twice a week dosing regimen; CSR=clinical study report; EMA=European Medicines Agency; EOW=every other week; PASI=Psoriasis Area and Severity Index; NICE=National Institute for Health and Care Excellence; PASI50= ≥50% improvement in Psoriasis Area and Severity Index; PASI75= ≥75% improvement in Psoriasis Area and Severity Index; PASI90= ≥90% improvement in Psoriasis Area and Severity Index; PASI100= 100% improvement in Psoriasis Area and Severity Index; QIW=Once weekly dosing regimen; Q2W=Every second week dosing regimen; Q4W=Every fourth week dosing regimen

4.9.8 Differences in patient populations of trials included in the NMA

Patient demographics and baseline characteristics for each of the studies include in the NMA can be seen in Table 49.

When comparing the proportion of males in the studies there was a high homogeneity with most trials including 60-80% of male patients. The mean proportion of males was 69.3% in the experimental arms and 70.7% in the control arms with similar calculated standard deviations of 4.6% and 5.3% for the experimental and control arms, respectively. The medians in both groups were also relatively close to each other with 67.7% and 70.3% in the experimental and control arms, respectively. Hence the variation in male proportions are not assumed to have an impact on the study results overall.

The average age was homogenous across all studies and ranges between 40 and 50 years. The mean age in all included studies was 45.0 years with a median age of 45.1 years. The standard deviation of the calculated mean was 1.77 years supporting the homogeneity of age within the included studies.

The studies included in the NMA were largely made up of Caucasian patients (mean proportion: 68.2% in the experimental arms versus 68.1% in the control arms). The median proportion of Caucasians was 91% and 90% for the experimental and control arms, respectively. However, some studies conducted in the Far East did not include any Caucasian patients - Asahina *et al.* 2010[94], Torii *et al.* 2010[103], Yang *et al.* 2012[106], Igarashi *et al.* 2012[116], Zhu *et al.* 2013[114], Tsai *et al*. 2011[111] The predictive impact of race has not been seen in psoriasis, however sensitivity analyses which excluded Asian patients from the evidence network confirmed that race did not impact the base case results (not presented in this submission).

The average patient weight in all trials was 85.7 kg with a standard deviation of the calculated mean of 7.4 kg. The median weight was 90.1 kg. There were a small number of outliers with respect to the average body weight, which were primarily the Asian studies. The impact of body weight might be a factor of patient race, which was examined in sensitivity analyses and did not impact on base case results (not presented in this submission).

The average duration of psoriasis in the majority of trials has been reported to be between 11.1 to 20 years with a mean duration of 17.8 years (standard deviation: 1.7 years) and a corresponding median of 17.9 years. The only major differences were again seen in Asian studies where the range of psoriasis duration was between 13 and 14 years. As previously

stated, the impact of patient race did not impact on base case results in sensitivity analyses (not presented in this submission).

The mean baseline PASI score across all studies was 21.1 with a calculated standard deviation of the reported mean values of 2.8, which indicates a homogenous PASI score between the included studies. Two Asian studies had a higher score than 25 at baseline Asahina *et al.* 2010[94], and Igarashi *et al.* 2012[116] Nonetheless, the median PASI score supports the findings that the baseline PASI scores are homogeneously distributed across the studies included in the psoriasis base case NMA (median PASI score=20.4).

In summary, on inspection of the baseline characteristics across the included studies no major imbalances were noted. As would be expected, chronologically newer studies were more likely to include patients with prior exposure to previous biologics but the assumption was made that this would not impact on the outcomes of the NMA. Furthermore, a feasibility assessment of the evidence for an indirect comparison of the population of patients who were inadequate responders to TNF-inhibitors found that such a comparison was not feasible.

4.9.9 Overview of studies included in the base case NMA analysis

The designs of the trials included in the base case NMA have been presented in Table 48. Baseline patient characteristics and results of the included trials can be seen in Table 49 and Table 50, respectively.

4.9.10 Risk of bias – QA of included trials

Bias assessments of all included studies are provided in Appendix 9.

4.9.11 Risk of bias – identified risk of bias within the included trials and adjustments made to the analysis

No trials were excluded following the risk of bias assessments; therefore no adjustments were made to the analysis.

4.9.12 NMA methodology

The analyses followed the principles given in the NICE DSU technical support document 3 by Dias and colleagues for ordered categorical data, the key details of which are reproduced below. The approach utilised uses a multinomial likelihood model with a probit link:

$$p_{ikj} = \Phi (\mu_i + z_{ij} + \delta_{i,bk} I_{\{k \neq 1\}}$$

where j represents the different PASI response thresholds, k is an arm of a trial i oand therefore p_{ijk} is the probability that a patient in arm k of trial i belongs to category j. The pooled effect of the experimental treatment versus the control (in this case, the placebo arm of the included studies) is to change the probit (Z) score of the control by $\delta_{i,bk}$ standard deviations. The term z_{ij} specifies the cut-offs at which the individual moves from one category to the next in trial i. This model allows inclusion of trials using different thresholds or trials reporting different numbers of thresholds- which is the case here as not all included studies reported PASI 100 outcomes.

The analysis also follows the guidance from TSD2 by Dias and colleagues to re-write the multinomial likelihood as a series of conditional binomials.. Analyses were carried out with 30,000 iterations and with a burn-in period of 10,000.

4.9.13 Programming language

The WinBUGS code used in the NMA is provided in Appendix 10.

4.9.14 Results

Pairwise comparisons of the relative risk (RR) of achieving a PASI ≥75 response for all the interventions evaluated in the base case NMA can be seen in Table 51. The RR for ixekizumab 80mg QIW achieving a PASI ≥75 response was significantly higher than all the biologic therapies; with the exception of infliximab 5mg/kg (1.03, 95% Cr.I: 0.94,1.17).

The conditional probability of each intervention achieving at least the given PASI response (PASI 50, 75, 90 and 100) can be seen in Table 52.

Table 51: Random effects multinomial NMA for PASI 75 response (RR at week 12)

Placebo	0.11 (0.06, 0.19)	0.09 (0.05, 0.16)	0.09 (0.05, 0.16)	0.07 (0.03, 0.15)	0.08 (0.04, 0.15)	0.06 (0.02, 0.14)	0.07 (0.03, 0.14)	0.07 (0.03, 0.14)	0.06 (0.02, 0.14)
9.48 (5.15, 15.87)	**Etanercept 25mg BIW & 50mg QIW**	0.78 (0.49, 1.07)	0.76 (0.49, 1.04)	0.62 (0.36, 0.87)	0.66 (0.40, 0.92)	0.54 (0.28, 0.80)	0.57 (0.31, 0.83)	0.57 (0.31, 0.82)	0.53 (0.26, 0.79)
12.56 (6.15, 21.05)	1.34 (0.93 2.04)	**Adalimumab 80mg/40mg EOW**	0.98 (0.77, 1.23)	0.80 (0.58, 0.96)	0.86 (0.65, 1.03)	0.69 (0.46, 0.89)	0.74 (0.51, 0.91)	0.73 (0.50, 0.91)	0.68 (0.44, 0.87)
12.85 (6.20, 21.60)	1.37 (0.96, 2.05)	1.03 (0.82, 1.31)	**Ustekinumab 45mg < 100kg & 90mg>100kg**	0.82 (0.60, 0.97)	0.88 (0.67, 1.05)	0.71 (0.47, 0.89)	0.75 (0.55, 0.91)	0.75 (0.53, 0.91)	0.69 (0.45, 0.88)
16.26 (6.82, 30.77)	1.71 (1.15, 2.79)	1.27 (1.04, 1.72)	1.25 (1.03, 1.65)	**Ustekinumab 90mg**	1.08 (1.01, 1.21)	0.87 (0.68, 0.98)	0.92 (0.77, 1.04)	0.91 (0.75, 1.04)	0.84 (0.66, 0.96)
14.96 (6.60, 27.03)	1.58 (1.09, 2.50)	1.18 (0.97, 1.54)	1.16 (0.96, 1.48)	0.93 (0.83, 0.99)	**Ustekinumab 45mg**	0.81 (0.60, 0.95)	0.86 (0.68, 0.98)	0.85 (0.66, 0.98)	0.79 (0.58, 0.93)
19.28 (7.18, 40.87)	2.00 (1.24, 3.62)	1.48 (1.13, 2.20)	1.45 (1.12, 2.12)	1.16 (1.02, 1.46)	1.25 (1.06, 1.66)	**Infliximab 5mg/kg**	1.07 (0.95, 1.25)	1.06 (0.94, 1.23)	0.97 (0.85, 1.07)
17.86 (7.03, 35.65)	1.87 (1.21, 3.19)	1.39 (1.10, 1.95)	1.35 (1.10, 1.82)	1.09 (0.96, 1.31)	1.17 (1.02, 1.48)	0.94 (0.80, 1.05)	**Secukinumab 300mg**	0.99 (0.87, 1.12)	0.91 (0.78, 1.00)
18.09 (7.05, 36.40)	1.89 (1.21, 3.28)	1.40 (1.10, 1.98)	1.37 (1.09, 1.91)	1.10 (0.97, 1.34)	1.19 (1.02, 1.51)	0.95 (0.81, 1.07)	1.01 (0.89, 1.14)	**Ixekizumab 80mg Q4W**	0.92 (0.82, 0.98)
19.93 (7.24, 42.96)	2.07 (1.26, 3.79)	1.53 (1.15, 2.29)	1.49 (1.14, 2.20)	1.20 (1.04, 1.52)	1.29 (1.08, 1.74)	1.03 (0.94, 1.17)	1.10 (1.00, 1.29)	1.09 (1.02, 1.22)	**Ixekizumab 80mg Q2W**

BIW=Twice a week dosing regimen; EOW=Every other week; PASI75=≥75% improvement in Psoriasis Area and Severity Index; QIW=Once weekly dosing regimen; Q2W=Every second week dosing regimen; Q4W=Every fourth week dosing regimen; RR=Relative risk

Table 52: PASI base case NMA random-effects model - absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment

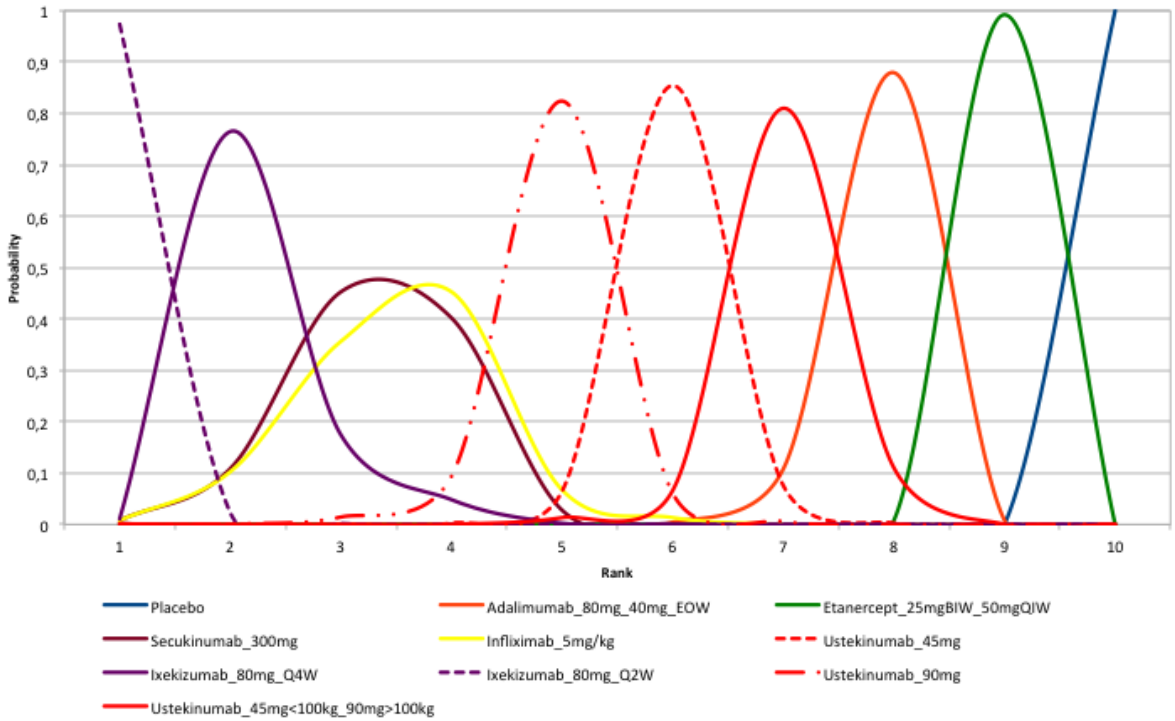
	PASI 50			PASI 75			PASI 90			PASI 100		
	Probability	95% CrI		Probability	95% CrI		Probability	95% CrI		Probability	95% CrI	
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	93.2%	89.5%	96.1%	81.8%	74.9%	88.1%	59.6%	50.0%	69.3%	28.6%	20.7%	37.9%
Infliximab 5 mg/kg	92.8%	88.1%	96.1%	81.1%	72.6%	88.1%	58.7%	47.2%	69.4%	27.8%	18.7%	38.0%
Ustekinumab 45 mg	87.1%	81.4%	91.7%	71.0%	62.2%	78.8%	45.6%	36.0%	55.2%	17.9%	12.0%	24.7%
Ustekinumab 90 mg	89.6%	84.2%	93.7%	75.1%	66.2%	82.7%	50.6%	40.1%	60.7%	21.4%	14.3%	29.5%
Ustekinumab 45 mg<100kg & 90 mg>100kg	82.8%	75.3%	89.0%	64.4%	54.0%	73.9%	38.4%	28.4%	48.8%	13.5%	8.3%	20.0%
Adalimumab 80 mg/40mg EOW	77.8%	68.9%	85.5%	57.5%	46.4%	68.2%	31.7%	22.3%	42.2%	10.0%	5.7%	15.6%
Etanercept	63.9%	52.8%	74.3%	41.3%	30.3%	52.8%	18.9%	11.8%	27.5%	4.6%	2.3%	7.9%
Placebo	13.7%	10.1%	17.9%	4.7%	3.1%	6.6%	1.0%	0.6%	1.5%	0.1%	0.0%	0.1%

CrI = credible intervals; EOW = every other week; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement in Psoriasis Area and Severity Index; PASI 75 = ≥75% improvement in Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in Psoriasis Area and Severity Index; PASI 100 = 100% improvement in Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks

Figure 30 shows the rankogram derived from the base case Bayesian analysis with the treatments ranked on the probability of best based on the posterior distributions for each intervention.

The rankogram shows a clear indication that ixekizumab twice weekly has the highest probability of being the best ranked treatment (over 95%)

Figure 30: Base case analysis rankogram



EOW = every other week; Q1W = once weekly; Q2W = every two weeks; Q4W = every four weeks; SA=Sensitivity analysis

For the scenario analysis that included etanercept 50mg BIW and standard systemic treatments as interventions, the results of the analysis expressed as probabilities of achieving at least the PASI response for each category are shown in Table 53.

Table 53: PASI scenario analysis 1 NMA random-effects model - absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment

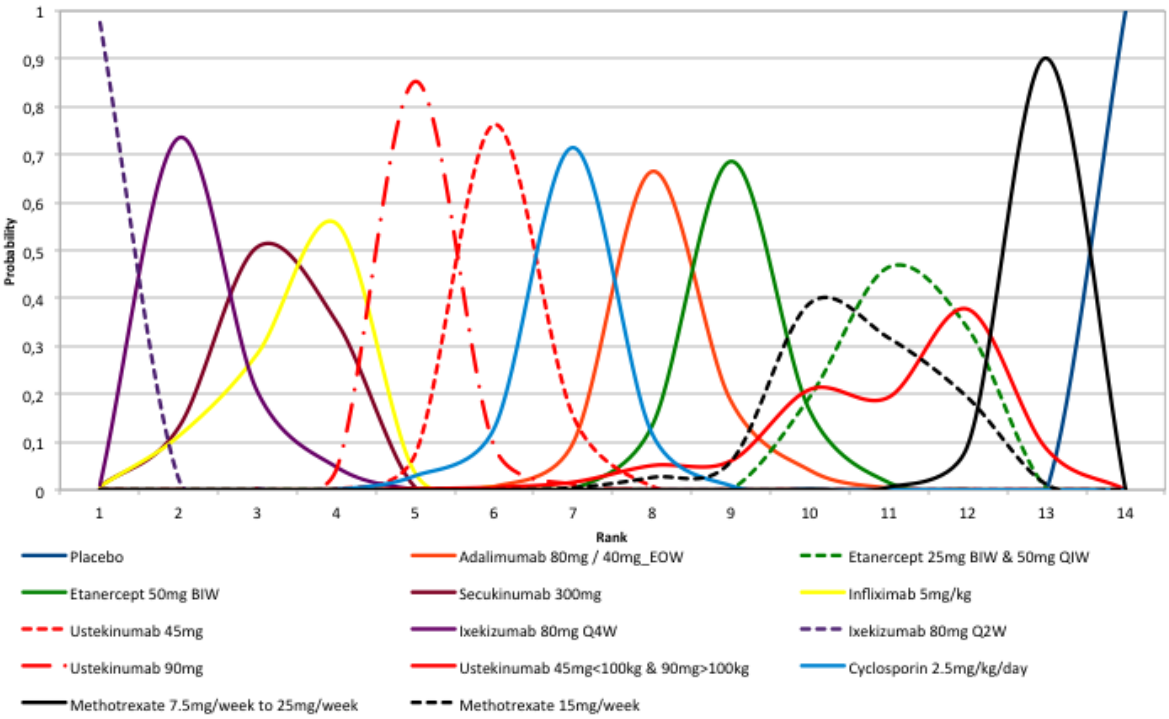
	PASI 50			PASI 75			PASI 90			PASI 100		
	Probability	95% CrI		Probability	95% CrI		Probability	95% CrI		Probability	95% CrI	
Ixekizumab 80mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	94.0%	90.6%	96.6%	82.6%	75.8%	88.5%	60.1%	50.4%	69.6%	29.4%	21.3%	38.6%
Infliximab 5mg/kg	93.3%	88.7%	96.6%	81.3%	72.3%	88.6%	58.2%	46.2%	69.6%	27.8%	18.3%	38.7%
Ustekinumab 45mg	86.7%	81.0%	91.4%	69.2%	60.4%	77.4%	42.8%	33.5%	52.5%	16.3%	10.9%	22.9%
Ustekinumab 90mg	89.1%	83.8%	93.3%	73.2%	64.5%	81.1%	47.4%	37.5%	57.6%	19.4%	13.0%	27.1%
Ustekinumab 45mg<100kg & 90mg>100kg	83.5%	76.1%	89.7%	64.3%	53.7%	74.2%	37.6%	27.5%	48.4%	13.3%	8.0%	19.9%
Adalimumab 80mg/40mg EOW	78.2%	69.0%	85.9%	56.8%	45.2%	67.8%	30.4%	20.9%	40.9%	9.5%	5.3%	15.1%
Etanercept 25mg BIW & 50mg QW	61.0%	51.0%	70.7%	37.1%	27.7%	47.2%	15.5%	10.0%	22.4%	3.5%	1.8%	5.9%
Etanercept 50mg BIW	74.4%	67.2%	80.9%	51.7%	43.3%	60.2%	26.0%	19.5%	33.3%	7.5%	4.8%	10.9%
Cyclosporin 2.5mg/kg/day	59.9%	33.3%	83.7%	37.1%	14.7%	64.4%	16.4%	4.1%	37.4%	4.1%	0.5%	13.0%
Methotrexate 15mg/week	64.2%	47.2%	79.5%	40.6%	24.6%	58.2%	18.2%	8.4%	31.5%	4.5%	1.4%	9.9%
Methotrexate 7.5 to 25 mg/week	39.9%	24.5%	56.4%	19.5%	9.6%	32.5%	6.3%	2.3%	12.7%	1.0%	0.3%	2.6%
Placebo	13.7%	10.2%	17.9%	4.4%	2.9%	6.3%	0.8%	0.5%	1.3%	0.1%	0.0%	0.1%

CrI = credible intervals; EOW = every other week; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement in Psoriasis Area and Severity Index; PASI 75 = ≥75% improvement in Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in Psoriasis Area and Severity Index; PASI 100 = 100% improvement in Psoriasis Area and Severity Index; QW = once weekly; Q2W = every 2 weeks; Q4W = every 4 weeks

Results for this network were largely consistent with the base case network - for example, ixekizumab Q2W has a mean probability of achieving PASI 100 of 41.5% in this analysis versus 41.3% in the base case analysis, together with similar credible intervals.

The rankogram for this network (Figure 31) again demonstrates similar outcomes with ixekizumab Q2W having the highest probability of being ranked the best treatment (>95%).

Figure 31: Scenario analysis 1 rankogram



BIW twice weekly; EOW = every other week; Q1W = once weekly; Q2W = every two weeks; Q4W = every four weeks

The third scenario analysis reported consisted of the decision set interventions for ixekizumab and the standard systemic treatments. Again, similar results are seen (Table 54 and Figure 32) for ixekizumab Q2W (e.g. PASI 100 mean probability 44.5%), although credible intervals were slightly broader, which could be expected due to the sparser network in this analysis.

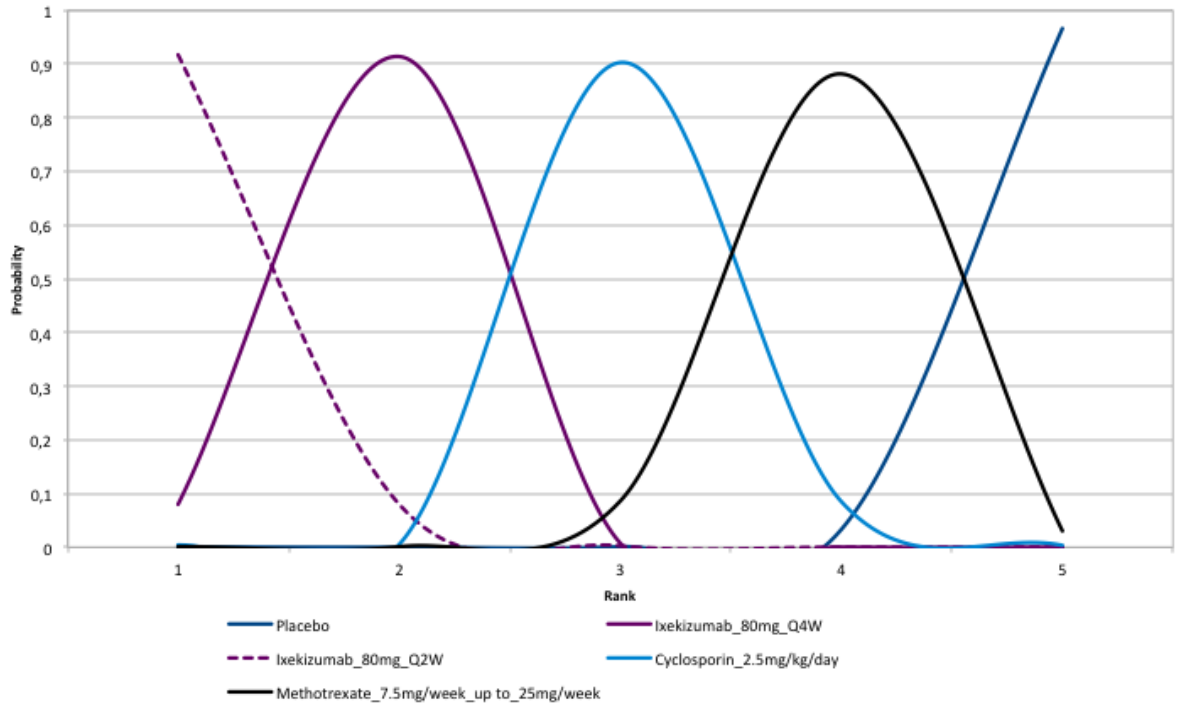
Table 54: PASI scenario analysis 2 NMA random-effects model - absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment

	PASI 50			PASI 75			PASI 90			PASI 100		
	Probability	95% CrI		Probability	95% CrI		Probability	95% CrI		Probability	95% CrI	
Ixekizumab 80mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclosporin 2.5mg/kg/day	58.2%	26.1%	87.1%	43.5%	14.7%	76.8%	23.5%	4.8%	54.7%	7.4%	0.7%	24.9%
Methotrexate 7.5mg/week up to 25mg/week	32.7%	12.1%	59.3%	20.4%	5.8%	43.4%	8.0%	1.4%	21.9%	1.6%	0.1%	5.8%
Placebo	13.7%	10.2%	17.9%	6.8%	4.6%	9.4%	1.8%	1.1%	2.7%	0.2%	0.1%	0.3%

CrI = credible intervals; EOW = every other week; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement in Psoriasis Area and Severity Index; PASI 75 = ≥75% improvement in Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in Psoriasis Area and Severity Index; PASI 100 = 100% improvement in Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks

The rankogram for this network (Figure 32) again demonstrates similar outcomes with ixekizumab Q2W having the highest probability of being ranked the best treatment (>95%).

Figure 32: Scenario analysis 2 rankogram



Q2W = every 2 weeks; Q4W = every 4 weeks

4.9.15 Assessment of heterogeneity

Section 4.9.7 discussed that the trials included in the networks were largely similar with respect to baseline patient characteristics. Table 55 summarises the tau heterogeneity parameter for base case and scenario analyses which suggests that there was low heterogeneity across the networks. Furthermore, the consistency of the results across the base case and scenario analyses conducted suggest that the outcomes of the NMA are relatively robust.[67] Multiple additional scenario analyses conducted but not reported here also showed similar results, with ixekizumab Q2W always being the treatment with the highest probability of being ranked best.

Table 55: Tau values as a measure of precision for base case and scenario analyses

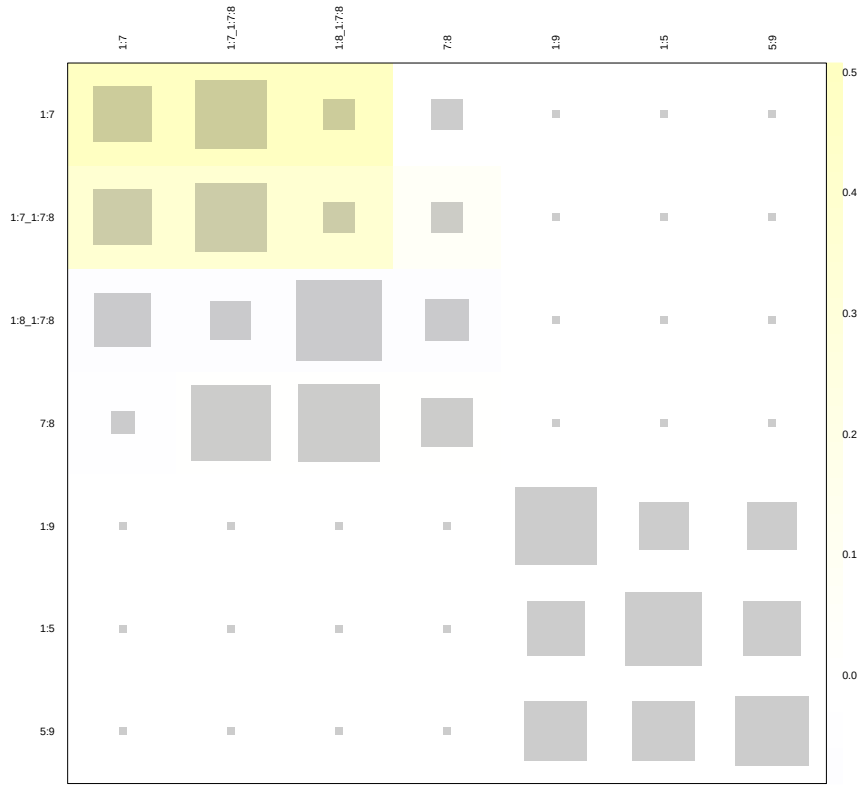
Sensitivity analysis	Mean tau	Tau SD	Median tau	97.5% CrI	
Base case analysis	129.2	207.5	72.3	22.0	632.5
Scenario analysis 1 (etanercept 50 mg BIW)	75.9	62.8	58.7	22.6	244.0
Scenario analysis 2 (conventional systemic therapies)	931.2	10760.0	30.5	1.8	3575.0

CrI = credible intervals; SD = standard deviation

A heat map was produced to examine inconsistency of indirect and direct evidence (Figure 33). For disclosure of potential drivers, the plot comprises the contribution of each direct estimate to network estimates resulting from regression diagnostics. In combination, the plot shows heat colours corresponding to the change in consistency between direct and indirect estimate when relaxing the assumption of consistency for one direct comparison. A clustering procedure is applied to the heat matrix in order to find hot spots of inconsistency.

The colours on the diagonal represent the inconsistency contribution of the corresponding design. The colours on the off-diagonal are associated with the change in inconsistency between direct and indirect evidence in a network estimate in the row after relaxing the consistency assumption for the effect of one design in the column. Cool colours indicate an increase and warm colours a decrease. Generally the colours could go from blue indicating that the evidence of the design in the column supports the evidence in the row to red, which indicates that the evidence of the design in the column contrasts to the evidence in the row. The net heat plot below only shows yellow spots,the area of the grey squares displays the contribution of the direct estimate in design d (shown in the column) to the network estimate in design d (shown in the row). The colours are associated with the change in inconsistency between direct and indirect evidence in design d (shown in the row) after detaching the effect of design d (shown in the column). The heat map shows that the inconsistency between direct and indirect evidence was limited in the base case network.

Figure 33: Net heat plot for consistency evaluation of base case analysis



1=Placebo, 2=Adalimumab 80mg / 40mg EOW, 3=Etanercept 25mg BIW & Etanercept 50mg QIW, 4=Secukinumab 300mg, 5=Infliximab 5mg/kg, 6=Ustekinumab 45mg, 7=Ustekinumab 90mg, 8=Ustekinumab 45mg<100kg & 90mg>100kg, 9=Ixekizumab 80mg Q4W, 10=Ixekizumab 80mg Q2W

4.9.16 Random vs fixed effects model

Deviance information criteria (DIC) were obtained for the random and fixed-effects models for the base case analysis in order to determine which would be the preferred analysis. The random-effects models had a lower DIC compared with the fixed effects models and were therefore chosen as the most appropriate analyses (Table 56).

Table 56: DIC for the random and fixed effects models for the base case analysis

DIC	Random-effects model	Fixed-effects model
Base case analysis	1 306.50	1 313.19

DIC = deviance information criteria

4.9.17 Conclusion

The results of the base case NMA demonstrated that ixekizumab 80 mg Q2W was ranked as the therapy with the highest probability of being ranked best, achieving PASI 75 and PASI 90 responses at week 12 of [redacted] and [redacted], respectively (Table 52).

The consistency and robustness of the NMA was confirmed with the results of the scenario analyses reported here which were consistent with the base case. Statistical tests of heterogeneity and inconsistency indicated that the results of the analysis were robust.

4.10 *Non-randomised and non-controlled evidence*

No relevant non-randomised or non-controlled evidence was identified from the evidence search.

4.11 *Adverse reactions*

Summary of ixekizumab safety profile:

Ixekizumab was well tolerated across the UNCOVER studies with a predictable safety profile which was comparable to etanercept. Adverse events (AEs) which occurred following treatment with ixekizumab were generally of mild to moderate severity and did not lead to discontinuation from ixekizumab.

- The safety profile of ixekizumab has been robustly evaluated through AE reporting in the UNCOVER studies, which included head-to-head assessments against etanercept (UNCOVER-2 and -3 only) and involved 3,866 patients.
- The incidence any treatment-emergent adverse events (TEAEs) was higher in the ixekizumab treatment groups, relative to placebo; however, most TEAEs were of mild or moderate severity and did not lead to discontinuation of study medication at week 12.
- The incidence of TEAEs was comparable between the ixekizumab and etanercept treatment groups at week 12.
- Serious adverse events (SAEs) and discontinuations did not differ between the ixekizumab, etanercept or placebo treatment groups at week 12. The incidence of discontinuations and SAEs in the ixekizumab Q2W treatment group across the UNCOVER studies ranged from 1.7% to 2.3% and 1.4% to 2.3%, respectively at week 12.
- The most frequent adverse events of special interest (AESIs) observed in the UNCOVER studies were infections and injection site reactions.
- The safety profile of ixekizumab was also evaluated in the maintenance period of UNCOVER-1 and -2 (up to week 60) to ensure any AEs which take more time to emerge were captured. Ixekizumab was well tolerated in the maintenance dosing period with similar AEs to those seen in the induction period.

The safety and tolerability of ixekizumab during a 12 week Induction Dosing Period was assessed by study drug discontinuation, adverse events (AEs) (including treatment emergent adverse events [TEAEs], serious adverse events [SAEs], and discontinuation due to AEs), laboratory measurements, vital signs, ECGs, and immunogenicity markers.

A serious adverse event (SAE) is any AE from these studies that resulted in one of the following outcomes: death, initial or prolonged inpatient hospitalisation, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, or any other outcome considered significant by the investigator for any other reason. TEAEs were further examined within topics of special interest (AESIs). Adverse events of special interest included categories of infections, cytopaenias, allergic/hypersensitivity reactions, injection site reactions, cerebrovascular events, hepatic events, malignancies, depression, pneumocystis pneumonia, interstitial lung disease, Crohn's disease, and ulcerative colitis.

In the UNCOVER studies, ixekizumab was well tolerated in patients with moderate to severe psoriasis with a comparable safety profile to the active comparator etanercept. The majority of TEAEs which occurred following treatment with ixekizumab were of mild or moderate severity and did not lead to discontinuation from study drug.

4.11.1 UNCOVER-1

Induction Dosing Period

During the 12-week Induction Dosing Period, safety data were obtained from 1,296 patients who were randomised to receive placebo (N=431), ixekizumab Q4W (N=432), or ixekizumab Q2W (N=433). This phase of the study was completed by 94.9% of all patients. Table 57 provides an overview of the adverse events reported during the Induction Dosing Period.[15,21]

During the induction dosing period, the proportion of patients with ≥1 TEAE and TEAEs judged to be possibly related to study drug was statistically significantly higher in the ixekizumab groups compared with the placebo group ($p<0.05$ for all comparisons). At week 12 the proportion of patients who experienced ≥1 TEAE was 59.4% in the ixekizumab 80 Q2W group, 61.1% in the ixekizumab 80 Q4W group and 48.7% in the placebo group, respectively. The proportion of patients who experienced TEAEs judged to be possibly related to study drug was 29.3% in the ixekizumab 80 Q2W group, 25.7% in the ixekizumab 80 Q4W group and 11.4% in the placebo group, respectively. The majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication Table 57.[15,21]

The proportion of patients who discontinued study medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab and placebo groups (IXE Q2W: 2.3%; IXE Q4W: 2.3%; PBO: 1.4%) Table 57.[15,21]

SAEs occurred in 1.8% of all patients (IXE Q2W: 1.4%; IXE Q4W: 2.8%; PBO: 1.2%) with no statistically significant differences between ixekizumab and placebo groups Table 57.[15,21]

The most frequently reported categories of AESI were infections and injection site reactions, reported by 27.6% and 10.3% of all patients, respectively. Injection site reactions were statistically significantly more common in both ixekizumab treatment groups occurring at a frequency of 15.9%, 12.0% and 3.0% in the ixekizumab Q2W, ixekizumab Q4W and placebo group, respectively ($p<0.001$ for both comparisons). The most frequently reported infection types in ixekizumab-treated patients were nasopharyngitis, upper respiratory tract infection, bronchitis, and sinusitis.[15,21]

Table 57: UNCOVER-1: Overview of AEs – safety population (Induction Dosing Period)[15,21]

	Placebo (N=431) n (%)	IXE80Q4W (N=432) n (%)	IXE80Q2W (N=433) n (%)	Total IXE (N=865) n (%)	Total (N=1,296) n (%)
Patients with ≥1 TEAE	210 (48.7%)	264 (61.1%)	257(59.4%)	521 (60.2%)	731 (56.4%)
Discontinuations from Study Drug due to AE (including death)	6 (1.4%)	10 (2.3%)	10 (2.3%)	20 (2.3%)	26 (2.0%)
Deaths	0	0	0	0	0
SAEs	5 (1.2%)	12 (2.8%)	6 (1.4%)	18 (2.1%)	23 (1.8%)
TEAEs possibly related to study drug	49 (11.4)	111 (25.7)	127 (29.3)	238 (27.5)	287 (22.1)
Treatment-Emergent AE of Special Interest					
Cytopenias	6 (1.4)	3 (0.7)	4 (0.9)	7 (0.8)	13 (1.0)
Hepatic	6 (1.4)	7 (1.6)	4 (0.9)	11 (1.3)	17 (1.3)
Infection	106 (24.6)	128 (29.6)	124 (28.6)	252 (29.1)	358 (27.6)
Injection-site reactions	13 (3.0)	52 (12.0)	69 (15.9)	121 (14.0)	134 (10.3)
Allergic reactions/ Hypersensitivities Anaphylaxis† Non-Anaphylaxis	10 (2.3) 2 (0.5) 8 (1.9)	19 (4.4) 2 (0.5) 17 (3.9)	14 (3.2) 2 (0.5) 12 (2.8)	33 (3.8) 4 (0.5) 29 (3.4)	43.3 (3.3) 6 (0.5) 37 (2.9)
Cerebrocardiovascular events	0 (0)	3 (0.7)	0 (0)	3 (0.3)	3 (0.2)
Malignancies	2 (0.5)	3 (0.7)	0 (0)	5 (0.4)	5 (0.4)
Depression	3 (0.7)	2 (0.5)	1 (0.2)	6 (0.5)	6 (0.5)
Pneumocystis pneumonia (PCP)	0	0	0	0	0
Interstitial lung disease	1 (0.2)	0 (0)	0 (0.0)	0	1 (0.1)
Crohn's Disease	0 (0)	1 (0.2)	0 (0)	1 (0.1)	1 (0.1)
Ulcerative Colitis	0 (0)	0 (0)	1 (0.2)	1 (0.1)	1 (0.1)

† Anaphylaxis as shown here refers to potential cases using broadly-defined Sampson criteria. There were no confirmed cases of anaphylaxis in the Induction Dosing Period

AE = adverse event; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: CSR RHAZ, Table RHAZ.12.4 (Page 1 and 2 of 3)

Maintenance Dosing Period

A total of 682 patients responded to ixekizumab treatment and continued to a Maintenance Dosing Period for which they were re-randomised to receive placebo (N=226), ixekizumab Q12W (N=227), or ixekizumab Q4W (N=229) as part of the maintenance dosing period primary population. Table 58 provides an overview of the adverse events reported during the maintenance dosing period.[15,21]

During the maintenance dosing period, the proportion of patients with ≥1 TEAE and TEAEs judged to be possibly related to study drug was statistically significantly higher in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W group compared with the ixekizumab 80 mg Q2W/placebo group (p<0.001 and p=0.017, respectively). At week 60 the proportion of patients who experienced ≥1 TEAE was 79.8% in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W group compared with 49.6% in the ixekizumab 80 mg Q2W/placebo. The proportion of patients who experienced TEAEs judged to be possibly related to study drug was 27.7% in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W group compared with 14.5% in the ixekizumab 80 mg Q2W/placebo. The majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication (Table 58).[15,21]

The proportion of patients who discontinued study medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups (IXEQ2W/Q4W: 3.4%; IXEQ2W/PBO: 0%)(Table 58).[15,21]

The proportion of patients who experienced SAEs was low across all treatment groups with no statistically significant differences between ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups (IXEQ2W/Q4W: 6.0%; IXEQ2W/PBO: 3.4%)(Table 58).[15,21]

The most frequently reported categories of AESIs observed during the maintenance period were infections (IXEQ2W/Q4W: 55.5%; IXEQ2W/PBO: 37.6%; p<0.001), non-anaphylactic allergic reactions/hypersensitivities (IXEQ2W/Q4W: 10.9%; IXEQ2W/PBO: 0.9%; p=0.001), and injection site reactions (IXEQ2W/Q4W: 4.2%; IXEQ2W/PBO: 0%; p=0.060).[15,21]

There were two deaths during the maintenance dosing period occurring in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and the ixekizumab 80 mg Q4W/ixekizumab 80 mg Q4W group; one by myocardial infarction and the other of unknown causes.[15,21]

Table 58: UNCOVER-1: Overview of AEs – safety population (Maintenance Dosing Period)[15,21]

	IXE80Q4W /PBO (N=109) n (%)	IXE80Q4W/ IXE80Q4W (N=110) n (%)	IXE80Q2W/ PBO (N=117) n (%)	IXE80Q2W/ IXE80Q4W (N=119) n (%)	IXE/PBO (N=226) n (%)	IXE/ IXE80Q4W (N=229) n (%)
Patients with ≥1 TEAE	65 (59.6)	87 (79.1)	58 (49.6)	95 (79.8)	123 (54.4)	182 (79.5)
Discontinuations from Study Drug due to AE (including death)	4 (3.7)	5 (4.5)	0	4 (3.4)	4 (1.8)	9 (3.9)
Deaths	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.9)
SAEs	3 (2.8%)	8 (7.3%)	4 (3.4%)	7 (6.0%)	7 (3.1%)	15 (6.6%)
TEAEs possibly related to study drug	22 (20.2)	38 (34.5)	17 (14.5)	33 (27.7)	-	-
Treatment-Emergent AE of Special Interest						
Cytopenias	1 (0.9)	3 (2.7)	1 (0.9)	4 (3.4)	2 (0.9)	7 (3.1)
Hepatic	3 (2.8)	5 (4.5)	1 (0.9)	7 (5.9)	4 (1.8)	12 (5.2)
Infection	41 (37.6)	63 (57.3)	33 (28.2)	66 (55.5)	74 (32.7)	129 (56.3)
Injection-site reactions	2 (1.8)	11 (10.0)	0	5 (4.2)	2 (0.9)	16 (7.0)
Allergic reactions/ Hypersensitivities Anaphylaxis† Non-Anaphylaxis	6 (5.5) 0 6 (5.5)	8 (7.3) 0 8 (7.3)	1 (0.9) 0 1 (0.9)	13 (10.9) 0 13 (10.9)	7 (3.1) 0 7 (3.1)	21 (9.2) 0 21 (9.2)
Cerebrocardiovascular events	0	2 (1.8)	1 (0.9)	1 (0.8)	1 (0.4)	3 (1.3)
Malignancies	0	0	0	0	0	0
Depression	0	1 (0.9)	0	0	0	1 (0.4)
PCP	0	0	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0
Crohn's Disease	0	0	1 (0.9)	0	1 (0.4)	0
Ulcerative Colitis	0	0	0	0	0	0

† Anaphylaxis as shown here refers to potential cases using broadly-defined Sampson criteria. There were no confirmed cases of anaphylaxis in the Maintenance Dosing Period

AE = adverse event; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: CSR RHAZ, Table RHAZ.12.5 (Page 1 and 2 of 3)

4.11.2 UNCOVER-2

Induction Dosing Period

During the 12-week Induction Dosing Period, safety data were obtained from 1,221 patients who were randomised to receive placebo (N=167), etanercept (N=357), ixekizumab Q4W (N=347), or ixekizumab Q2W (N=350). This phase of the study was completed by 94.9% of all patients. Table 59 provides an overview of the adverse events reported during the Induction Dosing Period.[22]

During the induction dosing period, the proportion of patients with ≥1 TEAE was similar across treatment groups. For TEAEs judged possibly related to the study drug, statistically significantly higher incidences were observed in both ixekizumab groups compared with the placebo group at week 12 (IXEQ2W: p<0.001; IXEQ4W: p=0.036). Only the ixekizumab 80 mg Q2W group had an incidence of TEAEs judged possibly related to the study drug that was statistically significantly higher than the incidence observed in the etanercept group (p=0.021). The proportion of patients who experienced TEAEs judged to be possibly related to study drug was 33.4% in the ixekizumab 80 Q2W group, 26.5% in the ixekizumab 80 Q4W group, 25.5% in the etanercept group and 18.0% in the placebo group, respectively. However the majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication (Table 59).[22]

The proportion of patients who discontinued study medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab, etanercept and placebo groups (IXEQ2W: 1.7%; IXE Q4W: 1.4%; ETN: 1.4%; PBO: 0.6%) (Table 59).[22]

SAEs occurred in 1.9% of all patients (IXEQ2W: 1.4%; IXE Q4W: 2.3%; ETN: 2.2%; PBO: 1.2%) with no statistically significant differences between treatment groups.[22]

The most frequently reported categories of AESI were infections and injection site reactions, reported by 28.5% and 14.7% of all patients, respectively. Injection site reactions were statistically significantly more common in each of the active treatment groups compared with placebo, occurring at a frequency of 19.7%, 12.1%, 17.4% and 4.2% in the ixekizumab Q2W, ixekizumab Q4W, etanercept and placebo groups, respectively (p<0.05 for all comparisons) (Table 59).

The most frequently reported infection types in ixekizumab-treated patients were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, and influenza; however, the incidences of these events were not statistically significant between any active treatment group and the placebo group.[22]

Table 59: UNCOVER-2: Overview of AEs – safety population (Induction Dosing Period)[22]

	PBO (N=167) n (%)	ETN (N=357) n (%)	IXE80Q4W (N=347) n (%)	IXE80Q2W (N=350) n (%)	Total IXE (N=697) n (%)	Total (N=1,221) n (%)
Patients with ≥1 TEAE	89 (53.3)	211 (59.1)	204 (58.8)	216 (61.7)	420 (60.3)	720 (59.0)
Discontinuations from Study Drug due to AE (including death)	1 (0.6)	5 (1.4)	5 (1.4)	6 (1.7)	11 (1.6)	17 (1.4)
Deaths	0	0	0	0	0	0
SAEs	2 (1.2)	8 (2.2)	8 (2.3)	5 (1.4)	13 (1.9)	23 (1.9)
TEAEs possibly related to study drug	30 (18.0)	91 (25.5)	92 (26.5)	117 (33.4)	209 (30.0)	330 (27.0)
Treatment-Emergent AE of Special Interest						
Cytopenias	1 (0.6)	5 (1.4)	4 (1.2)	5 (1.4)	9 (1.3)	15 (1.2)
Hepatic	0 (0)	6 (1.7)	3 (0.9)	6 (1.7)	9 (1.3)	15 (1.2)
Infection	46 (27.5)	98 (27.5)	100 (28.8)	104 (29.7)	204 (29.3)	348 (28.5)
Injection-site reactions	7 (4.2)	62 (17.4)	42 (12.1)	69 (19.7)	111(15.9)	180 (14.7)
Allergic reactions/ Hypersensitivities Anaphylaxis† Non-Anaphylaxis	3 (1.8) (0) 3 (1.8)	12 (3.4) 1 (0.3) 11 (3.1)	15 (4.3) 1 (0.3) 14 (4.0)	14 (4.0) 1 (0.3) 13 (3.7)	29 (4.2) 2 (0.3) 27 (3.9)	44 (3.6) 3 (0.2) 41 (3.4)
Cerebrocardiovascular events	0 (0)	2 (0.6)	5 (1.4)	1 (0.3)	6 (0.9)	8 (0.7)
Malignancies	0 (0)	1 (0.3)	0 (0)	3 (0.9)	3 (0.4)	4 (0.3)
Depression	1 (0.6)	5 (1.4)	1 (0.3)	2 (0.6)	3 (0.4)	9 (0.7)
PCP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interstitial lung disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Crohn's Disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ulcerative Colitis	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.1)	1 (0.1)

† Anaphylaxis as shown here refers to potential cases using broadly-defined Sampson criteria. There were no confirmed cases of anaphylaxis in the Induction Dosing Period

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; ETN = etanercept; ISE = injection-site reaction; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Source: CSR RHBA (36 week), Table RHBA.12.4 (Page 1 and 3 of 5)

Maintenance dosing period

A total of 544 patients who responded to ixekizumab treatment continued to a Maintenance Dosing Period for which they were re-randomised to receive placebo (N=176), ixekizumab 80 mg Q12W (N=181), or ixekizumab 80 mg Q4W (N=187) as part of the Maintenance Dosing Period Primary Population. Table 60 provides an overview of the adverse events reported during the Maintenance Dosing Period.[22]

During the maintenance dosing period, the proportion of patients with ≥1 TEAE was statistically significantly higher in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W group compared with the ixekizumab 80 mg Q2W/placebo group (p=0.043). At week 60 the proportion of patients who experienced ≥1 TEAE was 76.5% in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W group compared with 62.8% in the ixekizumab 80 mg Q2W/placebo group. The majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication. The proportion of patients who experienced TEAEs judged to be possibly related to study drug was not statistically significantly different between the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups (Table 60).[22]

The proportion of patients who discontinued study medication due to AEs was low across all treatment groups with no statistically significant differences between the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups (IXEQ2W/Q4W: 1.0%; IXEQ2W/PBO: 2.1%)(Table 60).[22]

The proportion of patients who experienced SAEs was low across all treatment groups with no statistically significant differences between the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W and ixekizumab 80 mg Q2W/placebo groups (IXEQ2W/Q4W: 2.0%; IXEQ2W/PBO: 6.4%)(Table 60).[22]

The most frequently reported categories of AESIs observed during the maintenance period were infections (IXEQ2W/Q4W: 60.8%; IXEQ2W/PBO: 39.4%; p=0.004) and injection site reactions (IXEQ2W/Q4W: 15.7%; IXEQ2W/PBO: 4.3%; p=0.060).[22]

No deaths were reported during this period.[22]

Table 60: UNCOVER-2: Overview of AEs – safety population (Maintenance Dosing Period)[22]

	IXE80Q4W /PBO (N=82) n (%)	IXE80Q4W/ IXE80Q4W (N=85) n (%)	IXE80Q2W/ PBO (N=94) n (%)	IXE80Q2W/ IXE80Q4W (N=102) n (%)	IXE/PBO (N=176) n (%)	IXE/ IXE80Q4W (N=187) n (%)
Patients with ≥1 TEAE	50 (61.0)	66 (77.6)	58 (61.7)	72 (70.6)	108 (61.4)	138 (73.8)
Discontinuations from Study Drug due to AE (including death)	2 (2.4)	2 (2.4)	2 (2.1)	1 (1.0)	4 (2.3)	3 (1.6)
Deaths	0	0	0	0	0	0
SAEs	2 (2.4)	8 (9.4)	6 (6.4)	2 (2.0)	8 (4.5)	10 (5.3)
TEAEs possibly related to study drug	18 (22.0)	28 (32.9)	24 (25.5)	30 (29.4)	42 (23.9)	58 (31.0)
Treatment-Emergent AE of Special Interest						
Cytopenias	1 (1.2)	2 (2.4)	1 (1.1)	1 (1.0)	2 (1.1)	3 (1.6)
Hepatic	3 (3.7)	3 (3.5)	2 (2.1)	3 (2.9)	5 (2.8)	6 (3.2)
Infection	31 (37.8)	44 (51.8)	37 (39.4)	58 (56.9)	68 (38.6)	102 (54.5)
Injection-site reactions	2 (2.4)	5 (5.9)	4 (4.3)	16 (15.7)	6 (3.4)	21 (11.2)
Allergic reactions/ Hypersensitivities Anaphylaxis† Non-Anaphylaxis	3 (3.7) 0 3 (3.7)	3 (3.5) 0 3 (3.5)	2 (2.1) 0 2 (2.1)	6 (5.9) 0 6 (5.9)	5 (2.8) 0 5 (2.8)	9 (4.8) 0 9 (4.8)
Cerebrocardiovascular events	1 (1.2)	1 (1.2)	0	0	1 (0.6)	1 (0.5)
Malignancies	1 (1.2)	0	0	1 (1.0)	1 (0.6)	1 (0.5)
Depression	1 (1.2)	2 (2.4)	1 (1.1)	0	2 (1.1)	2 (1.1)
PCP	0	0	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0
Crohn's Disease	0	0	2 (2.1)	0	2 (1.1)	0
Ulcerative Colitis	0	1 (1.2)	0	0	0	1 (0.5)

† Anaphylaxis as shown here refers to potential cases using broadly-defined Sampson criteria. There were no confirmed cases of anaphylaxis in the Maintenance Dosing Period

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; ETN = etanercept; ISE = injection-site reaction; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Source: CSR RHBA, Table RHBA.12.5 (Page 1, 3, 4 and 6 of 7)

4.11.3 UNCOVER-3

During the 12-week Induction Dosing Period, safety data were obtained from 1,341 patients across the treatments of placebo (N=193), etanercept 50 mg Q2W (N=382), ixekizumab 80 mg Q4W (N=382), and ixekizumab 80 mg Q2W (N=384). This phase of the study was completed by 94.7% of all patients. Table 61 provides an overview of the adverse events reported during the Induction Dosing Period.[23]

During the induction dosing period, the proportion of patients with ≥1 TEAE and TEAEs judged to be possibly related to study drug was statistically significantly higher in all active treatment groups compared with the placebo group ($p<0.05$ for all comparisons). At week 12 the proportion of patients who experienced ≥1 TEAE was 53.4% in the ixekizumab 80 Q2W group, 56.3% in the ixekizumab 80 Q4W group, 49.0% in the etanercept groups and 36.3% in the placebo group, respectively. The proportion of patients who experienced TEAEs judged to be possibly related to study drug was 26.8% in the ixekizumab 80 Q2W group, 21.7% in the ixekizumab 80 Q4W group, 22.3% in the etanercept group and 12.4% in the placebo group, respectively. The majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication (Table 61).[23]

The proportion of patients who discontinued study medication due to AEs was low across all treatment groups with no statistically significant differences between the ixekizumab, etanercept and placebo groups (IXEQ2W: 2.3%; IXE Q4W: 2.1%; ETN: 1.0%; PBO: 1.0%)(Table 61).[23]

SAEs occurred in 1.9% of all patients (IXEQ2W: 2.3%; IXE Q4W: 1.6%; ETN: 1.3%; PBO: 2.6%) with no statistically significant differences between treatment groups (Table 61).[23]

The most frequently reported categories of AESI were infections and injection site reactions, reported by 19.1% and 13.3% of all patients, respectively. A statistically significantly greater proportion of patients in the ixekizumab Q2W (21.4%) and Q4W (23.0%) reported an infection compared with the etanercept (15.4%) and placebo groups (14.0%) ($p<0.05$ for all comparisons). Infections reported by at least 1% of patients in the combined ixekizumab group were nasopharyngitis (7.2%), upper respiratory tract infection (2.1%), and urinary tract infection (1.3%). In addition, injection site reactions were statistically significantly more common in the active groups compared with the placebo groups ($p<0.001$ for all comparisons).[23]

Table 61: UNCOVER-3: Overview of AEs – safety population (Induction Dosing Period) [23]

	PBO (N=193) n (%)	ETN (N=382) n (%)	IXE80Q4W (N=382) n (%)	IXE80Q2W (N=384) n (%)	Total IXE (N=766) n (%)	Total (N=1,341) n (%)
Patients with ≥1 TEAEs	70 (36.3%)	187 (49.0%)	215 (56.3%)	205 (53.4%)	420 (54.8%)	677 (50.5%)
Discontinuations from Study Drug due to AE (including death)	2 (1.0%)	4 (1.0%)	8 (2.1%)	9 (2.3%)	17 (2.2%)	23 (1.7%)
Deaths	0	0	0	0	0	0
SAEs	5 (2.6%)	5 (1.3%)	6 (1.6%)	9 (2.3%)	15 (2.0%)	25 (1.9%)
TEAEs possibly related to study drug	24 (12.4)	85 (22.3)	83 (21.7)	103 (26.8)	186 (24.3)	295 (22.0)
Treatment-Emergent AE of Special Interest						
Cytopenias	1 (0.5)	6 (1.6)	5 (1.3)	3 (0.8)	8 (1.0)	15 (1.1)
Hepatic	1 (0.5)	9 (2.4)	4 (1.0)	8 (2.1)	12 (1.6)	22 (1.6)
Infection	27 (14.0)	59 (15.4)	99 (23.0)	82 (21.4)	170 (22.2)	256 (19.1)
Injection-site reactions	6 (3.1)	59 (15.4)	55 (14.4)	58 (15.1)	113 (14.8)	178 (13.3)
Allergic reactions/ Hypersensitivities	4 (2.1)	7 (1.8)	12 (3.1)	13 (3.4)	25 (3.3)	36 (2.7)
Anaphylaxis†	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)	3 (0.2)
Non-Anaphylaxis	4 (2.1)	7 (1.8)	11 (2.9)	12 (3.1)	23 (3.0)	34 (2.5)
Cerebrocardiovascular events	1 (0.5)	0 (0)	1 (0.3)	0 (0)	1 (0.1)	2 (0.1)
Malignancies	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Depression	1 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)	3 (0.4)	5 (0.4)
PCP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interstitial lung disease	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.1)	1 (0.1)
Crohn's Disease	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.1)	1 (0.1)
Ulcerative Colitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

† Anaphylaxis as shown here refers to potential cases using broadly-defined Sampson criteria. There were no confirmed cases of anaphylaxis in the Induction Dosing Period

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; ETN = etanercept; ISE = injection-site reaction; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Source: CSR RHBC, Table RHBA.12.3 (Page 1 and 3 of 5)

4.12 *Interpretation of clinical effectiveness and safety evidence*

4.12.1 Principal findings from the UNCOVER clinical studies

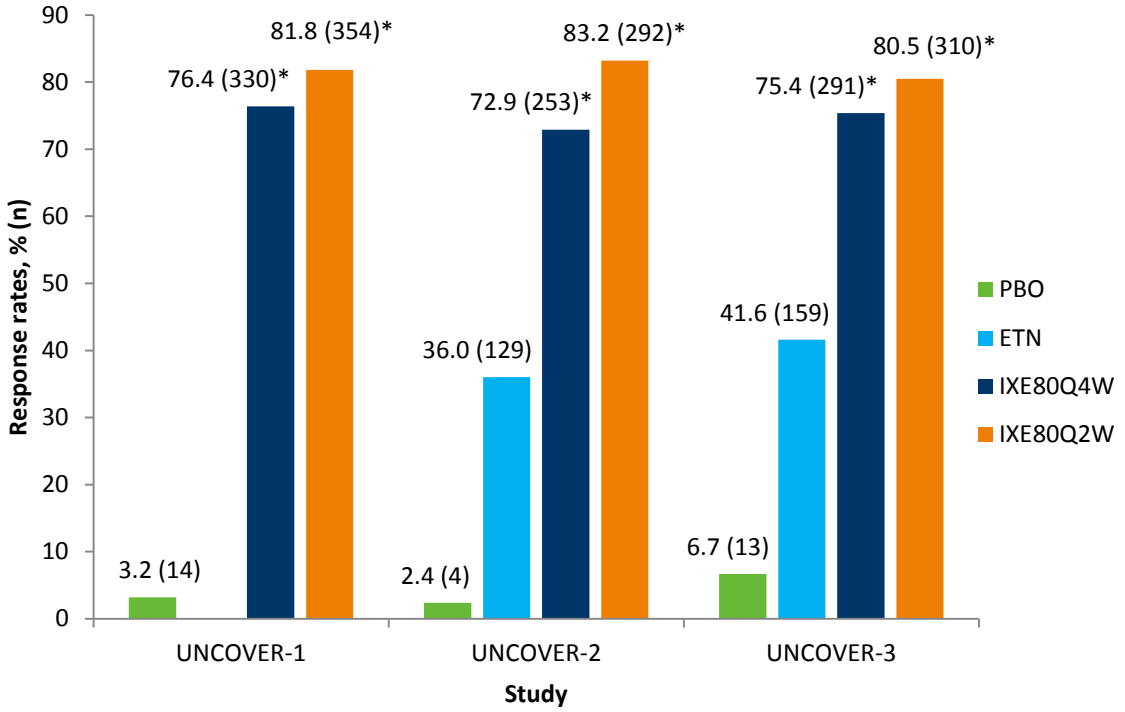
The clinical efficacy and safety of ixekizumab has been demonstrated in the three pivotal phase III studies – UNCOVER-1, -2 and -3. Ixekizumab demonstrated significant improvements in psoriasis symptoms and HRQoL compared with both active and placebo comparators, with an acceptable safety profile.

The co-primary objectives were met in all three UNCOVER studies with both ixekizumab treatment groups (ixekizumab 80 mg Q2W and 80 mg Q4W) showing greater efficacy than placebo (UNCOVER-1, -2 and -3) and etanercept (UNCOVER-2 and -3 only) at week 12 as measured by the proportion of patients achieving sPGA (0, 1) and PASI 75 ($p<0.001$ for all comparisons).[15,16]

The key findings from the UNCOVER studies are highlighted below:

- Across all three studies, both ixekizumab treatment groups were statistically significantly superior to placebo in the proportion of patients achieving sPGA (0,1) at week 12 ($p<0.001$ for all comparisons). In addition, for UNCOVER-2 and -3 statistically significantly more patients receiving ixekizumab 80 mg Q2W and Q4W achieved sPGA (0,1) at week 12, compared with patients receiving etanercept (83.2%, 72.9% and 36.0%, respectively in UNCOVER-2 and 80.5%, 75.4% and 41.6%, respectively in UNCOVER-3) (Figure 34).

Figure 34: sPGA (0,1) results at week 12 for all studies – NRI (ITT population)

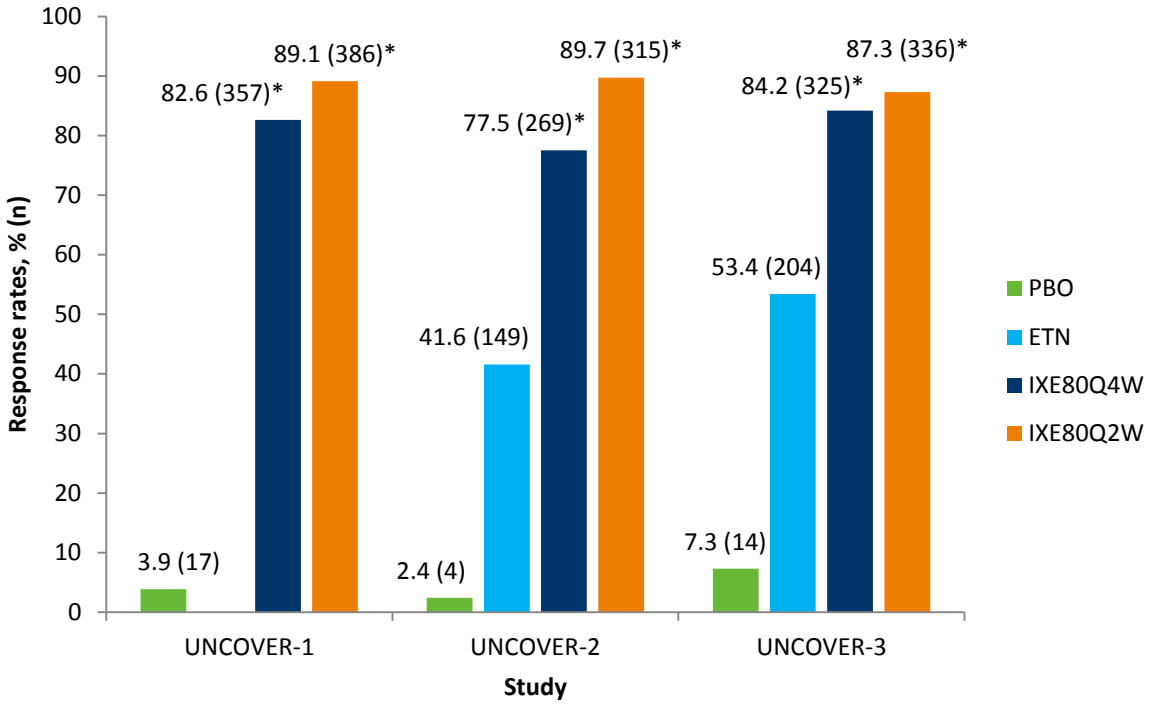


p<0.001 versus placebo and etanercept

ETN = etanercept; ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

- PASI 75 response rates across all UNCOVER studies were statistically significantly improved in both ixekizumab groups compared with placebo at week 12 (p<0.001). The proportion of patients achieving PASI 75 was also statistically significantly greater in the ixekizumab groups compared with etanercept (UNCOVER-2 and -3 only) at week 12 (p<0.001). In the UNCOVER-2 study, the proportion of patients achieving PASI 75 was 89.7% in the ixekizumab Q2W group, 77.5% in the ixekizumab Q4W group and 41.6% in the etanercept group. Similarly, in the UNCOVER-3 study, the proportion of patients achieving PASI 75 was 87.3% in the ixekizumab Q2W group, 84.2% in the ixekizumab Q4W group and 87.3% in the etanercept group (Figure 35).

Figure 35: PASI 75 results at week 12 for all studies – NRI (ITT population)



* p<0.001 versus placebo and etanercept

ETN = etanercept; ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 75 = at least a 75% improvement from baseline in Psoriasis Area and Severity Index score; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks

- The proportion of patients achieving complete clearance (PASI 100) and high-level responses (PASI 90) was significantly greater with ixekizumab compared with etanercept and placebo at week 12 (p<0.001). Across the studies, PASI 100 response rates ranged from 35.3% to 41.0% in the ixekizumab Q2W group, 30.8% to 35.0% in the ixekizumab Q4W group, 5.3% to 7.3% in the etanercept group and only 0.6% in the placebo group. Similarly, PASI 90 response rates ranged from 68.1% to 70.9% in the ixekizumab Q2W group, 59.7% to 65.3% in the ixekizumab in the Q4W group, 18.7% to 25.7% in the etanercept group and 0.5% to 3.1% in the placebo group.
- Rapid onset of efficacy is considered a driver of patient treatment.[19] In the UNCOVER-2 study 18.2% of patients treated with ixekizumab Q2W achieved PASI 75 at week 2, compared with 0.6% of patients who received placebo, and 0.6% of patients who received etanercept, respectively. Similarly, in the UNCOVER-3 study 22.9% of patients treated with ixekizumab Q2W achieved PASI 75 at week 2, compared with 0% of patients who received placebo, and 2.4% of patients who received etanercept, respectively.
- Responses achieved with ixekizumab treatment are sustained during the maintenance dosing period (UNCOVER-1 and -2 trials). At week 60, significant proportions of patients treated with ixekizumab 80 mg Q2W in the induction dosing period and ixekizumab 80

mg Q4W during the maintenance dosing period achieved or maintained sPGA (0,1) compared with placebo (p<0.001 for all comparisons). In the UNCOVER-1 study 74.8% of patients in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W achieved or maintained sPGA (0,1) at week 60 compared with 7.7% of patients in the and ixekizumab 80 mg Q2W/placebo group. Similarly, in the UNCOVER-2 study 82.4% of patients in the ixekizumab 80 mg Q2W/ixekizumab 80 mg Q4W achieved or maintained sPGA (0,1) at week 60 compared with 7.4% of patients in the and ixekizumab 80 mg Q2W/placebo groups. Maintenance of response was also observed in the proportion of patients achieving PASI 75, PASI 90 and PASI 100 at week 60.

- Presentation in difficult-to-treat areas (such as scalp and nails) adds to the overall burden of psoriasis, further reducing patient QoL.[9] At week 12, ixekizumab demonstrated superior efficacy to etanercept and placebo in difficult-to-treat areas, including psoriasis of the nail, scalp and palmoplantar areas (p<0.001 for all comparisons).
- Itch is reported by psoriasis patients as being the most bothersome of psoriasis symptoms.[9] Across all three UNCOVER studies treatment with ixekizumab significantly improved the severity of itch compared with etanercept and placebo at week 12 as measured by the proportion of patients achieving itch NRS ≥4 point reduction from baseline (p<0.001 for all comparisons). By reducing the severity of itch, ixekizumab is able to improve the HRQoL in patients with psoriasis.
- The high-levels of clearance and alleviation of the burdensome symptoms of psoriasis achieved with ixekizumab leads to improvements in the HRQoL of patients with psoriasis. After 12 weeks of treatment in the UNCOVER studies reductions in DLQI total scores were significantly improved in the ixekizumab groups compared with the etanercept and placebo groups (p<0.001 for all comparisons). In addition, the proportion of patients with DLQI scores of 0 or 1 (interpreted as no effect on patient HRQoL) was significantly higher for both ixekizumab dosing regimens, relative to or etanercept or placebo at week 12 (p<0.001 for all comparisons).
- High proportions of PASI 75 response rates were observed with ixekizumab treatment across different patient subgroups. These included subgroup variables such as patient demographics (geographic region, weight), disease-related variables (disease severity, presence of nail or scalp involvement, concomitant PsA) and previous exposure to therapies. Of particular importance, ixekizumab demonstrated consistent levels of efficacy in patients who had been previously treated with biologic therapy and in patients who had inadequate response to etanercept. Furthermore, ixekizumab was able to demonstrate consistent efficacy in patient populations who would be eligible for treatment with biologics according to NICE criteria (based on previous treatments and

disease severity).

- A NMA demonstrated that ixekizumab has superior efficacy to other biologic comparators including adalimumab, infliximab, ustekinumab and secukinumab as measured by the probability of achieving a given PASI response
- There were no major safety signals identified in the UNCOVER clinical development programme. Ixekizumab was well tolerated across the UNCOVER studies with a predictable safety profile which was comparable to etanercept.
- The incidence of ≥1 TEAE and TEAEs judged to be possibly to study drug was generally higher in the ixekizumab groups compared with the placebo group at week 12. However, the majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication.
- Of particular note, the incidence of ≥1 TEAE and TEAEs was comparable between the ixekizumab treatment groups and the etanercept group at week 12.
- The incidence of SAEs and discontinuations due to AEs did not differ between the ixekizumab, etanercept or placebo groups in any of the UNCOVER studies at week 12.
- The most frequent AESIs which were reported with ixekizumab treatment in the UNCOVER studies included infection and injection site reactions. After 12 weeks commonly observed types of infections in the studies were nasopharyngitis, upper respiratory tract infection, bronchitis, and sinusitis.
- Since many AEs take time to emerge, the safety of ixekizumab was evaluated beyond the 12-week efficacy primary endpoint. Ixekizumab was well tolerated in the maintenance dosing period with similar AEs to those seen in the induction period.

4.12.2 Strengths and limitations of the clinical evidence base for ixekizumab

The clinical evidence base provided by the phase III UNCOVER clinical development programme clearly demonstrates the efficacy and safety of ixekizumab in patients with moderate to severe psoriasis. All the UNCOVER studies met their co-primary and pre-specified key secondary endpoints and demonstrated consistent improvements in psoriasis symptoms and HRQoL compared with both active and placebo comparators. In addition, the unique designs of the UNCOVER-1 and -2 studies allowed an evaluation of short- and long-term efficacy of ixekizumab compared with placebo. The benefit of having two randomised treatment periods was that it helped to determine whether the dosing regimen that provided the most rapid and optimal initial response differed from the dosing regimen needed to maintain that response. The design also provided an opportunity to assess consistency in maintenance of response among initial ixekizumab responders. Further evidence for the

long-term efficacy of ixekizumab will come from the UNCOVER-3 study which includes a 5-year long-term extension period. The consistent benefits in the improvement of psoriasis symptoms and HRQoL form a strong evidence base for ixekizumab.

A limitation of the evidence base from the UNCOVER studies is the lack of direct comparisons with active comparators other than the inclusion of etanercept in the UNCOVER-2 and -3 studies. However, direct comparisons with all available comparators are not feasible in clinical trials and this has been a similar issue observed for other biologic therapies for psoriasis which have been assessed by NICE. To address this limitation a NMA was conducted to allow indirect comparisons of ixekizumab with all comparators outlined in the NICE decision problem. An additional limitation of the UNCOVER-2 and -3 studies was the limited 12-week duration of the active comparator treatment period. Full assessment of the maximum potential for attaining and sustaining high-level responses and safety signals relative to active comparator may require longer-term studies, however this 12-week treatment period has been a commonly used time point in other studies of biologic therapies in psoriasis.

The evidence base from the UNCOVER studies is highly relevant to the NICE decision problem. Patients included in the UNCOVER studies included those recruited in UK study centres with a severity of disease similar to that seen in patients who are eligible for biologic treatment according to NICE criteria (i.e. based on PASI and DLQI measures). The UNCOVER-2 and -3 studies included etanercept which was outlined as a relevant comparator in the decision problem. Indirect comparison techniques were used to extend this to other relevant comparators including ustekinumab and secukinumab. The co-primary measures of the UNCOVER studies were the sPGA (0, 1) and PASI 75 response rates at week 12. Both of these outcome measures are highly relevant to UK clinical practice and reflect the severity of psoriasis symptoms.

4.13 *Ongoing studies*

There are two additional studies involving ixekizumab which are ongoing and expected to report within the next 12 months (Table 62).

Table 62: Summary of ongoing studies expected to report within the next 12 months

Trial name/NCT identifier	Description	Intervention	Population	Primary outcome measure	Date expected to report
IXORA-S (RHBS) - NCT02561806[127]	A 52-week multicentre, randomised, blinded, parallel-group study comparing the efficacy and safety of ixekizumab with ustekinumab in patients with moderate to severe plaque psoriasis	Ixekizumab 160 mg via SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12. After week 12 maintenance dosing of 80 mg (one injection) every 4 weeks through week 52 Ustekinumab 45 mg via SC injection for participants ≤100kg and 90 mg for participants >100 kg at week 0, 4, 16, 28, and 40	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who have failed, are contraindicated or intolerant to ≥1 systemic therapy (including cyclosporine, methotrexate, or phototherapy)	PASI 90 at week 12	Data from RHBS is expected to become public in September/October 2017
IXORA-P (RHBP) - NCT02513550[128]	A multicentre, randomised, double-blind study comparing the efficacy and safety of ixekizumab dosing regimens in patients with moderate to severe plaque psoriasis	Ixekizumab 160 mg via SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 2 weeks through week 50 Ixekizumab 160 mg via SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks through week 50	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis (sPGA ≥3 and PASI ≥12) who were candidates for phototherapy and/or systemic therapy	• sPGA (0,1) at week 52 • PASI 75 at week 52	Estimated primary completion date April 2017

PASI = Psoriasis Area and Severity Index; SC = subcutaneous; sPGA = static Physician's Global Assessment

5 Cost effectiveness

Summary statement of cost-effectiveness

- A Markov model was developed in Visual Basic for Applications with a Microsoft Excel interface to assess the cost-effectiveness of ixekizumab Q2W versus existing biologic treatments in a treatment sequence in patients with moderate to severe psoriasis.
- Ixekizumab was compared to other biologics positioned within a treatment sequence for patients who had failed on prior systemic treatments and were eligible for a first-line biologic therapy (as defined by current NICE guidance). In a scenario analysis, the cost-effectiveness of ixekizumab was assessed as second-line therapy for patients with inadequate response or a contraindication to a TNF-alpha inhibitor.
- The model consists of four treatment-related health states, which determine cost and resource use:
    - Induction; patients initiate a biologic treatment and continue to receive it until assessed for response at 10 to 16 weeks, depending on the treatment continuation rule recommended by NICE for each biologic treatment.
    - Maintenance; patients meeting the response criteria continue to receive the treatment until discontinuation due to any cause.
    - Best Supportive Care (BSC); after receiving up to three biologic treatments, patients who fail to meet the response criteria of the last biologic treatment in the sequence or discontinue from maintenance receive a bundle of non-biologic supportive therapies, collectively referred to as BSC, for the remainder of the model time horizon.
    - Death; an absorbing state to which transition is possible from any of the above treatment states.
- At the end of the induction period, patients are assessed for PASI response measured as the percentage reduction in PASI score from baseline:
    - PASI <50 (no response)
    - PASI 50-74
    - PASI 75-89
    - PASI 90-99
    - PASI 100 (complete psoriasis symptom clearance).
- These five PASI response categories comprise response-related health states, which determine the assignment of health utility gains.
- In the base case, the probability of continuing treatment from the induction period into

the maintenance period is the proportion of patients achieving the threshold of a PASI 75 response.

- Health effects were applied as changes from baseline EQ-5D-5L utility corresponding to each health state. These were obtained from the UNCOVER trials and estimated using a linear regression model controlling for baseline EQ-5D.
- Cost and resources modelled included drug acquisition, administration, monitoring, best supportive care (BSC) and non-responder costs. A confidential discount on the list price of ixekizumab was approved under a patient access scheme (PAS) and applied in the analysis.
- The ixekizumab sequence was associated with the greatest QALY gain of 1.45 and an ICER of £33,858/QALY vs the referent comparator, the etanercept sequence.
- All other comparator treatment sequences were dominated (secukinumab, using the list price) or extendedly dominated by the ixekizumab sequence.
- Pairwise ICERs for ixekizumab versus adalimumab sequence, ustekinumab 45 mg sequence, ustekinumab 90 mg sequence and infliximab sequence all fell below £20,000/QALY.
- Deterministic sensitivity analyses were undertaken for pairwise comparisons and indicated that acquisition costs, annual all-cause discontinuation rate and discount rates for costs and QALYs had the greatest impact on the ICER.
- The cost-effectiveness of ixekizumab versus ustekinumab 45 mg, ustekinumab 90 mg and secukinumab as second-line therapy was evaluated in patients who had inadequate response or contraindication to a TNF-α inhibitor. The ixekizumab sequence was associated with lower costs and greater QALY gains compared to the other sequences.

5.1 *Published cost-effectiveness studies*

A systematic literature review was undertaken in October 2014 to identify published economic evaluations and HTA appraisals in order to address the decision problem and inform the economic model structure. The scope of this review was to review all available published data on economic evaluations of conventional and biologic systemic therapies in the treatment of patients with moderate to severe psoriasis in accordance with the decision problem and using methodology and inclusion criteria that were consistent with the NICE reference case.

An update to the review was carried out in November 2015 to identify more recent studies of interest. The review also summarized studies that provided model inputs (costs/utilities) but additional systematic searches were conducted for resource use and utility data (Sections 5.4.3 and 5.5.1).

5.1.1 Identification of studies

Search strategies were designed for each of the databases required by NICE: Medline® using the PubMed platform, Embase, the Centre for Reviews and Dissemination, and the Health Economic Evaluations Database. In addition, all the main HTA agencies were searched for appraisals or assessments of relevant therapies for psoriasis describing cost-effectiveness models (CEM):

- UK - NICE; SMC; All Wales Medicines Strategy Group (AWMSG)
- France - Haute Autorité de Santé (HAS)
- Canada - CADTH
- Australia - PBAC
- Sweden - Tandvårds- och läkemedelsförmånsverket (TLV)
- Norway - Nasjonalt kunnskapssenter for helsetjenesten (NOKC)
- Germany - G-BA; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)
- Netherlands - College Voor Zorgverzekeringen (CVZ)

Search strategies for bibliographic databases and HTA agencies are presented in Appendix 11.

The inclusion and exclusion criteria are presented in Table 63. In line with the decision problem and NICE reference case, studies of interest related to cost-effectiveness analyses that evaluated conventional and biologic systemic therapies in adult patients with moderate to severe plaque psoriasis and reported QALY-based ICER results. The PRISMA flow diagrams for the original and updated reviews are presented in Figure 36 and Figure 37.

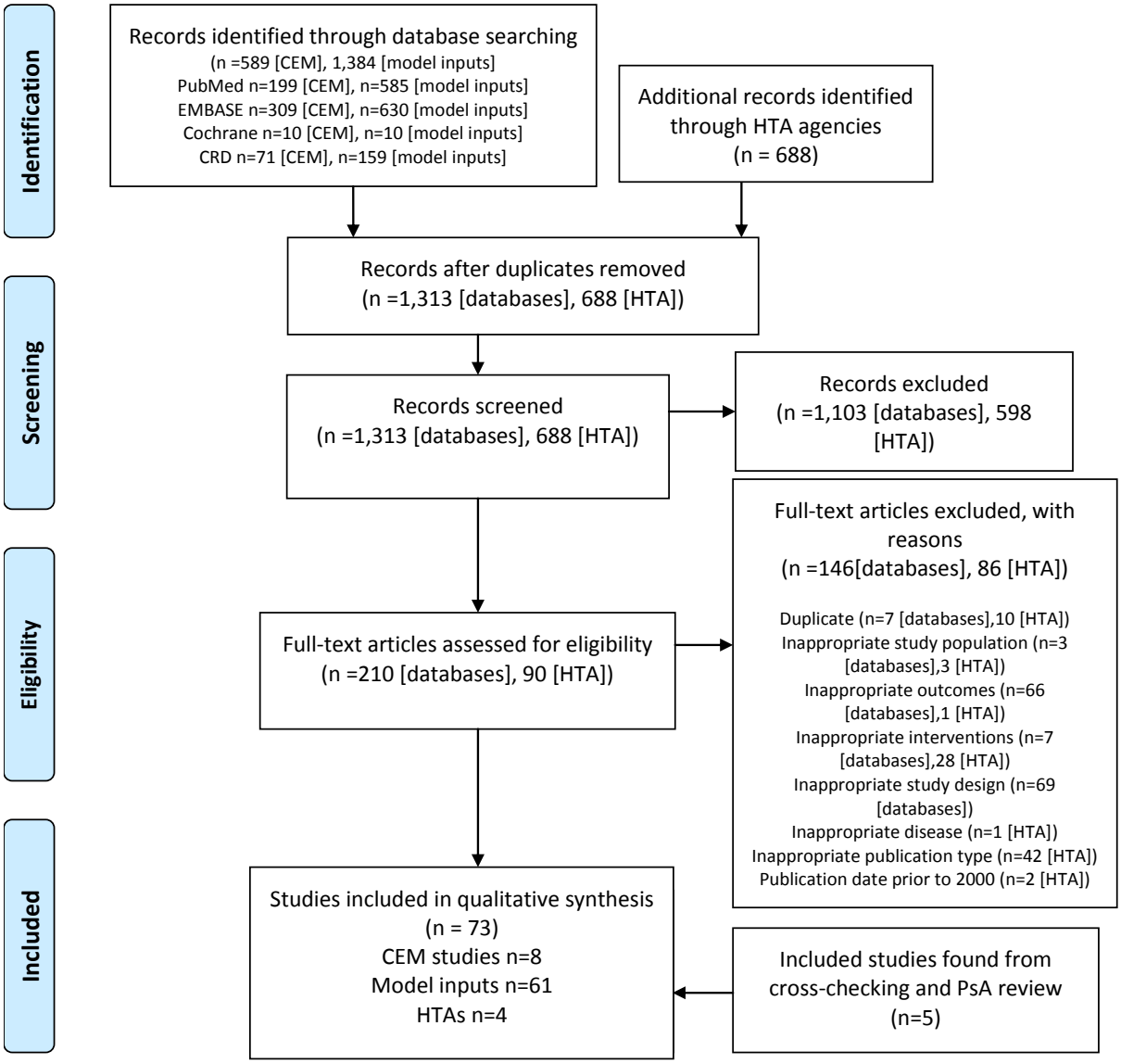
A manual review of bibliographies from key articles, economic evaluations and HTA reports was performed in order to identify additional studies that may have been missed using the computer-assisted search strategies. This resulted in one additional article which met the inclusion criteria and was therefore included in the review.

Table 63: Inclusion and exclusion criteria for identification of cost-effectiveness and model input studies

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adult populations with moderate to severe psoriasis	Non-adult populations
Intervention and Comparators	Conventional systemic therapies (fumaric acid, methotrexate, ciclosporin and acitretin) and biologic therapies (efalizumab, etanercept, adalimumab, infliximab, ustekinumab, secukinumab and apremilast) for psoriasis.	Therapies other than conventional and biologic systemic therapies
Outcomes	Only studies focused on CEMs using quality-adjusted life years (QALY) as outcome measure. For studies on model inputs, this review focused on health utilities (irrespective of study countries), UK-specific healthcare resource utilisation and costs.	CEMs without QALYs
Study type	Appraisals/assessments from HTA agencies and published studies presenting CEMs for which only full publications were available. For studies on model inputs (i.e., health utilities, UK-specific healthcare resource utilisation and costs), all types of publications were of interest, including abstracts or posters reporting the outcomes of interest.	Economic evaluations for which full publications were not available.
Other restrictions	Study language was restricted to English, French, German, Italian and Spanish. Studies published after January 1 2000.	Other study languages. Studies published before January 1, 2000 (original review) and studies published before September 22, 2014 (updated review)

CEM = cost-effectiveness model; HTA = health technology assessment; QALY = quality-adjusted life year; UK = United Kingdom

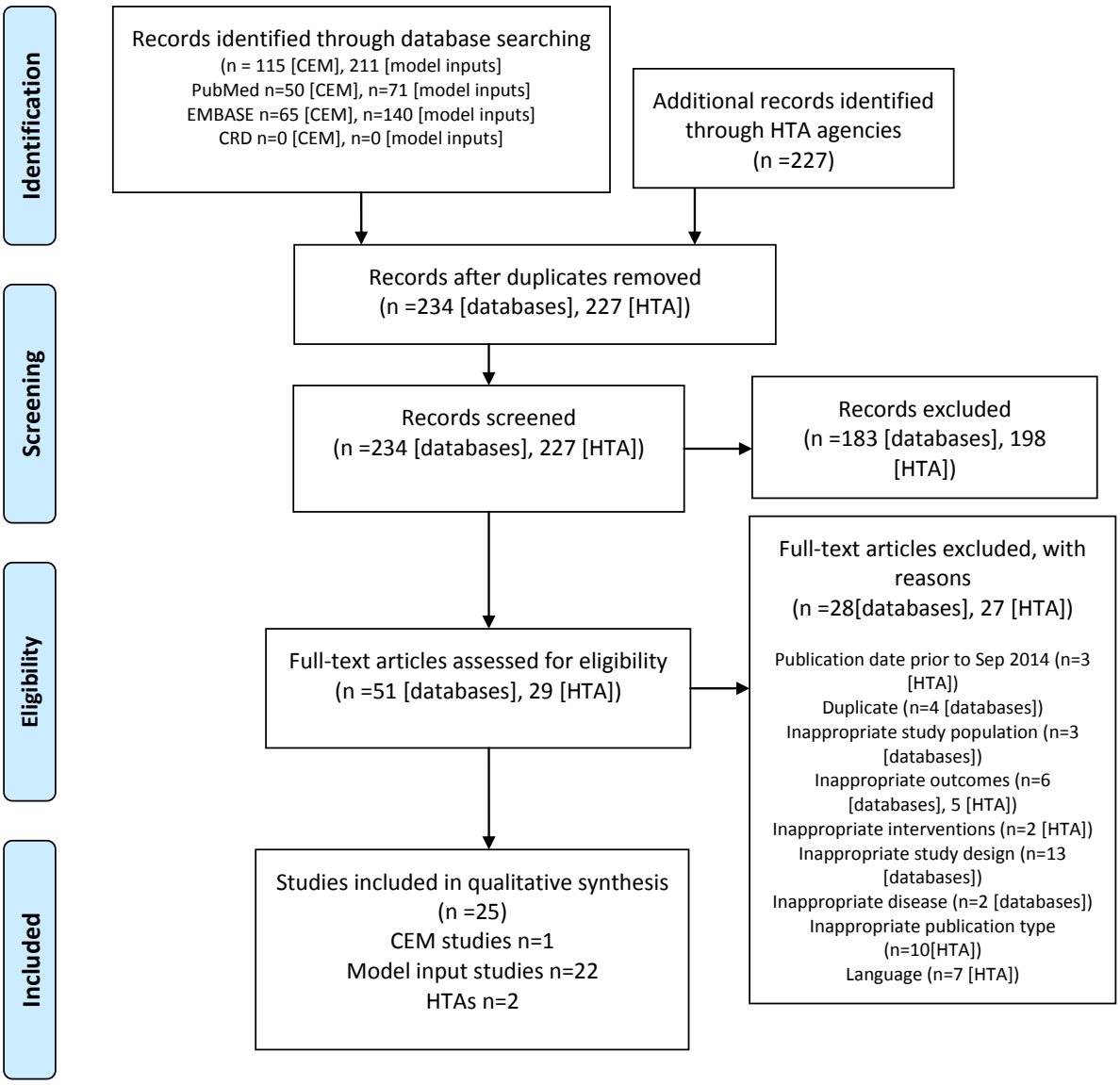
Figure 36: Selection process for studies included in original literature review, October 2014



CEM = cost-effectiveness model; CRD = Centre for Reviews and Dissemination; HTA = health technology assessment; PsA = psoriatic arthritis

Studies may have been excluded for more than one reason, therefore the reasons for exclusion will exceed the total number of studies excluded at each stage.

Figure 37: Selection process for studies included in updated literature review, November 2015



CEM = cost-effectiveness model; CRD = Centre for Reviews and Dissemination; HTA = health technology assessment; PsA = psoriatic arthritis

5.1.2 Description of identified studies

The review identified nine cost-utility studies[129-137] that met the inclusion criteria, of which only three were UK-based studies[134,136,137] and six NICE TAs[67-72] Studies that were identified in the targeted review of model inputs that did not report a formal economic evaluation are not described in this section. A separate systematic review was conducted to identify model input studies relating to HRQoL, cost and resource use in psoriasis (Section 5.4.3 and 5.5.1).

A summary of model characteristics is presented in Table 64 for the UK based cost-effectiveness studies and Table 65 for the NICE TAs. A quality assessment of all publications, including non-UK based studies, was undertaken using the Drummond (1996) checklist.[138] Due to the unavailability of the manufacturer submissions for etanercept and efalizumab, a quality assessment was not carried out for these models. Details of the quality assessment are provided in Appendix 11.

Table 64: Summary list of published cost-effectiveness studies

Study	Lloyd *et al*. (2009)[136]	Sizto *et al*. (2009)[137]	Sawyer *et al*. (2015)[134]
Model approach	Markov model	Treatment sequence Markov model	Decision tree (induction period) and Markov model (maintenance period)
Perspective used	NHS	NHS	NHS and PSS
Model horizon	10 years	NR	10 years
Cycle length	4 weeks	NR	1 year
Justification of model horizon	York model	NR	Sufficiently long to capture relevant costs and benefits associated with treatment
Discount rates	3.50% (costs, utilities)	NR	3.50% (costs, utilities)
Mortality	Likely not considered	Not included	Not included
Study drug	ETN 50 mg BIW int.	MTX; CICLO; EFA; ETN 25 mg int.; ETN 50 mg int.; INF; ADA; Non-systemics	Pooled efficacy of UST and INF
Comparators	ETN 25 mg BIW int. No systemic therapy	All	Placebo
Treatment sequence	N/A	Theoretically optimal treatment sequence (result from analysis: ADA -> ETN -> EFA-> INF)	N/A
Health states	Treatment PASI 75 response PASI 50 but not PASI 75 PASI 50 not reached PASI 75 not reached Re-treat 25 mg BIW when response lost Withdraw: Do not re-treat Usual care: No treatment	NR	PASI response <50 PASI 50 response PASI 75 response PASI 90 response
Response criteria	Full responder: ΔPASI≥75 Partial responder: 50≤△PASI≤74 Non-responder: ΔPASI<50	ΔPASI 50, ΔPASI 75, ΔPASI 90	ΔPASI

Study	Lloyd *et al*. (2009)[136]	Sizto *et al*. (2009)[137]	Sawyer *et al*. (2015)[134]
Link between health utility and efficacy	Converting DLQI into utility using a formula (based on UK data) EQ-5D utility = 0.956–0.0248*DLQI	Between PASI response and EQ-5D, analysis of EQ-5D data from CHAMPION and REVEAL trials; assessed using U.K. population weights	Two-stage linear regression analyses from three ETN trials taken from Woolacott *et al*.[139]
Treatment efficacy data	Gordon *et al*. (2006) [92] Gottlieb *et al*. (2003) [100] Papp *et al*. (2005) [98] Leonardi *et al*. (2003) [97]	Mixed-treatment comparisons of 22 RCTs: Bansback *et al*. (2009) [140]	Stated to be generated from a meta-analysis using ordered probit model
Cost results	No systemic therapy: £41,985 ETN 25: £44,855 ETN 50: £47,587	Relative to BSC: Methotrexate -£3,844 Ciclosporin -£1,987 Supportive care £0 ETN 25 mg intermittent £4,114 ETN 50 mg intermittent £4,699 Efalizumab £4,942 Adalimumab £4,993 ETN £5,058 Infliximab £7,736	BSC: £93,591 2L Biologics: £99,338
Total QALYs	No systemic therapy: 0.70 ETN 25: 1.37 ETN 50: 1.61	Relative to BSC: Methotrexate 0.129 Ciclosporin 0.079 Supportive care 0 ETN 25 mg intermittent 0.110 ETN 50 mg intermittent 0.123 Efalizumab 0.124 Adalimumab 0.164 ETN 0.134 Infliximab 0.182	BSC: 0.479 2L Biologics: 0.804

Study	Lloyd *et al*. (2009)[136]	Sizto *et al*. (2009)[137]	Sawyer *et al*. (2015)[134]
Base case ICERs	- ETN 50 mg vs. No systemic therapy: £6,217 per QALY - ETN 25 mg vs. No systemic therapy: £4,297 per QALY - ETN 50 mg vs. ETN 25 mg: £11,710 per QALY	Comparator vs. Supportive care (£ per QALY): MTX: -£29,759 CICLO: -£25,135 ETN 25 mg inter: £37,284 ETN 50 mg inter: £38,358 EFA: £39,948 ADA: £30,538 ETN: £37,676 INF: £42,492 Incremental analysis vs Supportive care (excluding traditional systemics) Etanercept 25 mg intermittent Extendedly dominated Etanercept 50 mg intermittent Extendedly dominated Efalizumab Extendedly dominated Adalimumab £30,538 Etanercept Dominated Infliximab £147,906	£17,681/QALY gained
Stated drivers of CE results	- Assumed requirement for hospitalisation in untreated individuals; - Response rate achieved in re-treatment; - Cost of topical medications used were excluded from the analysis due to no difference between treatments.	Number of hospitalised days due to non-response to treatment	- Alternative assumptions relating to the cost and annual dropout rates of biologic therapies - The efficacy of BSC - The likelihood of hospitalisation and length of inpatient stay

Δ = change in; ADA = adalimumab; BIW = twice weekly; BSC = Best supportive care; CE = cost-effectiveness; CICLO = ciclosporin; DLQI = Dermatology Life Quality Index; EFA = efalizumab; EQ-5D = European Quality of Life – 5 Dimensions; ETN = etanercept; INF = infliximab; int. = intermittent; MTX = methotrexate; N/A = not applicable; NHS = National Health Service; NR = not reported; PASI = Psoriasis Area and Severity Index; PSS = Personal Social Services; RCT = randomised controlled trial; UST = ustekinumab

Table 65: Summary list of NICE TAs

	Etanercept, Efalizumab [71,139]			Infliximab [72,141]	Adalimumab [70,142]	Ustekinumab [69,143]	Apremilast [67,144]	Secukinumab [68,145]
	2006/7			2007/8	2008	2009	2015	2015
Study	TA103			TA134	TA146	TA180	TA368	TA350
Model approach	- ETN: Markov model	- EFA: Decision-tree model	Markov model (York model)	Based closely on the York model	Based on the York model	Based closely on the York model	Markov model	Decision tree and Markov model
Study drug	ETN 25 mg int./ cont. ETN 50 mg int./ cont.	EFA	- EFA - ETN 25 mg BIW cont. - ETN 25 mg BIW int. - ETN 50 mg BIW int.	INF	ADA	- UST 45 mg - UST 90mg	APR	SEC
Comparators	Topical therapy only/no systemic treatment	Calcipotriol and betamethasone	Primary analysis: BSC Secondary analysis: CICLO, Fumaderm, METHO, INF	ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA BSC	INF ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA BSC	ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA INF ADA BSC	ADA ETN BSC	ETN UST ADA INF BSC
Model horizon	96 weeks	10 years	10 years	10 years	10 years	10 years	10 years	10 years
Cycle length	12 months	12 months	12 months	12 months	12 months	3 months	28 days	12 months
Justification of model horizon	Based on follow-up in the registration trials	NR	NR	Sufficient time for all future costs and outcomes to be included	Based on York model	Based on York model	Maintain consistency with previous analyses and in the base case majority of patients are on BSC by the end of 10 years	Time horizon reflective of treatment duration of moderate to severe plaque psoriasis

	Etanercept, Efalizumab [71,139]			Infliximab [72,141]	Adalimumab [70,142]	Ustekinumab [69,143]	Apremilast [67,144]	Secukinumab [68,145]
Discount rates (costs, utilities)	No discounting	6.00%, 1.50%	6.00%, 1.50%	3.50%	3.50%	3.50%	3.50%	3.50%
Mortality	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Not considered	Modelled, not disease- or treatment-specific
HRQoL instrument	DLQI mapped to EQ-5D	TTO method	DLQI mapped to EQ-5D	Utilities from York model	EQ-5D	DLQI mapped to EQ-5D; SF-6D in sensitivity analysis	EQ-5D; DLQI mapped to EQ-5D	EQ-5D
Link between health utility and efficacy	EQ-5D utility score=0.956-[0.0248*(DLQI total score)	Utilities based on TTO method: Severe state: 0.59 on a 0 (equivalent to death) to 1 (equivalent to good health) scale; Mild: 0.89; Responders: 0.945 (average of full health (1) and mild (0.89)).	Map △PASI & △DLQI to EQ-5D (coefficients not reported)	Manufacturer submission stated utilities from the York model, but not details SF-36 from EXPRESS I and II trials were not used in the model	EQ-5D associated with DLQI and changes in PASI are provided by 2 RCTs	Map △PASI & △DLQI to EQ-5D (used for base case analysis, coefficients estimated based on the published scatter-plot in the York model): EQ-5D = -0.0162*DLQI + 0.8554	PASI>10, DLQI>10: mapping from Woolacott PASI>10, DLQI≤10: direct link between %ΔPASI and ΔEQ5D in patients with DLQI≤10	Changes in EQ-5D from baseline at a given time point as function of: - PASI response at that time point - baseline DLQI difference from the pooled mean baseline DLQI - interaction between these terms
Total costs	12 week analysis: No systemic treatment £72 ETN 25 mg £2,352 ETN 50 mg £4,474 96 week	10 year: Efalizumab: £5,611 Topical: £123	Supportive Care £0 Etanercept 25 mg £7,743 Efalizumab £9,382 Etanercept 25 mg Continuous £9,665	Continuous ETN 25: £1,531 Infliximab: £4,562	Incremental vs. supportive care: - Methotrexate £3,844 - Ciclosporin £1,987 - Supportive Care £0 - Etanercept Intermittent	Incremental vs. supportive care: - Supportive care £0 - EFA £5,264 - ETN 25 mg intermittent £3,989 - ETN 25 mg continuous	DLQI>10 Apremilast sequence: £89,374 Comparator sequence: £92,589	Standard of care £73,610 ETN 25 mg BIW £75,788 SEC 300 mg £76,361 ADA 40 mg £76,981 UST 45 mg £79,544 UST 90 mg £79,732 INF 5 mg/kg

	Etanercept, Efalizumab [71,139]			Infliximab [72,141]	Adalimumab [70,142]	Ustekinumab [69,143]	Apremilast [67,144]	Secukinumab [68,145]
	analysis: No systemic treatment £578 ETN 25 mg £8,635 ETN 50 mg £12,175 96 week analysis PASI>15, DLQI>20: No systemic treatment £578 ETN 25 mg £8,655 ETN 50 mg £10,867		Etanercept 50 mg £14,860		£4,114 - ETN High Intermittent £4,699 - EFA £4,942 - ADA £4,993 - ETN £5,058 - INF £7,736	£4,829 - ETN 50 mg continuous £5,333 - ADA £4,660 - UST £4,615 - INF £6,327		£93,539
Total QALYs	12 week analysis: No systemic treatment 0.011 ETN 25 mg 0.029 ETN 50 mg 0.031 96 week analysis: No systemic treatment 0.084 ETN 25 mg 0.236	10 year: Efalizumab: 1.39 Topical: 0.36	Supportive Care 0 Etanercept 25 mg 0.116 Efalizumab 0.112 Etanercept 25 mg Continuous 0.116 Etanercept 50 mg 0.123	Continuous ETN 25 mg: 0.089 Infliximab: 0.205	Incremental vs. supportive care - Methotrexate 0.129 - Ciclosporin 0.079 - Etanercept Intermittent 0.11 - Etanercept High Intermittent 0.123 - Efalizumab 0.124 - Adalimumab 0.164	Incremental vs. supportive care: - Efalizumab 0.1308 - ETN 25 mg intermittent 0.1325 - Etanercept 25 mg continuous 0.1409 - Etanercept 50 mg continuous 0.1483 - Adalimumab 0.1502 - Ustekinumab	DLQI>10 Apremilast sequence: 6.83 Comparator sequence: 6.69	Standard of care 0.97 ETN 25 mg BIW 1.13 SEC 300 mg 1.36 Adalimumab 40 mg 1.22 Ustekinumab 45 mg 1.30 Ustekinumab 90 mg 1.33 Infliximab 5 mg/kg 1.36

	Etanercept, Efalizumab [71,139]			Infliximab [72,141]	Adalimumab [70,142]	Ustekinumab [69,143]	Apremilast [67,144]	Secukinumab [68,145]
	ETN 50 mg 0.264 96 week analysis PASI>15, DLQI>20: No systemic treatment 0.139 ETN 25 mg 0.451 ETN 50 mg 0.415				- Etanercept 0.134 - Infliximab 0.1616 - Infliximab 0.182	0.156		
Base case ICERs	12 week analysis: - ETN 25 mg vs no systemic therapy: £124,732 - ETN 50 mg vs ETN 25 mg: £1,255,840 96 week analysis: - ETN 25 mg vs no systemic therapy: £53,056 - ETN 50 mg vs ETN 25 mg: £127,464	10 year ICER: Efalizumab vs topicals: £25,582	Incremental analysis: Etanercept 25 mg £66,703 Efalizumab Dominated Etanercept 25 mg Continuous Dominated Etanercept 50 mg £1,035,121 ICER vs Supportive care: Etanercept 25 mg £66,703	- INF vs. Supportive care: £22,240 per QALY - INF vs. Cont ETN 25 £26,095 per QALY	ICER relative to supportive care: - Methotrexate £-29,759 - Ciclosporin £-25,135 - Supportive Care N/A - Etanercept Intermittent £37,284 - Etanercept High Intermittent £38,358 - Efalizumab £39,948 - Adalimumab £30,538 - Etanercept	ICERs vs. Supportive care: - Efalizumab £40,250 - Etanercept 25 mg intermittent £30,111 - Etanercept 25 mg continuous £34,281 - Etanercept 50 mg continuous £35,964 - Adalimumab £31,022 - Ustekinumab £29,587 - Infliximab £39,153	Apremilast sequence dominated the comparator sequence.	Incremental analysis: Standard of care N/A Etanercept 25 mg BIW £13,948* Secukinumab 300 mg £2,464 Adalimumab 40 mg Dominated Ustekinumab 45 mg Dominated Ustekinumab 90 mg Dominated Infliximab 5 mg/kg Dominated Note: *ETN extendedly domintated by SEC

	Etanercept, Efalizumab [71,139]			Infliximab [72,141]	Adalimumab [70,142]	Ustekinumab [69,143]	Apremilast [67,144]	Secukinumab [68,145]
	96 week analysis PASI>15 and DLQI>20: - ETN 25 mg vs no systemic therapy: £25,926 - ETN 50 mg vs ETN 25 mg: Dominated		Efalizumab £84,018 Etanercept 25 mg Continuous £83,258 Etanercept 50 mg £120,855		£37,676 - Infliximab £42,492 ICER vs. supportive care (biologics only) Etanercept Intermittent: Extendedly dominated Etanercept High Intermittent: Extendedly dominated Efalizumab: Extendedly dominated Adalimumab: £30,538 Etanercept: Dominated Infliximab: £147,906 Note: Discrepancy in adalimumab ICERs carried over from the manufacturer submission.	ICER ustekinumab vs other treatments: - Supportive care £29,587 - Efalizumab Dominant - Etanercept 25 mg intermittent £26,637 - Etanercept 25 mg continuous Dominant - Etanercept 50 mg continuous Dominant - Adalimumab Dominant - INF vs. UST £304,566		

	Etanercept, Efalizumab [71,139]			Infliximab [72,141]	Adalimumab [70,142]	Ustekinumab [69,143]	Apremilast [67,144]	Secukinumab [68,145]
Stated drivers of CE results	NR	2-way sensitivity analysis of the utility values assigned to responders and non-responders	- Baseline QoL (as assessed using the DLQI) - Probability of the patient being hospitalised if they fail to respond to treatment	- Non responders' inpatient LOS - patient weight - changes in response rate	- Cost of adalimumab per vial - Cost of inpatient stay - Annual length of inpatient stays for non-responders	- Number of hospital days for BSC - Estimated cost of dosing for inter. ETN 25 mg - SF-6D utility scores instead of EQ-5D	Differences in costs and outcomes with APR compared with BSC	- Costs assumed for BSC (Fonia *et al* (2010) [146] vs NICE CG153 and hospital episode statistics) - Small changes in incremental health benefits between different biological treatments, thus ICERs could vary dramatically with small QALY changes

ADA = adalimumab; APR = apremilast; BIW = twice weekly; BSC = Best supportive care; CE = cost-effectiveness; CICLO = ciclosporin; cont. = continuous; DLQI = Dermatology Life Quality Index; EFA = efalizumab; EQ-5D = European Quality of Life – 5 Dimensions; ETN = etanercept; HRQoL = health-related quality of life; INF = infliximab; int. = intermittent; LOS = length of stay; METHO = methotrexate; NR = not reported; PASI = Psoriasis Area and Severity Index; SEC = secukinumab; SF-6D = Short Form – 6 Dimension; TA = technology appraisal; TTO = time trade-off; UST = ustekinumab

Key model features in the published economic evaluations are described below.

Model framework

The York model[139] (Table 65) appears widely accepted: Among the nine cost-utility publications[129-137], four models [129,130,133,137] were explicitly based on the York model publication with three more models [132,134,135] using similar frameworks. The five NICE submissions for the treatment of moderate to severe psoriasis (adalimumab[70], infliximab[72], ustekinumab[69], apremilast[67] and secukinumab[68] that came after the publication of the York model also explicitly followed the York model framework and were accepted by NICE as being relevant to psoriasis. The two model publications that did not follow the York model framework[131,136] both evaluated the cost-effectiveness of intermittent etanercept which may be less suited to the York model framework which assumes continuous treatment after an initial treatment period.

The manufacturers' models were constructed based on systematic and comprehensive approaches to identify evidence relevant to inform development of decision analytical models that compared biologics and/or conventional systemics for the treatment of moderate to severe psoriasis. After the advent of the York model, the combination of a decision tree ("trial period", also referred to as an induction period elsewhere in the literature) and a Markov model ("treatment period") were used in the manufacturers' submission models. The duration of the induction period reflected the duration of treatment response assessment in the respective clinical trials. For the "treatment period", a time horizon of 10 years was used. Following the York model[139], a yearly cycle was used in the adalimumab[70], infliximab[72] and secukinumab[68] submissions, whereas the model for the ustekinumab[69] submission applied a 3-month cycle length on the basis that it reflects: i) the clinical course of the disease, ii) the time frame of clinical decision making; and iii) the dosing intervals for ustekinumab. The apremilast submission[67] applied a 28-day cycle to account for the different lengths of induction periods.

Although the York model publication was used as a framework for the majority of the models identified in the literature review, hence providing a widely accepted modelling framework for psoriasis, changes have occurred in the treatment landscape and new data has become available since the publication of the York model in 2005. Criticism directed at the York model by NICE commissioned Evidence Review Group (ERG) reports has questioned key parameters in the model such as the definition of BSC, the methodology for linking efficacy estimates to health utility and modelling of time on treatment via annual drop-out rates.

Health states

Health states within the models were based on PASI response. In the NICE appraisals[67-72], individuals were assumed to be in one of two health states: responders or non-responders. In the base case, response was typically defined as a 75% reduction in baseline PASI score (PASI 75), but varied to PASI 50 and PASI 90 in scenario analyses. These categories were based on response to treatment in the initial induction period. Patients who achieved relevant improvements in PASI were assigned an associated improvement in health utility with higher responses associated with larger health utility improvements. Responders remained on treatment (with PASI assumed to remain the same) until they discontinued treatment (see below). Non-responders moved directly to BSC after the induction period and were assigned lower health utilities and additional costs. In all manufacturer submission models, the treatment response rate in BSC was set equal to placebo response rates from the meta-analyses used to populate the models with treatment efficacy estimates. Hence, whilst all patients continuing treatment after the induction period are responders until they drop out of treatment, virtually all patients in BSC are non-responders and non-responders were assumed to incur an annual hospitalisation.

Two of the peer-reviewed CEM publications[129,130] that were explicitly based on the York model took a slightly different approach than the York model with separate health states for partial and full-response with intermittent etanercept. However, the approaches in those publications are not well-described. Furthermore, two peer-reviewed models that estimated the cost-effectiveness of intermittent etanercept had model structures where response to treatment was assessed every cycle and patients not achieving the relevant response discontinued treatment.[131,136] Four peer-reviewed CEM publications[132-135,137] had the same health states as the York model, albeit Villacorta *et al*. (2013) used a ΔPASI 50 threshold to determine treatment response, instead of the more commonly used ΔPASI 75. One model[134] appears to have used separate health states for the different PASI response categories.

Model population

Each of the published peer-reviewed CEMs estimates the cost-effectiveness in a population with moderate to severe psoriasis. Four model publications did not provide a formal definition of moderate to severe psoriasis.[131-133,135] The remaining four publications[67,129,130,134,136,137] provided definitions which were consistent with a threshold for moderate to severe disease of DLQI>10 and PASI≥ 10, as defined in Clinical Guideline 153.[8]

Treatment sequence

Whilst a number of CEMs identified in the systematic review for economic evaluations, [133,137] including the original York model publication[139], assess the theoretical cost-effectiveness of treatment sequences; treatment sequences are not actually modelled. Instead theoretically optimal treatment sequences are derived based on comparisons of the individual treatments to BSC. Sawyer *et al* (2015)[134] explicitly assesses the cost-effectiveness of second line biologic treatment in patients who have received prior treatment with a biologic therapy. However, it is not a treatment sequence model per se as only one line of biologic treatment is modelled.

Treatment effectiveness

In all included cost-utility publications[129-137] and NICE TAs[67-72], treatment effectiveness was defined in terms of a relative change in PASI from baseline, achieved at the end of the induction period. No other indicator of effectiveness was used in the models. In the York model[139] and the subsequent submissions[67-72], evidence was synthesised from a variety of trials by using direct or indirect comparisons to obtain response rates for all therapies considered in the respective models. The base case definition of response in most models was ΔPASI 75, albeit four models[131,135,139] defined ΔPASI 50 as the base case response rate. In the ERG reports for adalimumab, infliximab and ustekinumab, response criteria were varied in scenario analyses to assess the impact of defining response as ΔPASI 50 and ΔPASI 90. It may be noted that in European consensus guidelines, PASI 50 combined with an improvement in DLQI of at least 5 points is also viewed as treatment response[147]; this definition of response is also incorporated (along with ΔPASI 75) in the UK treatment guidelines.

Health utilities

All identified CEMs linked PASI response categories to improvements in health utility from baseline. The methodology for deriving health utilities associated with different response rates varied with three principal approaches used. The first approach is to link PASI response categories to studies that elicited health state utility values using the time trade-off method (TTO). This approach assumed that given health states corresponded to PASI response categories (albeit the health states were not described in terms of PASI). The second approach was to use mapping exercises whereby relative PASI response rates were associated with changes in DLQI. Changes in DLQI were subsequently associated with changes in health utility. The third approach was to associate PASI response categories directly with changes in health utility. A number of studies[69,135,143] used multiple approaches in scenario analysis. Given the small number of studies and differences in methodology among the studies, it is difficult to compare results. Nevertheless, there appears to be a

positive association between baseline HRQoL and health utility gain for a given ΔPASI category.[72,139] Furthermore, EQ-5D appears to be more sensitive to changes in PASI compared to the SF-6D.

Resource use and costs

The resource use categories in the York model[139] and subsequent manufacturers' submissions[69,70,72] were: treatment (biologics), administration visits, monitoring visits, laboratory tests, and inpatient care. Subsequently, unit costs were assigned to the resources using standard sources such as the British National Formulary (BNF). Whilst the assumptions on monitoring visits and laboratory tests were similar across the models, some differences were noted with regards to the assumed dosage of intermittent etanercept (74% in the York model vs. 88% in the ustekinumab and adalimumab submissions), and the number of administration visits for infliximab.

Except for the cost of biologic treatment, the most important driver of costs in the model was the resource use required in BSC. How patients are treated in BSC differs between countries but from a UK perspective, hospitalisations appear to be important. In the York model publication and subsequent HTA submissions, the base case assumption was that all patients who were non-responders were hospitalised once every year with a mean duration of 20.8 days. Given the low PASI 75 response rates in patients treated with BSC, virtually all patients on BSC (but no patients who remained on biologic treatment) were hospitalised. Extensive scenario analyses were conducted by the ERGs on this point [141-143] and the assumption was deemed important for the cost-effectiveness estimates. In addition to hospitalisation, patients on BSC were assumed to incur 18 additional outpatient visits in the infliximab submission. The secukinumab submission[68] followed roughly the same assumptions as the previous models, though patients on BSC were also assumed to incur costs for UVB phototherapy and visits to the day care centre. In the apremilast submission[67] non-responders were assumed to incur costs for hospitalisations in all subsequent biologic treatments during the induction periods and in the BSC treatment state at the end of the sequence.

5.2 *De novo analysis*

A de novo model was constructed to determine the cost-effectiveness of ixekizumab with reference to the information derived from the literature search described in Section 5.1.1.

5.2.1 Patient population

Ixekizumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The base case economic evaluation considers biologic-naïve patients who have failed to respond to prior conventional systemic therapies and are eligible to receive systemic biologic therapies approved in the UK, i.e. the cost-effectiveness of ixekizumab as a first-line biologic therapy is assessed.

The NICE scope covers all potential populations eligible under the licensed indication, which includes conventional systemic treatments. Comparison with conventional systemic therapies has been included as a scenario analysis, but in the NHS in England, it is anticipated that ixekizumab will be used in the population currently eligible for biologic treatment for psoriasis (i.e. patients who have failed to respond to, or are unable to be treated with conventional systemic treatments who have a PASI score≥10 and a DLQI>10).

It should be noted that the definition of moderate to severe psoriasis for the patients included in the UNCOVER trial programme is not strictly adherent to UK clinical guidelines (PASI≥10 and DLQI>10, as stated in Section 5.1.2)[8] as a baseline PASI≥12 was required to enroll in the UNCOVER trials. This baseline PASI score is common to all recent clinical studies for biologics in psoriasis. However, patients with PASI≥12 (the inclusion criteria in the UNCOVER trial programme) can be appropriately classified as having moderate to severe psoriasis.[139]

In accordance with UK clinical guidelines, moderate to severe psoriasis in the model population is defined as patients with baseline PASI≥10 and DLQI>10. Clinical outcomes used to inform ixekizumab efficacy in the model, i.e. the proportion of patients achieving specific PASI response thresholds, are pooled from the ITT populations in the UNCOVER trials, in which the mean baseline DLQI score across the trials was 12.5[148], and health state utility estimates used in the base case were informed by HRQoL assessments of patients with DLQI>10.

5.2.2 Model structure

Model schematic

A de novo Markov state-transition model was developed in Visual Basic for Applications (VBA) with a Microsoft Excel interface. The model consists of five PASI response health states and four treatment-related health states.

PASI response states determine the HRQoL impact of treatment in the model associated with specific thresholds of percentage reduction in baseline PASI score. The following PASI

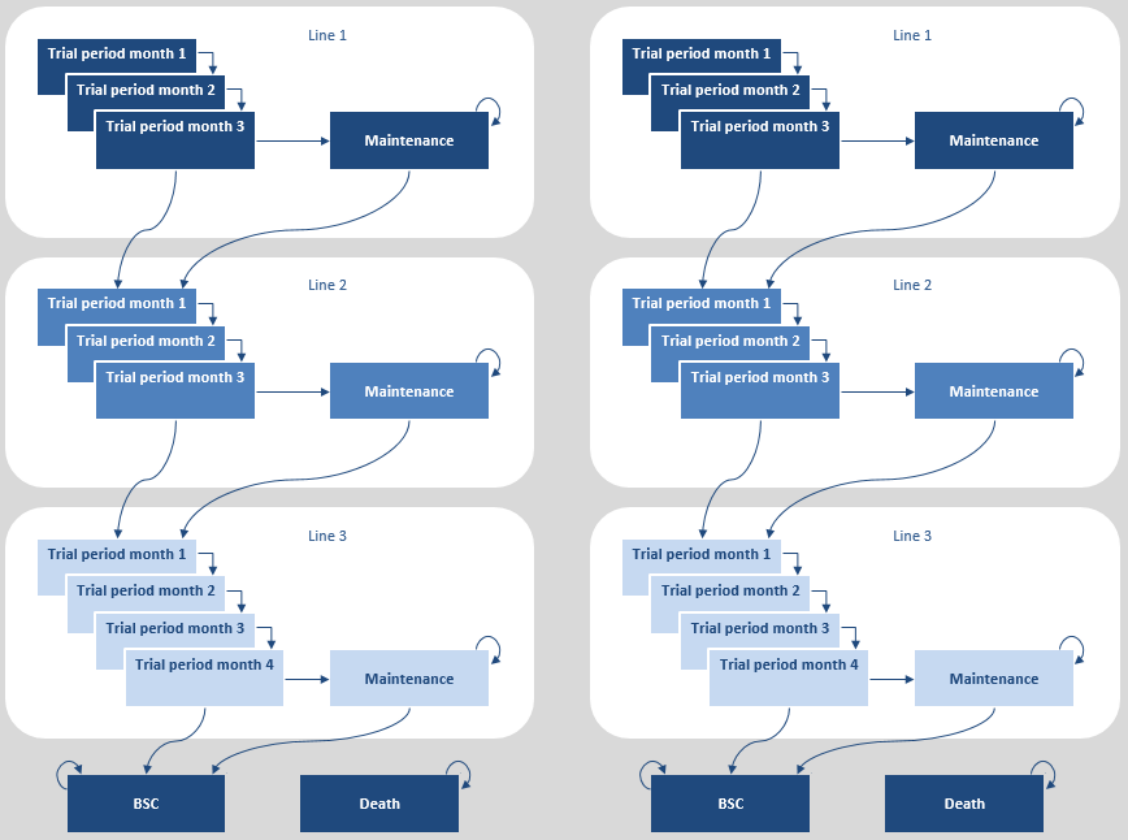
response categories constituted a set of mutually exclusive and collectively exhaustive states in the model:

- PASI<50 (no response)
- PASI 50-74
- PASI 75-89
- PASI 90-99
- PASI 100 (complete clearance of symptoms)

Treatment states determine the cost impact of a treatment in the model as they are associated with specific resource use rates. The following treatment states are depicted in Figure 38:

- Induction (trial) period
- Maintenance period
- BSC
- Death

Figure 38: Model structure schematic



BSC = best supportive care

Arrows to Death state from all other states removed to simplify diagram

Induction period

The induction period consists of a series of tunnel states from which patients either die or transition to the next temporary state. In the final temporary state, patients are assessed for response to treatment. The induction period length is dependent on the biologic and can last from 10 to 16 weeks in alignment with the response assessment time points reported in CG153.[8] At the end of the induction period, patients are assessed on the basis of PASI response and assigned in the model to one of the five PASI response health states.

Patients who meet the minimum base case response criterion of PASI 75 continue treatment in the maintenance state. If patients do not have an adequate level of response, they enter another series of tunnel states upon initiating the next treatment line, whether active treatment or BSC. At the end of the subsequent induction period, these patients are once again assessed for response.

Maintenance

During the maintenance period, patients continue to receive the active therapy and are assumed to maintain their level of response until discontinuation due to any cause, such as loss of efficacy or AEs.

Upon discontinuing, a patient is assumed to revert to their baseline PASI score. These patients proceed to the induction period of the subsequent treatment in the sequence and are assumed to experience no improvement from baseline HRQoL until the next response assessment for the subsequent biologic therapy or BSC.

BSC

BSC is the final treatment in the sequence, consisting of a bundle of non-biologic supportive therapies. The only transition out of the BSC treatment state is death.

When patients have exhausted the biologic therapy options in the sequence, they proceed to receive BSC in the final induction period of the treatment sequence and are assessed at the end of the induction period. All patients, including non- or partial responders, continue to receive BSC and maintain the level of response until death.

Death

Death is an absorbing health state to which transition is possible from any other state. Mortality is not conditioned on treatment or treatment response and has been derived from life tables for the UK.

Model characteristics

A summary of model characteristics is presented in Table 66. The economic evaluation is consistent with the NICE reference case. The model takes the form of a cost-utility analysis with a fully incremental analysis, and NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. Health effects were measured in QALYs based on EQ-5D-5L responses that were collected in the UNCOVER trial programme.

Table 66: Features of the de novo analysis

Factor	Chosen values	Justification	Source
Time horizon	Lifetime (45 years to 99.9 years)	NICE reference case: patients expected to spend more than 10 years on active pharmacological treatment	NICE Guide to the Methods of Technology Appraisal 2013 [149]
Cycle length	1 month	Captures induction periods when patients switch to a treatment	NICE Guide to the Methods of Technology Appraisal 2013[149]
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	NICE Guide to the Methods of Technology Appraisal 2013 [149]
Discount of 3.5% for utilities and costs	Yes	NICE reference case	NICE Guide to the Methods of Technology Appraisal 2013 [149]
Perspective (NHS/PSS)	Yes	NICE reference case	NICE Guide to the Methods of Technology Appraisal 2013 [149]

NICE = National Institute for Health and Care Excellence; NHS = National Health Service; PSS = personal social services; QALYs = quality-adjusted life years

The model structure is similar to that of the York model[139], which has been used in four of eight published models[129-133,135-137] as well as in all submissions to NICE subsequent to the original publication of the York model (adalimumab[70], infliximab[72], secukinumab[68], apremilast[67] and ustekinumab[69]). Furthermore, the York model has also been used to estimate the cost-effectiveness of second line biologic treatment in patients with psoriasis to support the UK clinical guidelines for the management of psoriasis commissioned by NICE. This evaluation has also recently been published in a peer-reviewed journal.[134]

Whilst the York model has been accepted as relevant to psoriasis by NICE and is widely used, it is relatively dated and several aspects of the model can potentially be amended to better reflect current clinical practice and new data that have become available since the original York model publication, such as the expansion of therapy options with implications for treatment sequencing, definition of BSC, methodology for linking efficacy estimates to health utility and modelling of time on treatment. Expert input obtained from an advisory board in March 2015 supported preserving a York model framework as a foundation for the

ixekizumab global CEM and adding in factors that align the model better to the current treatment landscape and data availability.

As described in Section 5.1.2, a key difference between the ixekizumab CEM and relevant economic evaluations identified in the literature is that the current model uses a fully incremental analysis framework to estimate the cost-effectiveness of all approved biologics in the UK in the same position in a biologic treatment sequence.

Ixekizumab is expected to be used in the same position of the NICE clinical pathway of care as other biologics that are approved in England and Wales. Patients initiate a systemic biologic therapy following failure on conventional systemics (Section 3.3). Switching to an alternative biologic treatment is advised if treatment response is inadequate at response assessment time point (primary failure) or in the maintenance period after an initially adequate level of response (secondary failure), or if the drug cannot be tolerated or becomes contraindicated. Patients may therefore receive multiple biologic treatments as part of a treatment sequence. Once patients have received up to the designated number of lines of biologic treatments, they go on to receive BSC. Response assessment in the clinical pathway is measured using relative reductions in baseline PASI score, which forms the basis of the decision to continue treatment.

In the base case analysis, ixekizumab as a first-line therapy in a biologic treatment sequence is compared to each currently approved biologic as first-line therapy followed by subsequent biologic therapies in a similar treatment sequence (Section 5.2.3). The model has the flexibility to assess the cost-effectiveness of ixekizumab positioned in second-line within a treatment sequence. This is assessed in a scenario analysis in which the patient group of interest has failed to respond to a previous biologic therapy.

Facilitating analysis of the cost-effectiveness of ixekizumab in different places in actual treatment sequences in the cost-effectiveness model is important for two reasons.

Firstly, a treatment sequencing approach is reflective of clinical practice in the UK with potential variation in biologic treatment algorithms between Clinical Commissioning Groups (CCG).[150-152] Secondly, events such as treatment discontinuation in the first line of an analysed treatment sequence may have down-stream consequences. For example, time to BSC, which may be associated with poorer clinical outcomes than biologic therapy, may be affected depending on how much time patients spend on treatment. Modelling actual treatment sequences may therefore be important to accurately reflect the decision problem and consequently, the ixekizumab CEM incorporates treatment sequences.

As modelling treatment sequences results in patients remaining longer on treatment, the model time horizon required extension beyond 10 years which is the most frequently used and longest time horizon among the reviewed models.[69,70,72,129-132,135,136,139] While a time horizon of 10 years may be sufficient in a comparison of single treatments (sequences), the current analysis incorporates active treatment after ixekizumab. A lifetime model horizon is therefore considered appropriate for modelling treatment sequences. Specifically in the model, this runs from a starting age of 45, corresponding to the mean age of patients at baseline in the UNCOVER trials[15] until 99.9 years.

A monthly cycle (equivalent to 52 weeks divided by 12) is used in the current analysis. This is in contrast to the York model which has a decision tree model structure for the induction period and one year cycles for the maintenance treatment period. The reason for this is due to the treatment sequence approach for which the cycle needs to be sufficiently short to capture induction periods when patients switch between treatments. Expert opinion gathered from the advisory board supported the choice of a one month cycle length.

In a Markov cohort, it is assumed that transitions happen at the end of each cycle. In reality, however, patient transition is a continuous process, which may occur during any time in the cycle.[153] To address this, a half-cycle correction may be used, which assumes that state transitions occur, on average, half way through the cycle. In this case, the cycle length (one month) is considered to be sufficiently short and patients repeatedly enter tunnel states, therefore half-cycle corrections may not be appropriate and were not applied. Furthermore, it has been argued that half-cycle corrections do not affect estimated incremental costs and benefits and may therefore not be needed in economic evaluations.[154]

5.2.3 Intervention technology and comparators

The European Commission granted marketing authorisation for ixekizumab on 26 April 2016 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Each of the comparator treatments in the base case analysis are all biologics recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or for patients who are intolerant or have a contraindication to these treatments.[65] It should be noted that infliximab is currently recommended by NICE only for patients with very severe psoriasis with PASI≥20 and DLQI>18, but it has been included in the base case analysis alongside the biologics recommended by NICE for patient with moderate to severe psoriasis.

Switching from one biologic to another, either for primary or secondary lack of efficacy or for AEs has become common practice.[150] This sequential approach is also supported in national and local guidelines.[8,32,151,152] According to the NICE pathway for psoriasis, physicians should consider switching biologics if a patient does not respond, loses response or does not tolerate the treatment.[8] Furthermore, for adults in whom there is an inadequate response to a second biologic, physicians are advised to seek supra-specialist advice from clinicians with expertise in biologics. Sequences with three biologic treatment options followed by BSC are considered in the current analysis, which aligns with the treatment algorithm proposed in CCG guidance.[151,152]

The model allows only logical treatments to be sequenced. For example, it is assumed that a patient who has not responded to treatment is not given a different dosage of the same treatment or its biosimilar counterpart later in the sequence, therefore treatment sequence restrictions have been incorporated into the model. A full list of restrictions is displayed below in Table 67.

Table 67: Treatment sequence restrictions

Treatment	Restriction: what treatment(s) cannot follow
Ixekizumab Q2W	Ixekizumab Q2W
Adalimumab	Adalimumab
Etanercept 50 mg	Etanercept 50 mg, Biosimilar etanercept
Infliximab	Infliximab, Biosimilar infliximab
Ustekinumab 45 mg	Ustekinumab 45 mg, Ustekinumab 90 mg
Ustekinumab 90 mg	Ustekinumab 45 mg, Ustekinumab 90 mg
Secukinumab 300 mg	Secukinumab 300 mg
Biosimilar etanercept	Biosimilar etanercept, Etanercept 50 mg
Biosimilar infliximab	Biosimilar infliximab, Infliximab

Q2W = every 2 weeks

Dosing regimens for each treatment are in line with their marketing authorisation. These are presented in Table 68 along with stopping rules as stated in the corresponding NICE guidance and SmPC.[155-159]

Table 68: Dosing regimens, stopping rules and model doses

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model induction period (weeks)	Induction period doses	Annual maintenance doses	Doses in year 1
Ixekizumab Q2W	80 mg every two weeks for 12 weeks, following a 160 mg starting dose. Maintenance: 80 mg every 4 weeks	N/A	Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.	12	8	13	18
Adalimumab	Injection, initially 80 mg, then 40 mg on alternate weeks starting 1 week after initial dose	Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks[70]	Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period[155]	16	10	26	28
Etanercept 50 mg	Injection, 50 mg once weekly for up to 24 weeks	Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks[71]	Treatment should be discontinued in patients who show no response after 12 weeks[159]	12	12	52	52
Infliximab	By IV infusion, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks	Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks[72]	If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given[157]	10	3	6.5	8
Ustekinumab 45 mg	Injection, body-weight <100 kg, initially 45 mg, then 45 mg 4 weeks after initial dose, then 45 mg every 12 weeks	Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment[69]	Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment[156]	16	2	4.33	5

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model induction period (weeks)	Induction period doses	Annual maintenance doses	Doses in year 1
Ustekinumab 90 mg	Injection, body-weight >100 kg, initially 90 mg, then 90 mg 4 weeks after initial dose, then 90 mg every 12 weeks	Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment[69]	Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment[156]	16	2	4.33	5
Secukinumab 300 mg	Injection of 300mg at weeks 0, 1, 2 and 3 followed by monthly* dosing from week 4. Each 300mg injection is administered as two injections of 150 mg	Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks[68]	Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment[158]	12	7	13	16

IV = intravenous; N/A = not applicable; NICE = National Institute for Health and Care Excellence; Q2W = every 2 weeks; SmPC = summary of product characteristics

Note: Data based on National Clinical Guideline Centre (2012)[160] and SmPC for ixekizumab [1]

*4-weekly dosing schedule assumed for secukinumab maintenance therapy.

The absence of national guidance on the positioning of biologic treatments in a sequence and lack of precedence in using a fully incremental analysis framework to model a sequential approach in psoriasis necessitated the use of assumptions in formulating the sequences for the first-line indication in Table 69.

These specific treatments and their ordering have been selected on the basis of market shares in second-line; alternating between mechanisms of action following failure on an initial biologic treatment, where possible[150,152]; and maintaining a common treatment algorithm between sequences for easier comparison.

Patients who would be eligible to receive a sequence of biologic treatments are unlikely to be treated with BSC following failure on conventional systemic or first biologic therapy for the remainder of their lifetime, therefore BSC as a standalone comparator is not included in the full comparator set in the base case analysis.

Table 69: Intervention and comparators as first-line in treatment sequence

Sequence	1st Line	2nd Line	3rd Line	4th Line
1A	Ixekizumab	Ustekinumab 90 mg	Infliximab	BSC
1B	Adalimumab	Ustekinumab 90 mg	Infliximab	BSC
1C	Etanercept 50 mg	Ustekinumab 90 mg	Infliximab	BSC
1D	Infliximab	Ustekinumab 90 mg	Adalimumab	BSC
1E	Secukinumab	Ustekinumab 90 mg	Infliximab	BSC
1F	Ustekinumab 45 mg	Adalimumab	Infliximab	BSC
1G	Ustekinumab 90 mg	Adalimumab	Infliximab	BSC

BSC = best supportive care

Each biologic therapy approved by NICE for adult patients with moderate to severe psoriasis or very severe psoriasis (infliximab) is assessed as first-line in a treatment sequence.

Ustekinumab had the largest market share of 48.6% in 2016 in second-line therapy for psoriasis.[161] In the model it is therefore used as a common second-line therapy across sequences in which it provides an alternative mechanism of action to first-line (i.e. all sequences except 1E and 1F, Section 3.3)

Ustekinumab dosage is weight-based: the 45 mg dose is indicated for patients with a weight of less than 100kg and the 90 mg dose is indicated for those with a weight of 100kg or greater. A singular dose is used in second-line in the model to minimise duplicating sequences. The 90 mg dose has the same acquisition cost but greater efficacy than the 45 mg dose (Section 4.9), therefore is associated with a conservative estimate of the incremental costs and benefits of ixekizumab versus all other treatment sequences with

second-line ustekinumab. Ustekinumab 90 mg is therefore positioned in second-line in the model.

In sequences 1E and 1F, adalimumab is selected as the second-line option as it is associated with the second-largest market share in second-line therapy and provides an alternative mechanism of action to first-line ustekinumab 45 mg and ustekinumab 90 mg.

Infliximab is recommended in the UK for patients with very severe psoriasis. Although disease severity progression is not modelled, it is assumed that following discontinuation from second-line treatment, all patients would receive infliximab on the basis of its rapid onset of efficacy. Kerdel *et al* 2015[150] suggests that discontinuation from a TNFα inhibitor does not preclude response to a different TNF-α inhibitor in the subsequent line of therapy, hence infliximab follows adalimumab in sequences 1E and 1F.

5.2.4 Treatment continuation

Treatment continuation in the model is conditioned on response to treatment at the end of the induction period, which is presented for each therapy in Table 68**.** The model induction period aligns with the time point for response assessment reported in CG153 in line with NICE guidance for all currently approved biologics.[8] While the SmPC for ixekizumab suggests a longer period over which treatment continuation is assessed (16 to 20 weeks), the model assumes that response assessment begins at week 12, which corresponds to the induction dosing period in the UNCOVER trial programme and the point at which the draft SmPC suggests switching to Q4W dosing.

Treatment response is defined in CG153 and BAD guidelines for psoriasis as achieving at least:[8,162]

- PASI 75; or
- PASI 50 and a five-point decrease in the DLQI.

PASI 75 is the most commonly used primary efficacy measure[147] and has been employed in previous NICE TAs as the sole base case response criterion for treatment continuation at the end of the induction period.[67-72] In the current analysis, patients must achieve at least PASI 75 to proceed to the maintenance period. PASI 50 and a five-point decrease in DLQI is not implemented as a treatment continuation rule in the model due to limited data availability on the coupling of these measures of response. Instead, PASI 50 alone as a treatment continuation rule is used in a scenario analysis (Section 5.8.3).

Treatment continuation in the maintenance period is not conditioned on response. An assumption is made in line with previous identified economic evaluations[67,69,70,72,132,135] that, irrespective of treatment line, patients in the maintenance period face a constant annual discontinuation rate of 20%.[66,68,69,71,130,133] This represents all-cause drop-out due to loss of efficacy and adverse events.

This annual drop-out rate is corroborated by a recent large British study of 3,523 biologic-naïve patients.[14] The study presented long-term drug survival for four biologics (adalimumab, etanercept, infliximab and ustekinumab). Results showed that loss of efficacy was a major reason for treatment discontinuation, with a 53% overall drug survival rate after three years, which equates to approximately 20% discontinuing per year. Similar results were reported by Gniadecki *et al.* (2015) in a publication on drug survival of a large Danish cohort.[163] The authors note that the discontinuation rate among the biologically treated patients appears to be constant over the treatment period, with no obvious plateau.

5.3 *Clinical parameters and variables*

5.3.1 Clinical outcomes

The measure of treatment effectiveness used in the current model is the proportion of patients achieving specific thresholds of relative change in PASI from baseline. Alternative measures of treatment effectiveness were collected in the UNCOVER trial programme such as sPGA, DLQI or absolute change in PASI from baseline; however, these were not used. The current model is instead aligned with current UK practice in assessing response to biologic therapy[65] and with all identified cost-effectiveness models, which have used relative PASI response thresholds. Furthermore, relative change in PASI score appears to be the most widely reported outcome in RCTs and, as the model response criterion, facilitates evidence synthesis.

Response rates used to inform the model are taken from the NMA described in Section 4.9. In the base case, patients who met the PASI 75 threshold are classed as responders and assumed to maintain their response for as long as they are on maintenance therapy until discontinuation due to any cause. PASI non-responders are assumed to revert to baseline PASI score until the end of the induction period for the subsequent treatment in the sequence at which point in the model they are reassessed for response.

The response rates used to inform the model are presented in Section 4.9. PASI response rates for BSC are assumed to be equivalent to placebo.

Prior biologic treatment

In a Danish observational study[163], prior (primary or secondary) failure of a biologic treatment was shown to be a significant negative predictor of drug survival (i.e. time to discontinuation). The data identified for the NMA was assessed for feasibility of a network of evidence of biologic efficacy in patients who had failed a prior biologic (see Section 4.9) and it was deemed that there was not sufficient evidence available for connected network.

The efficacy of ixekizumab was consistent across different prior treatment subgroups during the induction dosing period. Following inadequate response with etanercept in the initial randomisation phase of the UNCOVER-2 trial, patients who were treated with ixekizumab did not receive either a 160 mg loading dose or Q2W induction phase dosing and yet experienced similar PASI response rates to the primary population, i.e. patients randomised to ixekizumab in the induction period (Section 4.7.4). In addition, the response to ixekizumab was not dissimilar between biologic-naïve and biologic-experienced patients (Section 4.7.5).

In the absence of a feasible network on efficacy for treatments following relapse from a prior biologic and the lack of evidence to suggest that the efficacy of ixekizumab varies according to prior treatment, prior biologic treatment is assumed not to be a treatment effect modifier in the base case analysis. This assumption was applied to all treatments in the absence of robust alternative evidence.

5.3.2 Transition probabilities

Psoriasis is associated with an unpredictable natural history.[7] In the absence of data to model time-varying transition probabilities after the induction period, fixed transition probabilities are used: PASI 75 response rates from the induction period to maintenance and a fixed discontinuation rate for maintenance to the induction period of the subsequent treatment in the sequence. The exception to this is the probability of death, which is derived from UK life tables and gender-weighted. The derivation of transition probabilities between treatment states is described below.

5.3.3 Treatment states

Induction

After initiating treatment in the induction period, patients transition to the next temporary state in the tunnel unless they die within the temporary state.

At the end of the induction period, assessment of whether patients have achieved a minimum response of PASI 75 determines their transition to the maintenance period or to the induction period for the next treatment. Response is assessed in the model at the same

time point as recommended in the NICE clinical pathway.[65] No further adjustment is therefore required to the PASI response rates obtained from the NMA in order for these to be applied as transition probabilities.

Maintenance period

Patients who have achieved a minimum response of PASI 75 are assumed to continue treatment into the maintenance period until they drop out due to any cause. A constant annual dropout rate of 20% is applied in the maintenance treatment state and represents discontinuation due to any cause, namely loss of efficacy and safety concerns. The annual drop-out rate,d_a, is converted to a monthly drop-out rate,d_m, using Equation 1 and applied in each model cycle in the maintenance treatment state to patients receiving any biologic therapy to arrive at a monthly drop-out rate of 1.84%.

Equation 1

$$d_m = 1 - e^{(\frac{ln(1-d_a)}{12})}$$

Mortality

Normal population mortality of the UK was obtained from the Human Mortality Database for 2013[164] and is presented in Appendix 12. In order to reflect the patient population of the model, the gender-specific mortality rate is combined into a blended rate, using the proportion of males across the UNCOVER trials, 67.8%[21]).

5.4 *Measurement and valuation of health effects*

Health effects in the current analysis are expressed in QALYs, in accordance with NICE's reference case, which combine quality of life and life expectancy into a single index. Life expectancy is assumed not to differ across therapies, therefore the key driver behind the valuation of health effects is the HRQoL measure used.

5.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D health status questionnaire is a standardized instrument self-completed by patients to assess their general health states [165] and is not specific to a disease condition. The questionnaire is made up from two components, a health state description and a single index evaluation, which consists of a visual analogue scale ranging from a score of 0-100. The health state description component comprises five dimensions of health status: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression.

Hitherto, the EQ-5D-3L had been the sole preferred measure of health-related quality of life in adults, with each dimension rated under three levels of severity (no problems, some problems, or extreme problems/unable to undertake any tasks in the dimension). The EQ-5D-5L is a recent development in which each of these dimensions is rated under five levels of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems/unable to undertake any tasks in the dimension). Both the 3L and 5L questionnaires are consistent with NICE's reference case: the valuation of HRQoL measured in patients is based on a valuation of public preferences from a representative sample of the UK (3L) or English (5L) population using choice-based methods: time trade-off (TTO) for the 3L and a hybrid of TTO and discrete choice experiments (DCE) for the 5L. These are used to derive utility weights associated with each possible health state.

The EQ-5D-5L questionnaire was administered to patients in the UNCOVER-1, 2 and 3 trials for ixekizumab at baseline and at week 12.[21-23] For implementation in the de novo model, the change in EQ-5D-5L derived utility weights from baseline to week 12 was calculated for each patient, pooled across treatment arms and then stratified by PASI response criteria achieved from treatment.

In the base case, the patient group of interest in the main analysis of variance (ANOVA) model approach were those with DLQI>10, who comprised 2,085 of a total of 3,731 patients for whom EQ-5D-5L data were available. The criterion aligns the estimates of HRQoL with the definition of moderate to severe psoriasis as described in NICE Clinical Guidelines 153 (CG153).[8]

For all patients who dropped out before the end of the induction period, EQ-5D-5L value, if collected at the visit prior to drop-out, was used as an estimate for the week 12 value using the last-observation carried forward (LOCF) approach. This approach also ensured that all available EQ-5D-5L values were used.

The extent to which PASI response category affected change from baseline EQ-5D-5L utility in the UNCOVER trial programme was estimated using a least squares regression model. Change in EQ-5D-5L from baseline to 12 weeks was modelled as a function of PASI response at week 12 and baseline EQ-5D-5L, as per Equation 2.

Equation 2 - EQ-5D-5L regression model, adjusted for baseline EQ-5D-5L

$$\text{Change from baseline EQ} - 5\text{D} - 5\text{L} = \alpha + \beta_1 \times (\text{PASI} - \text{response at week 12}) + \beta_2 \times (\text{baseline EQ} - 5\text{D} - 5\text{L}) + \varepsilon$$

Adjusting the model for baseline EQ-5D-5L utility improved the model fit (explained variance=0.512) relative to an unadjusted model (explained variance=0.052). The higher explained variance of the baseline EQ-5D-5L utility-adjusted model can be explained by two reasons.

First, patients with a response category of PASI 100 at week 12 started with a slightly higher mean baseline EQ-5D-5L score than patients with a lower PASI response category. Adjusting the analyses for baseline EQ-5D-5L utility therefore increased the mean utilities in higher PASI response categories and decreased them in lower PASI response categories. Second, baseline EQ-5D-5L is a highly significant factor in the adjusted model ($p<0.0001$), i.e. the change in EQ-5D-5L depends on where the patient started from. This is mainly due to the ceiling effect associated with the EQ-5D-5L utility upper bound of one.

Parameter estimates for the intercept and PASI response categories in the DLQI>10 patient group are presented in Table 70. PASI 100 was the reference category therefore the coefficients for the intercept and baseline EQ-5D-5L, α and β_2, correspond to the improvement from baseline EQ-5D-5L associated with complete psoriasis clearance. The coefficients β_1 represents the decrement in EQ-5D-5L for achieving a response level that is less than complete clearance. 'No response' is associated with the largest decrement and PASI 90-99 is associated with the smallest non-zero decrement.

Table 70: Parameter coefficients from ANOVA model, ITT population with baseline DLQI>10 (main analysis approach)

ANOVA model	Coefficient, DLQI>10
Intercept	0.6465086155
No Response	-0.1408543935
PASI 50-74	-0.0529486119
PASI 75-89	-0.0224581658
PASI 90-99	-0.0086372007
PASI 100	0 (reference)
Baseline EQ-5D-5L	-0.6490599844

ANOVA = analysis of variance; DLQI = Dermatology Life Quality Index; ITT = intent-to-treat; PASI = Psoriasis Area and Severity Index

An EQ-5D-5L bolt-on questionnaire was administered in UNCOVER-3 to capture aspects of HRQoL that are specific to psoriasis. The EQ-PSO incorporates "skin irritation" and "self-confidence" as dimensions additional to the EQ-5D-5L to capture condition-specific impacts on HRQoL to which the generic measure may be insensitive. Two additional levels in the EQ-PSO, "Ambiguous" and "Missing", were treated as missing in the derivation of the bolt-on index value. The associated patient-level index scoring algorithm for the EQ-5D-PSO index

score was elicited through interviews with a sample of the UK general public and valued using the TTO method.[166]

5.4.2 Mapping

No mapping was required to assess health state utility values, as directly elicited EQ-5D-5L data were collected in the UNCOVER trial programme, which is consistent with the NICE reference case.

5.4.3 Health-related quality-of-life studies

A SLR was conducted in February 2016, with the aim to identify relevant HRQoL studies that report patient utilities as well as cost and resource use data for patients with moderate to severe plaque psoriasis in the UK. The time frame of publications was restricted to the past ten years, i.e. from year 2006 onwards. Only publications in English were considered.

Both published studies and conference abstracts were identified from the following databases: MEDLINE (via PubMed), MEDLINE-IN-PROCESS (via PubMed), EMBASE (via Ovid), the Cochrane Library (via Cochrane), EconLit (via Ovid), and the NHS Economic Evaluation Database (EED; via Cochrane). The search terms were developed using a combination of MeSH/EMTREE terms and free-text terms to capture different components of the PICOS (Population, Intervention, Comparator, Outcome and Study type) study question, including population, outcomes and study type (detailed in Table 71 below). The full search strategy is presented in Appendix 13.

Table 71: PICOS framework

Parameter	Inclusion criteria	Exclusion criteria
Population	Adult patients with moderate to severe plaque psoriasis	Non-adult, non-human, non-moderate to severe plaque psoriasis
Intervention and comparators	Interventions of interest include biological therapies recommended by NICE: Adalimumab Etanercept Secukinumab Ustekinumab Infliximab	Interventions not of interest: Phototherapy alone Non-biological therapies alone (acitretin, ciclosporin, methotrexate) Topical treatments Online management, writing exercises, counselling, etc.
Outcomes	Patients utility scores and quality-of-life data Costs and resource use Any relevant economic evidence	Not outcome of interest
Study type	Health economic evaluations Observational studies Retrospective chart reviews Clinical trials Population-based studies	Not study type of interest

Publication time frame	Last 10 years (2006-present)	Studies published prior to 2006
Additional restriction	Country of focus for observational, and economic evaluation studies is UK	Countries other than the UK

NICE = National Institute for Health and Care Excellence; PICOS = patient, intervention, comparator, outcome, study type; UK = United Kingdom

In addition to the database searches, manual searches were undertaken to identify relevant conference abstracts and posters presented in the past three years at key scientific conferences. Clinical trial and health technology assessment (HTA) websites reporting information on treatments for patients with moderate to severe psoriasis were also searched. The list of sources considered for the hand searches was as follows:

- Conferences:
    - European Academy of Dermatology & Venereology Congress
    - International Conference on Psoriasis
    - Congress of the Psoriasis International Network
    - World Psoriasis & Psoriatic Arthritis Conference
    - International Society For Pharmacoeconomics and Outcomes Research
    - International Health Economics Association
    - International Society for Quality of Life Research
    - American Academy of Dermatology
- Clinical trials:
    - ClinicalTrials.gov
    - Cochrane CENTRAL
    - EU Clinical Trials Register
    - WHO ICTRP
- HTAs:
    - International Network of Agencies for Health Technology Assessment
    - NICE, SMC, AWMSG

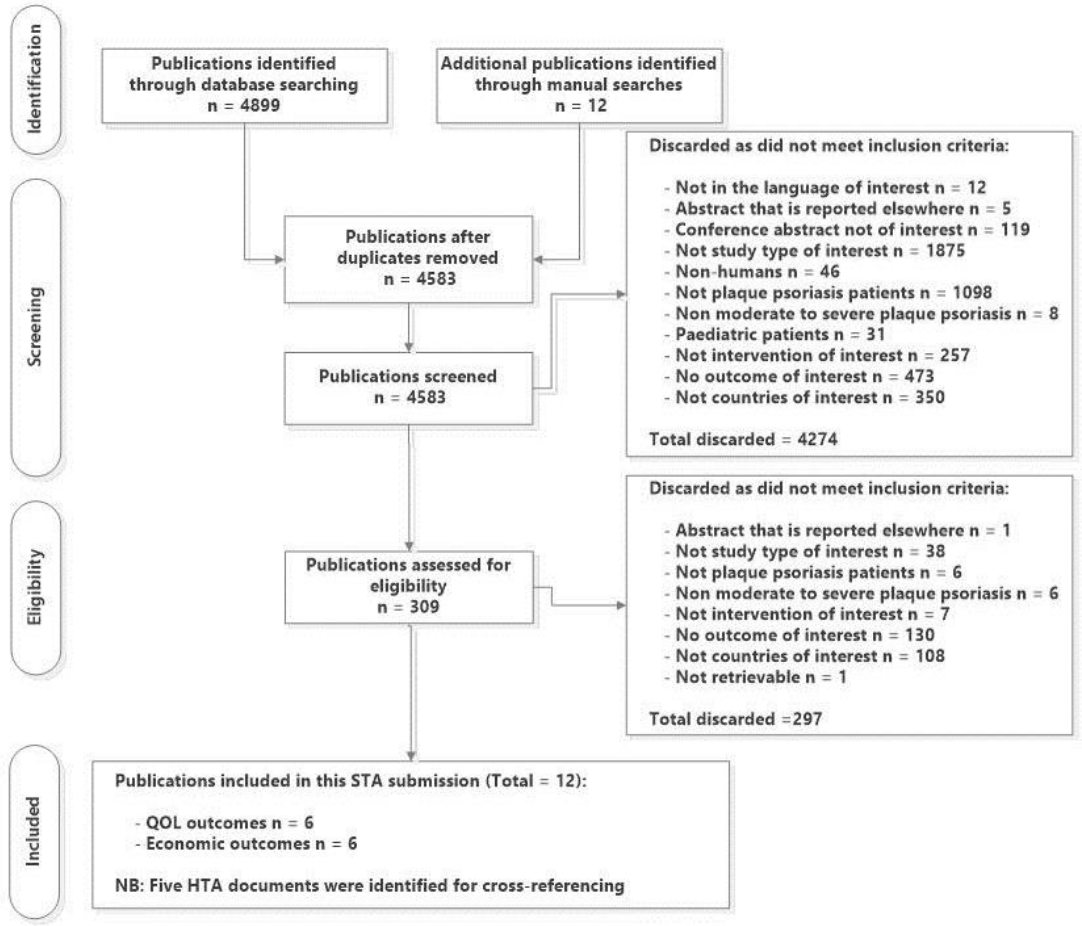
Only studies for which results were available were included based on the same eligibility criteria applied in the database search (see Table 71 and Appendix 13).

During the study selection process, titles and, where available, abstracts of studies retrieved by the search were reviewed by two independent reviewers according to the pre-specified inclusion/exclusion criteria in Table 71. Articles identified as potentially relevant during the first phase of the screening were then reviewed in full and assessed for inclusion according

to the list of pre-specified inclusion/exclusion criteria. Records for which no information was reported in the title or abstract, or abstracts that were not available were excluded if no further information could be retrieved based on the citation. Any discrepancy was resolved through discussion and/or involvement of a third reviewer.

A total of 4,899 citations were captured from the electronic searches and 12 additional publications were identified through hand searches. After removal of duplicates, 4,583 citations remained, and the screening of these titles and abstracts led to the review of 309 publications to assess their eligibility for inclusion. Upon full-text review, 6 HRQoL studies were chosen to be extracted and included in this STA submission as these studies contained EQ-5D data at comparable assessment time points, relevant resource, and cost information. The reasons for excluding 11 other studies which also contained EQ-5D data were due to limited information in the abstracts or incomparable assessment time points (see Appendix 13). The process of study selection and final results of the searches are shown in the PRISMA flow diagram in Figure 39.

Figure 39: PRISMA diagram for combined resource use /HRQoL SLR



HTA = health technology assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QOL = quality of life; SLR = systematic literature review; STA = single technology appraisal

Following full text review, six studies with HRQoL outcomes based on EQ-5D questionnaires were included in this STA submission. These studies are listed in chronological order [167-172], with EQ-5D or EQ-VAS data reported at week 12, 16, and or 24. A summary of each study is provided in the tables below.

Table 72: Shikiar *et al*. 2007

Reference	**Shikiar *et al*. 2007[167]**
Population	Patients with moderate to severe psoriasis and an affected body surface area (BSA) of > 5% for at least 1 year.
Information on recruitment	Patients included in this study were enrolled at 18 sites in the United States and Canada
Intervention and comparators	• Adalimumab 80 mg at week 0, followed by 40 mg every other week (eow) beginning at week 1 (eow group) • Adalimumab 80 mg at week 0 and week 1, followed by 40 mg once weekly beginning at week 2 (weekly group) • Placebo weekly beginning at week 0 (placebo group)
Sample size	147 patients
Response rate	Blinded data were available for 147 patients at baseline and 140 patients at week 12.
Description of health states	Not reported
Adverse events	Not reported
Method of elicitation	Questionnaires
Method of valuation	EQ-5D, EQ-VAS, DLQI, SF-36 (Physical Component Summary [PCS] and Mental Component Summary [MCS])
Mapping	Not reported
Results (mean; uncertainty values)	<u>Mean change from baseline scores at 12 weeks</u> EQ-5D index score • Placebo = 0.01 (95% CI -0.07, 0.10) • Adalimumab 80mg eow = 0.21 (95% CI 0.11, 0.31) • Adalimumab 80mg weekly = 0.19 (95% CI 0.09, 0.28) EQ-VAS • Placebo = 0.5 (95% CI -5.7, 6.8) • Adalimumab 80mg eow = 17.9 (95% CI 10.5, 25.2) • Adalimumab 80mg weekly = 10.7 (95% CI 4.1, 17.4) DLQI • Placebo = -1.3 (95% CI -3.3, 0.7) • Adalimumab 80mg eow = -10.8 (95% CI -13.1, -8.5) • Adalimumab 80mg weekly = 11.5 (95% CI -13.6, -9.4) SF-36 PCS • Placebo = 0.5 (95% CI -2.4, 3.5) • Adalimumab 80mg eow = 3.6 (95% CI 0.2, 7.0) • Adalimumab 80mg weekly = 5.5 (95% CI 2.1, 8.6) SF-36 MCS • Placebo = -0.1 (95% CI -3.5, 3.3) • Adalimumab 80mg eow = 7.8 (95% CI 3.9, 11.8) • Adalimumab 80mg weekly = 5.2 (95% CI 1.6, 8.9)
Consistency with reference case	Mean change from baseline in EQ-5D data at week 12 from the UNCOVER trial ranged between 0.01 and 0.15. Adalimumab-treated patients from this study reported higher mean change values compared to those in the UNCOVER trial.

Reference	Shikiar *et al*. 2007[167]
Appropriate for CEA	Not suitable as patient population is American and Canadian

BSA = body surface area; CEA = cost-effectiveness analysis; CI = confidence interval; DLQI = Dermatology Life Quality Index; eow = every other week; EQ-5D = European Quality of Life – 5 Dimensions; EQ-VAS = European Quality of Life Visual Analogue Scale; MCS = mental component summary; PCS = physical component summary; SF-36 = Short Form (36) Health Survey

Table 73: Revicki *et al*. 2008

Reference	Revicki *et al*. 2008[168]
Population	Adult patients (≥ 18 years old) with moderate to severe chronic plaque psoriasis (defined by ≥ 10% body surface area involvement and PASI score of ≥ 10 at baseline). Inclusion criteria are clinical diagnosis of psoriasis for ≥ 1 year and stable plaque psoriasis for ≥ 2 months before screening and at baseline visits, as determined by medical history interviews. All patients were naïve to TNF-antagonist therapies and to MTX.
Information on recruitment	Patients included in this study were enrolled at 23 centres in eight European countries and at 5 centres in Canada.
Intervention and comparators	Adalimumab 80 mg Methotrexate 7.5–25 mg capsule(s) Placebo
Sample size	271 patients
Response rate	A total of 264 of the 271 randomized patients completed the EQ-5D, EQ-VAS, and DLQI (97.4%) at baseline, with at least one follow-up assessment (103 receiving adalimumab, 108 receiving methotrexate and 53 receiving placebo).
Description of health states	The health states were categorized according to percentage improvement in PASI scores compared with baseline: PASI ≥ 75% PASI 50% to 75% PASI 25% to 50% PASI < 25%
Adverse events	Not reported
Method of elicitation	Questionnaires
Method of valuation	EQ-5D, EQ-VAS, DLQI, Psoriasis-Related Pruritus Assessment (PRPA), Visual analogue scale for plaque psoriasis (VASp), Patient's Global Assessment of disease severity (PatGA)
Mapping	Not reported
Results (mean; uncertainty values)	Mean change from baseline at week 12 EQ-5D Adalimumab = 0.1 (95% CI 0.0, 0.2) Methotrexate = 0.1 (95% CI 0.1, 0.2) Placebo = 0.2 (95% CI 0.1, 0.2) EQ-VAS Adalimumab = 5.9 (95% CI -1.4, 13.2) Methotrexate = 10.2 (95% CI 5.3, 15.2) Placebo = 20.4 (95% CI 15.3, 25.4) DLQI Adalimumab = -3.4 (95% CI -5.2,-1.6) Methotrexate = -4.9 (95% CI -5.9, -3.8) Placebo = -9.1 (95% CI -10.4, -7.8)

Reference	Revicki *et al*. 2008[168]
	Mean change from baseline at week 16 EQ-5D Adalimumab = 0.1 (95% CI 0.0, 0.2) Methotrexate = 0.1 (95% CI 0.1, 0.2) Placebo = 0.2 (95% CI 0.2, 0.3) EQ-VAS Adalimumab = 5.7 (95% CI -1.4, 12.8) Methotrexate = 11.5 (95% CI 6.5, 16.5) Placebo = 21.4 (95% CI 16.6, 26.3) DLQI Adalimumab = -3.4 (95% CI -5.2, -1.6) Methotrexate = -5.7 (95% CI -6.8, -4.5) Placebo = -9.1 (95% CI -10.4, -7.8) Mean changes in DLQI score stratified by PASI response at week 16 PASI ≥ 75 = -9.5 (SD 5.8) PASI 50 to 75 = -5.8 (SD 4.5) PASI 25 to 50 = 4.2 (SD 4.6) PASI < 25 = -0.7 (SD 4.7)
Consistency with reference case	Mean change from baseline in EQ-5D data at week 12 from the UNCOVER trial ranged between 0.01 and 0.15. Adalimumab and methotrexate-treated patients in this trial reported comparable data to those of the UNCOVER trial.
Appropriate for CEA	Not suitable as EQ-5D data not stratified by PASI health states.

CEA = cost-effectiveness analysis; CI = confidence interval; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life – 5 Dimensions; EQ-VAS = European Quality of Life Visual Analogue Scale; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PatGA = Patient's Global Assessment of disease severity; PRPA = Psoriasis-Related Pruritus Assessment ; SD = standard deviation; TNF = tumour necrosis factor; VASp = Visual analogue scale for plaque psoriasis

Table 74: Reich *et al*. 2009

Reference	Reich *et al*. 2009[169]
Population	Adult patients with moderate to severe plaque psoriasis, involving ≥ 10% of BSA and a minimum PASI score of 10 at screening. These patients would also have failed to respond to, had a contraindication for, or were intolerant of at least one systemic treatment or phototherapy at an adequate dose of sufficient duration.
Information on recruitment	Not reported
Intervention and comparators	Etanercept 50 mg once weekly for 24 weeks Placebo once weekly for 12 weeks After 12 weeks, placebo-treated patients switched to etanercept 50 mg once weekly for further 12 weeks
Sample size	142 patients
Response rate	126 (89%) patients completed 12 weeks of double-blind treatment, and all 126 patients entered the open-label phase; 122 (97%) of the latter group completed 24 weeks.
Description of health states	PASI and DLQI scores were measured at baseline, week 12, and week 24. DLQI score range and its effect on patient's life are categorised as follow based on Hongbo *et al*. 2005 [173]: 21-30 = Extremely large 11-20 = Very large

Reference	Reich *et al*. 2009[169]
	6-10 = Moderate 2-5 = Small 0-1 = None
Adverse events	Not reported
Method of elicitation	Questionnaires
Method of valuation	DLQI, EQ-5D, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
Mapping	Not reported
Results (mean; uncertainty values)	<u>Mean change from baseline at week 12</u> EQ-5D Etanercept = 0.12 (uncertainty not reported) Placebo = 0.02 (uncertainty not reported) EQ-VAS Etanercept = 6.8 (uncertainty not reported) Placebo = -4.9 (uncertainty not reported) DLQI Etanercept = -7.4 (SD 56.1) Placebo = -1.2 (SD 8.8) FACIT-F Etanercept = 1.3 (uncertainty not reported) Placebo = 0.3 (uncertainty not reported) <u>Mean change from baseline at week 24</u> EQ-5D Etanercept = 0.16 (uncertainty not reported) Placebo → Etanercept = 0.07 (uncertainty not reported) EQ-VAS Etanercept = 17 (uncertainty not reported) Placebo → Etanercept = 3.9 (uncertainty not reported) DLQI Etanercept = -9.6 (SD 72.7) Placebo → Etanercept = -7.1 (SD 52.6) FACIT-F Etanercept = 3.7 (uncertainty not reported) Placebo → Etanercept = 2.9 (uncertainty not reported)
Consistency with reference case	Mean change from baseline in EQ-5D data at week 12 from the UNCOVER trial ranged between 0.01 and 0.15. The EQ-5D data reported from etanercept-treated patients were consistent with those of the reference case.
Appropriate for CEA	Publication did not provide uncertainty values to the EQ-5D results reported and the data was not stratified by PASI response, thus there is insufficient detail to assess appropriateness of the data for CEA.

BSA = body surface area; CEA = cost-effectiveness analysis; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life – 5 Dimensions; EQ-VAS = European Quality of Life Visual Analogue Scale; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; PASI = Psoriasis Area and Severity Index; SD = standard deviation

Table 75: Pfizer 2010

Reference	Pfizer 2010[170]
Population	Adult patients (≥ 18 years old) with moderate to severe plaque psoriasis,

Reference	Pfizer 2010[170]
	covering at least 10% of total body surface area.
Information on recruitment	Patients were recruited at 122 locations internationally (Argentina, Austria, Belgium, Bosnia Herzegovina, Bulgaria, Chile, Colombia, Croatia, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Israel, Korea, Netherlands, Poland, Russia, Singapore, Slovakia, Spain, Sweden, Switzerland, Turkey, UK).
Intervention and comparators	Tofacitinib 5 mg per oral dosage, twice daily for 12 weeks Tofacitinib 10 mg per oral dosage, twice daily for 12 weeks Etanercept 50 mg SC, weekly for 12 weeks Placebo for 12 weeks
Sample size	1101 patients
Response rate	1020 patients completed the study
Description of health states	The health states were categorised according to PASI response and Physician's Global Assessment (PGA). PASI (at baseline week 2, 4, 8, and 12) PASI 50% PASI 75% PASI 90% Increase in baseline PASI ≥ 125% PGA (at baseline, week 2, 4, 8, and 12) “Clear” “Almost clear” Mild Moderate Severe
Adverse events	% of patients affected by serious adverse events Tofacitinib 5 mg = 2.13% Tofacitinib 10 mg = 1.52% Etanercept 50 mg = 2.09% Placebo = 1.87% % of patients affected by other (not including serious) adverse events Tofacitinib 5 mg = 31.31% Tofacitinib 10 mg = 36.67% Etanercept 50 mg = 32.54% Placebo = 31.78%
Method of elicitation	Questionnaires
Method of valuation	DLQI, SF-36, EQ-5D, EQ-VAS, Psoriasis Quality of Life 12 (PQOL-12)
Mapping	Not reported
Results (mean; uncertainty values)	<u>Mean change from baseline at week 4</u> DLQI Tofacitinib 5 mg = -5.28 (SE 0.35) Tofacitinib 10 mg = -7.43 (SE 0.36) Etanercept 50 mg = -5.80 (SE 0.33) Placebo = -1.64 (SE 0.55) <u>Mean change from baseline at week 12</u> EQ-5D Tofacitinib 5 mg = 0.14 (SE 0.011)

Reference	Pfizer 2010[170]
	Tofacitinib 10 mg = 0.21 (SE 0.011) Etanercept 50 mg = 0.19 (SE 0.011) Placebo = 0.03 (SE 0.021) EQ-VAS Tofacitinib 5 mg = 11.6 (SE 1.4) Tofacitinib 10 mg = 16.6 (SE 1.5) Etanercept 50 mg = 15.7 (SE 1.4) Placebo = 3.0 (SE 2.4) DLQI Tofacitinib 5 mg = -7.33 (SE 0.43) Tofacitinib 10 mg = -9.72 (SE 0.40) Etanercept 50 mg = -8.97 (SE 0.40) Placebo = -1.85 (SE 0.66) SF-36 PCS Tofacitinib 5 mg = 4.1 (SE 0.4) Tofacitinib 10 mg = 5.0 (SE 0.5) Etanercept 50 mg = 5.2 (SE 0.5) Placebo = 0.8 (SE 0.7) SF-36 MCS Tofacitinib 5 mg = 5.0 (SE 0.6) Tofacitinib 10 mg = 7.6 (SE 0.6) Etanercept 50 mg = 5.8 (SE 0.6) Placebo = 1.5 (SE 1.1) PQOL-12 Tofacitinib 5 mg = -35.2 (SE 1.9) Tofacitinib 10 mg = -47.9 (SE 1.8) Etanercept 50 mg = -44.3 (SE 1.8) Placebo = -9.6 (SE 2.6)
Consistency with reference case	Mean change from baseline in EQ-5D data at week 12 from the UNCOVER trial ranged between 0.01 and 0.15. Patients treated with Tofacitinib 5 mg reported EQ-5D scores within the range, whilst those treated with Tofacitinib 10 mg and Etanercept 50 mg showed slightly higher improvement in EQ-5D scores.
Appropriate for CEA	Not suitable as EQ-5D data not stratified by PASI health states.

CEA = cost-effectiveness analysis; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life – 5 Dimensions; EQ-VAS = European Quality of Life Visual Analogue Scale; IGA = Investigator's Global Assessment; MCS = mental component summary; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PGA = Physician's Global Assessment; PQOL-12 = Psoriasis Quality of Life 12; SE = standard error; SF-36 = Short Form (36) Health Survey; UK = United Kingdom

Table 76: Novartis 2011

Reference	Novartis 2011[171]
Population	Patients with moderate to severe chronic plaque-type psoriasis, defined as follow: PASI score of ≥ 12 Investigator's Global Assessment (IGA) score of ≥ 3 Total BSA affected of ≥ 10% Inadequate control by prior use of topical treatment, phototherapy and/or systemic therapy
Information on recruitment	Patients were recruited at 130 locations internationally (USA, Austria, Bulgaria, Canada, Czech Republic, France, Germany, India, Italy, Japan, Poland, Singapore, Slovakia, Switzerland, UK, Vietnam).
Intervention and	Secukinumab 150 mg

Reference	Novartis 2011[171]
comparators	Secukinumab 300 mg
Sample size	966 patients
Response rate	928 patients completed the study
Description of health states	The health states were categorised according to PASI responses and Investigator's Global Assessment modified version 2011 (IGA mod 2011). PASI at week 0, 2, 4, 6, 8, 12,16,20,24,28,32,36,40,44,48 and 52: PASI ≥ 50% PASI ≥ 75% PASI ≥ 90% PASI ≥ 100% IGA mod 2011 0 = clear 1 = almost clear 2 = mild 3 = moderate 4 = severe
Adverse events	% of patients affected by serious adverse events Secukinumab 150 mg = 5.91% Secukinumab 300 mg = 8.29% % of patients affected by other (not including serious) adverse events Secukinumab 150 mg = 66.01% Secukinumab 300 mg = 63.13%
Method of elicitation	Questionnaires
Method of valuation	EQ-5D, DLQI
Mapping	Not reported
Results (mean; uncertainty values)	Mean change from baseline at week 2 EQ-5D Secukinumab 150 mg = 5.9 (SD 14.64) Secukinumab 300 mg = 7.6 (SD 12.86) DLQI Secukinumab 150 mg = -5.5 (SD 5.02) Secukinumab 300 mg = -6 (SD 5.10) Mean change from baseline at week 4 EQ-5D Secukinumab 150 mg = 10.8 (SD 17.79) Secukinumab 300 mg = 13.6 (SD 18.63) DLQI Secukinumab 150 mg = -8.2 (SD 6.11) Secukinumab 300 mg = -8.7 (SD 6.29) Mean change from baseline at week 8 EQ-5D Secukinumab 150 mg = 17.5 (SD 20.79) Secukinumab 300 mg = 18.3 (SD 21.51) DLQI Secukinumab 150 mg = -10.2 (SD 6.40) Secukinumab 300 mg = -10.3 (SD 6.73) Mean change from baseline at week 12

Reference	Novartis 2011[171]
	EQ-5D Secukinumab 150 mg = 20.2 (SD 23.47) Secukinumab 300 mg = 21.2 (SD 24.08) DLQI Secukinumab 150 mg = -10.8 (SD 6.75) Secukinumab 300 mg = -11 (SD 7.01) Mean change from baseline at week 16 EQ-5D Secukinumab 150 mg = 21.4 (SD 25.11) Secukinumab 300 mg = 23 (SD 22.44) DLQI Secukinumab 150 mg = -11 (SD 6.63) Secukinumab 300 mg = -11.4 (SD 7.12) Mean change from baseline at week 20 EQ-5D Secukinumab 150 mg = 20.6 (SD 25.07) Secukinumab 300 mg = 23 (SD 23.27) DLQI Secukinumab 150 mg = -10.6 (SD 6.50) Secukinumab 300 mg = -11 (SD 7.18) Mean change from baseline at week 24 EQ-5D Secukinumab 150 mg = 20.6 (SD 25.05) Secukinumab 300 mg = 22.9 (SD 23.32) DLQI Secukinumab 150 mg = -10.5 (SD 6.67) Secukinumab 300 mg = -11.1 (SD 7.39) Mean change from baseline at week 28 EQ-5D Secukinumab 150 mg = 19.4 (SD 26.46) Secukinumab 300 mg = 23 (SD 22.71) DLQI Secukinumab 150 mg = -10.5 (SD 6.68) Secukinumab 300 mg = -11 (SD 7.22) Mean change from baseline at week 32 EQ-5D Secukinumab 150 mg = 20.4 (SD 24.95) Secukinumab 300 mg = 22.8 (SD 23.22) DLQI Secukinumab 150 mg = -10.5 (SD 6.76) Secukinumab 300 mg = -10.9 (SD 7.17) Mean change from baseline at week 36 EQ-5D Secukinumab 150 mg = 19.6 (SD 25.79) Secukinumab 300 mg = 23 (SD 22.67) DLQI Secukinumab 150 mg = -10.2 (SD 6.94) Secukinumab 300 mg = -10.9 (SD 7.30) Mean change from baseline at week 40 EQ-5D

Reference	Novartis 2011[171]
	Secukinumab 150 mg = 19.8 (SD 25.39) Secukinumab 300 mg = 22.8 (SD 22.69) DLQI Secukinumab 150 mg = -10.1 (SD 6.83) Secukinumab 300 mg = -10.8 (SD 7.33) <u>Mean change from baseline at week 44</u> EQ-5D Secukinumab 150 mg = 19.8 (SD 25.53) Secukinumab 300 mg = 22.3 (SD 23.10) DLQI Secukinumab 150 mg = -10.2 (SD 6.72) Secukinumab 300 mg = -10.8 (SD 7.46) <u>Mean change from baseline at week 48</u> EQ-5D Secukinumab 150 mg = 19.7 (SD 25.33) Secukinumab 300 mg = 22.7 (SD 22.85) DLQI Secukinumab 150 mg = -10 (SD 6.57) Secukinumab 300 mg = -10.8 (SD 7.38) <u>Mean change from baseline at week 52</u> EQ-5D Secukinumab 150 mg = 18.3 (SD 25.63) Secukinumab 300 mg = 23 (SD 22.40) DLQI Secukinumab 150 mg = -9.8 (SD 7.06) Secukinumab 300 mg = -10.9 (SD 7.31)
Consistency with reference case	Mean change from baseline in EQ-5D data at week 12 from the UNCOVER trial ranged between 0.01 and 0.15. Secukinumab-treated patients in this study reported 20 times higher improvement in EQ-5D scores compared to those in the UNCOVER trial.
Appropriate for CEA	Not suitable as EQ-5D data not stratified by PASI health states.

BSA = body surface area; CEA = cost-effectiveness analysis; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life – 5 Dimensions; EQ-VAS = European Quality of Life Visual Analogue Scale; IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index; SD = standard deviation; UK = United Kingdom; USA = United States of America

Table 77: Puig *et al*. 2015

Reference	Puig *et al*. 2015[172]
Population	Adult patients (≥ 18 years old) with moderate to severe psoriasis, defined as ≥10% of the total BSA involvement or PASI of ≥10
Information on recruitment	Patients were recruited at 38 locations internationally (Argentina, Austria, Belgium, Czech Republic, Germany, Greece, Hungary, Italy, Korea, Mexico, Spain, Taiwan, Thailand)
Intervention and comparators	Etanercept 50 mg twice weekly for 12 weeks, followed by Etanercept 50 mg once weekly for 12 weeks (BIW/QW) Etanercept 50 mg once weekly for 24 weeks (QW/QW)
Sample size	273 patients
Response rate	270 patients were included in the modified intent-to-treat (mITT) population (n = 137, QW/QW; n = 133, BIW/QW).
Description of health states	Patients were categorised into those with PsA and those without.

Reference	Puig *et al*. 2015[172]
Adverse events	% of patients affected by serious adverse events Etanercept 50 mg BIW/QW = 2.21% Etanercept 50 mg QW/QW = 2.92% % of patients affected by other (not including serious) adverse events Etanercept 50 mg BIW/QW = 71.32% Etanercept 50 mg QW/QW = 66.42%
Method of elicitation	Questionnaires
Method of valuation	DLQI, EQ-5D, Hospital Anxiety and Depression Scale (HADS), Medical Outcomes Study (MOS) Sleep Scale Scores, Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Questionnaire
Mapping	Not reported
Results (mean; uncertainty values)	Mean change from baseline at week 12 EQ-5D Etanercept 50 mg BIW/QW = 0.21 (SE 0.2) Etanercept 50 mg QW/QW = 0.17 (SE 0.2) For patients with PsA = 0.23 (uncertainty not reported) For patients with no PsA = 0.16 (uncertainty not reported) DLQI Etanercept 50 mg BIW/QW = -10.2 (SE 0.5) Etanercept 50 mg QW/QW = -10.5 (SE 0.5) HADS anxiety scores Etanercept 50 mg BIW/QW = -1.6 (SE 0.3) Etanercept 50 mg QW/QW = -1.6 (SE 0.3) HADS depression scores Etanercept 50 mg BIW/QW = -1.9 (SE 0.3) Etanercept 50 mg QW/QW = -1.3 (SE 0.3) Mean change from baseline at week 24 EQ-5D Etanercept 50 mg BIW/QW = 0.21 (SE 0.2) Etanercept 50 mg QW/QW = 0.15 (SE 0.2) For patients with PsA = 0.24 (uncertainty not reported) For patients with no PsA = 0.15 (uncertainty not reported) DLQI Etanercept 50 mg BIW/QW = -8.1 (SE 0.5) Etanercept 50 mg QW/QW = -9.2 (SE 0.5) HADS anxiety scores Etanercept 50 mg BIW/QW = -1.9 (SE 0.3) Etanercept 50 mg QW/QW = -1.8 (SE 0.3) HADS depression scores Etanercept 50 mg BIW/QW = -2.2 (SE 0.3) Etanercept 50 mg QW/QW = -1.9 (SE 0.3)
Consistency with reference case	Mean change from baseline in EQ-5D data at week 12 from the UNCOVER trial ranged between 0.01 and 0.15. Etanercept-treated patients in this study reported slightly higher improvement in EQ-5D scores compared to those in the UNCOVER trial.
Appropriate for CEA	Not suitable as EQ-5D data not stratified by PASI health states.

BSA = body surface area; BIW = twice weekly; CEA = cost-effectiveness analysis; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life – 5 Dimensions; FACIT-F = Functional Assessment of Chronic Illness Therapy –F; HADS = Hospital Anxiety and Depression Scale; mITT = modified intent-to-treat; MOS = Medical Outcomes Study; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; QW = once weekly; SE = standard error

All the extracted publications underwent a formal quality assessment using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, which is a checklist of items that should be included in reports of observational studies.[174] Quality assessments of the included studies in this submission are shown in Appendix 13.

EQ-5D utility values identified from the SLR are summarised in Table 78, together with the values reported in the present and previous STA submissions.[67-72] EQ-5D-5L scores were derived from the data collected across all the UNCOVER clinical trials and analysed to apply to the health states in the economic model. These utility values generally lie within the range of estimates identified from the SLR and in previous NICE technology appraisals.

However, it should be noted that the utility values obtained from the SLR were typically not stratified by PASI health states. Therefore, they are generally not comparable to those used in the cost-effectiveness model of ixekizumab.

Table 78: A summary of EQ-5D utility values identified from the SLR, previous technology appraisals, and the present submission

Reference source	Reference	Results
Mean change in utility values from baseline to week 12 by treatments		
SLR	Shikiar *et al*. 2007	Placebo = 0.01 (95% CI -0.07, 0.10) Adalimumab 80mg eow = 0.21 (95% CI 0.11, 0.31) Adalimumab 80mg weekly = 0.19 (95% CI 0.09, 0.28)
SLR	Revicki *et al*. 2008	Adalimumab = 0.1 (95% CI 0.0, 0.2) Methotrexate = 0.1 (95% CI 0.1, 0.2) Placebo = 0.2 (95% CI 0.1, 0.2)
SLR	Reich *et al*. 2009	Etanercept = 0.12 (uncertainty not reported) Placebo = 0.02 (uncertainty not reported)
SLR	Pfizer 2010	Tofacitinib 5 mg = 0.14 (SE 0.011) Tofacitinib 10 mg = 0.21 (SE 0.011) Etanercept 50 mg = 0.19 (SE 0.011) Placebo = 0.03 (SE 0.021)
SLR	Novartis 2011	Secukinumab 150 mg = 20.2 (SD 23.47) Secukinumab 300 mg = 21.2 (SD 24.08)
SLR	Puig *et al*. 2015	Etanercept 50 mg BIW/QW = 0.21 (SE 0.2) Etanercept 50 mg QW/QW = 0.17 (SE 0.2) Patients with PsA = 0.23 (uncertainty not reported) Patients with no PsA = 0.16 (uncertainty not reported)

Mean change in utility values from baseline to week 12 by health states						
		No PASI response	PASI 50-74	PASI 75-89	PASI ≥ 90	PASI 100
Previous STA	Secukinumab (TA350) (DLQI > 10)	0.109	0.193	0.226	0.264	NR

Previous STA	Ustekinumab (TA180) (DLQI > 10)	0.04	0.17	0.22	0.25	NR
Previous STA	Infliximab (TA134) (4th quartile DLQI)	0.12 (SE 0.03)	0.29 (SE 0.06)	0.38 (SE 0.08)	0.41 (SE 0.09)	NR
Previous STA	Adalimumab (TA146)	0.054 (SE 0.017)	0.14 (SE 0.016)	0.14 (SE 0.016)	0.219 (SE 0.021)	NR
Previous STA	Adalimumab (TA146) (DLQI ≤ 10)	0.045 (SE 0.024)	0.102 (SE 0.022)	0.102 (SE 0.022)	0.13 (SE 0.031)	NR
Previous STA	Adalimumab (TA146) (DLQI > 10)	0.063 (SE 0.025)	0.178 (SE 0.023)	0.178 (SE 0.023)	0.308 (SE 0.027)	NR
Previous STA	Etanercept and Efalizumab (TA103)	0.05 (SE 0.01)	0.17 (SE 0.04)	0.19 (SE 0.04)	0.21 (SE 0.05)	NR
Previous STA	Etanercept and Efalizumab (TA103) (4th quartile DLQI)	0.12 (SE 0.03)	0.29 (SE 0.06)	0.38 (SE 0.08)	0.41 (SE 0.09)	NR
Present STA	Ixekizumab (DLQI > 10)	0.0123 (SE 0.006)	0.100 (SE 0.010)	0.131 (SE 0.008)	(PASI 90-99) 0.144 (SE 0.007)	0.153 (SE 0.007)

CI = confidence interval; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life – 5 Dimensions; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; SD = standard deviation; SE = standard error; SLR = systematic literature review; STA = single technology appraisal; TA = technology appraisal

5.4.4 Adverse reactions

Costs for adverse events were included in three of eight peer-reviewed model publications identified in Section 5.1.2.[130,135,136] However, the costs of the modelled adverse events were very small in these studies. The probable lack of economic impact was the most frequently cited reason to exclude adverse events in the remaining peer-reviewed model publications.[129,133,137] For the HTA publications, the two submissions predating the York model included AEs.[139] However, neither the York model, nor four of the following model publications included costs of AEs, mainly citing lack of data, comparability of AE rates among biologics, and probable low economic impact as the main reasons.[69,70,139,141] Costs for adverse events were however included in the secukinumab submission.[145]

HRQoL impact associated with adverse events (AEs) is not explicitly modelled in the current analysis. The serious AEs of interest requiring hospitalisation in the model are aligned with those included in the secukinumab submission[145] and encompass non-melanoma skin cancer, malignancies other than NMSC and severe infections. Each of these AEs is likely to be associated with significant HRQoL impacts that may exceed the duration of treatment with any given biologic; therefore, given the delayed onset of malignancies, there would be

uncertainty in identifying which element of the treatment sequence may have been associated with the AE. For these reasons, the HRQoL impact is not explicitly modelled.

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

Psoriasis is a chronic skin disorder generally characterised by patches of abnormal skin, typically red, itchy, and scaly. Plaque psoriasis, also known as plaque vulgaris, is the most common form of the disease. It accounts for over 80% of the cases.[175] Symptoms of the disease are dry, red skin lesions with overlaying white scale.

Disease severity is typically measured by PASI to reflect on the health states of the patients. This scoring system divides the body into four areas: (1) head and neck (10% skin coverage), (2) arms (20%), (3) trunk (30%), and legs (40%). The scores of each area are illustrated in Table 79 below. The final resulting index ranges from 0 (no disease) to 72 (maximal disease).

Table 79: PASI

	% Coverage	Severity of redness	Severity of thickness	Severity of scaling
Head & Neck	0-100%	0-4	0-4	0-4
Arms	0-100%	0-4	0-4	0-4
Trunk	0-100%	0-4	0-4	0-4
Legs	0-100%	0-4	0-4	0-4

NB: Severity parameters are measured on a scale of 0-4, from none to maximum
PASI = Psoriasis Area and Severity Index

It has been well-documented that psoriasis has significant psychological impacts on the patients, particularly in the aspects of body image and self-esteem which in turn contribute to emotional distress.[176-178] The impact of psychological burden was evident in patients with mild severity of psoriasis to depression in severe cases.[179] Studies have shown that the prevalence of depression in patients with psoriasis ranges from 10% to 58%.[180,181]

It has also been reported that psoriasis has a direct impact on disability, affecting the patients' work productivity and employment. Due to physical discomfort and pain, daily activities and physical function of the patients are often restricted.[182,183] Further evidence supporting this can be observed in studies which indicated significant improvement in disability and quality of life of patients following treatments for psoriasis.[184-186]

EQ-5D-5L data were collected alongside efficacy measurements in all the UNCOVER trials (UNCOVER-1, 2, and 3), thus they were considered the most robust source of utility data for the cost-effectiveness analysis. As discussed in Section 5.4.5, EQ-5D-5L data from the UNCOVER trials were within the range of those identified in the literature and are presented

in Table 80. These scores were pooled across all treatment arms in the trials. This included the placebo arm as BSC efficacy was informed by response rates for placebo obtained from the NMA.

Table 80: Summary of EQ-5D -5L utility values for patients with baseline DLQI>10 in the cost-effectiveness analysis (n = 2,085)

State	Utility value: mean	SE	Reference in submission (section and page number)	Justification
PASI <50 response	0.012	0.006	UNCOVER trials, Section 5.4.1	Trial-based directly elicited data, within the range of placebo arms identified in the SLR, in accordance with NICE Guide to the Methods of Technology Appraisal [149]
PASI 50-74	0.100	0.010	UNCOVER trials, Section 5.4.1	Trial-based directly elicited data, within the range of patients treated with other biologics in the submissions
PASI 75-89	0.131	0.008	UNCOVER trials, Section 5.4.1	Trial-based directly elicited data, within the range of patients treated with other biologics in the submissions
PASI 90-99	0.144	0.007	UNCOVER trials, Section 5.4.1	Trial-based directly elicited data, within the range of patients treated with other biologics in the submissions
PASI 100	0.153	0.007	UNCOVER trials, Section 5.4.1	Trial-based directly elicited data, within the range of patients treated with other biologics in the submissions

DLQI = Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life – 5 Dimensions, 5 levels; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; SE = standard error; SLR = systematic literature review

HRQoL is assumed to be constant over time in the analysis. Although EQ-5D-3L population norms for the UK general population are shown to decrease with age[187], survival is assumed to be equivalent across all treatments, therefore incorporating population norms in the model to inform baseline utility would not be expected to have an impact on the incremental results. In line with previous TAs and economic evaluations in psoriasis, HRQoL is expressed in terms of change from baseline EQ-5D-5L associated with PASI response and is modelled as invariant to the time that has elapsed since initiating a sequence.

HRQoL inputs in the model are linked only to PASI response rather than stratified by treatment (Table 80). The total change from baseline utility is dependent on treatment only to the extent that PASI response rates are specific to each treatment. No other health effects are explicitly modelled.

Utility values identified from the SLR were not included in the base case analysis, because data from those studies were not stratified by PASI responses, were based on non-UK populations, or were reported without uncertainty estimates.

As described in Section 5.4.1, EQ-PSO (EQ-5D 5L with 2 additional bolt-on dimensions for psoriasis) data were collected in UNCOVER-3. The estimated changes in utility using the bolt-on measure are presented in Table 81. These were applied in a sensitivity analysis.

Table 81: EQ-PSO utility scores of the UNCOVER-3 trial, ITT population with DLQI>10 (n=663)

Health state	Mean change at week 12 from baseline EQ-PSO
No PASI response	0.021
PASI 50-74	0.117
PASI 75-89	0.141
PASI 90-99	0.148
PASI 100	0.198

DLQI = Dermatology Life Quality Index; EQ-PSO = European Quality of Life – Psoriasis bolt-on; ITT = intent-to-treat; PASI = Psoriasis Area and Severity Index

Assignment of utility values

Biologic treatment induction and maintenance

In the base case analysis, patients are assumed to accrue no health utility gains relative to baseline within the induction period. Utility gains are assigned only to responder patients on biologic therapy in the maintenance period. If a patient meets the minimum of a PASI 75 response and proceeds to the maintenance period, a simplifying assumption is made that they maintain that level of response until drop-out and accrue the health utility gain in each cycle while continuing to receive biologic therapy. The utility accrued while responding is calculated using the following equation:

Equation 3 Health utility assignment for responders – gain in maintenance period only

$$u_t = [u_{75} \times (p_{trt}^{PASI\ 75} - p_{trt}^{PASI\ 90}) + u_{90} \times (p_{trt}^{PASI\ 90} - p_{trt}^{PASI\ 100}) + u_{100} \times (p_t^{PASI\ 100})]$$

The rationale for excluding health utility gains within the induction period is that compared to the two alternatives to modelling health utility gain assignment, instantaneous assignment at the start of the induction period and linear gains throughout the induction period (Section 5.6.2), the exclusion of health utility gains in the induction period is associated with a more conservative HRQoL outcome for ixekizumab.

Post-biologic treatment

Patients who have discontinued from all three biologic treatment lines in the sequence progress to BSC. A 12 week period in which patients are assumed not to accrue any utilities is incorporated, similar to a biologic treatment induction period. This is to minimise imbalances in QALY accrual between a treatment sequence in which patients relapse and progress to BSC sooner and a treatment sequence in which patients remain on biologic treatment for longer and progress to BSC later.

At the end of the BSC 'induction period', all patients, including partial or non-responders, accrue utility gains according to PASI response associated with placebo. This calculation is presented in Equation 4:

Equation 4 - Health utility assignment in best supportive care

$$u_t = [u_{00} \times (1 - p_{bsc}^{PASI\ 50}) + u_{50} \times (p_{bsc}^{PASI\ 50} - p_{bsc}^{PASI\ 75}) + u_{75} \times (p_{bsc}^{PASI\ 75} - p_{bsc}^{PASI\ 90}) + u_{90} \times (p_{bsc}^{PASI\ 90} - p_{bsc}^{PASI\ 100}) + u_{100} \times (p_{bsc}^{PASI\ 100})]$$

On entering the death state, patients are assigned a utility value of zero.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

In line with recent NICE TAs of treatments in psoriasis, cost and healthcare resource use inputs considered in the base case analysis are as follows:

- Biologic treatment acquisition cost
- Biologic treatment administration
- Monitoring costs
- Best supportive care

Only direct medical costs are included in the model. Adverse event management costs are considered only in a sensitivity analysis.

Costs were sourced from the NHS Reference Costs 2014-15, Monthly Index of Medical Specialities (MIMS), Personal Social Services Research Unit (PSSRU) and published literature. The NHS Reference Costs were chosen as the preferred source over the Payment by Results (PbR) tariff as the former contains national average unit costs to the NHS of providing defined services to NHS patients in England[188] whereas the PbR tariff is reflective of the payment system within the NHS in which commissioners pay healthcare providers for each patient seen or treated.[189]

Where not available for 2015-16, costs are inflated to 2015 using the Special Aggregate: 06 Health component of the Consumer Price Index from the Office for National Statistics[190] presented in Appendix 14.

5.5.1 Resource identification, measurement and valuation studies

A SLR was conducted to identify publications with relevant information about costs and resource use for psoriasis patients within the UK. This search was conducted alongside the SLR for HRQoL under the same PICOS frame work (Table 71, and Appendix 13). The same eligibility criteria were applied for selection of studies (see Appendix 13).

A total of six publications reporting resource use and/or costs data were identified and were specific to the UK setting.[146,162,191-194] A summary of the resource data from each study is provided in the Table 82, whilst a summary of the cost data is shown in Table 83.

All the extracted publications in this section also underwent a formal quality assessment using the STROBE Statement.[174] Assessments of the included studies in this section are shown in Appendix 13.

Table 82: Summary of resource data identified from SLR

Reference	**Wood *et al*. 2008[193]**	**Eedy *et al*. 2009[162]**	**Fonia *et al*. 2010[146]**				**Iskandar *et al*. 2014[192]**		**Schaefer *et al*. 2015[191]**
Type of analysis	Multicentre prospective service review	Audit	Retrospective observational study				Prospective observational cohort (Abstract)		Observational (Abstract)
Study population	Patients with psoriasis recruited from 4 dermatology centres in the UK	Patients with psoriasis from 100 units in UK	Adult patients (≥ 18 years) with plaque psoriasis who had been initiated on biologic therapy				Patient with plaque psoriasis enrolled in the British Association of Dermatologists' Biologic Interventions Register		61 patients with plaque or erythrodermic psoriasis from 107 hospital stays across 9 UK hospitals
Country of study	UK	UK	UK				UK and Ireland		UK
Date of study	Apr 2004 - Jan 2005	Apr 2005 - Mar 2006	-				Sep 2007 - Oct 2013		-
Intervention	-	-	Biologics: adalimumab, infliximab, efalizumab, etanercept				Biologics Standard treatments		-
Patient age (mean)	-	-	47.3 years				Biologic treatment = 46 years Standard treatment = 44 years		45.5 years
Resource use data	*Across all enrolled patients*	*Across all units*	*Before biologic initiations*		*After biologic initiations*		*% of patients in biologics arm*	*% of patients in standard treatment arm*	*Across all enrolled patients*
			% patients	*Mean day (SE) on treatment*	*% patients*	*Mean day (SE) on treatment*			
Acitretin	-	-	24%	58 (13.9)	1%	7.6 (15.5)	0%	18%	-
Adalimumab	-	-	0%	0	8%	15.9 (7.5)	51%	0%	-
Ciclosporin	-	-	47%	119.5 (17.3)	22%	36.9 (10.8)	0%	23%	-
Efalizumab	-	-	0%	0	12%	18.5 (8.3)	-	-	-
Etanercept	-	-	0%	0	71%	229.3 (18.6)	27%	0%	-

Fumaric acid ester	-	-	25%	45.7 (10.8)	4%	2.9 (1.7)	0%	8%	-
Infliximab	-	-	0%	0	32%	82.2 (16.1)	5%	0%	-
Hydroxycarbamide	-	-	5%	15.1 (7.5)	0%	0	-	-	-
Methotrexate	-	-	41%	104.3 (17.2)	36%	100.2 (17.3)	0%	44%	-
Mycophenolate mofetil	-	-	4%	2.6 (1.8)	0%	0	-	-	-
Ustekinumab	-	-	-	-	-	-	17%	0%	-
Biologics	-	75%	-	-	-	-	-	-	-
Mean no. (SE) phototherapy session	-	-	-	2.76 (1.20)	-	0.26 (0.26)	-	-	-
Mean length of hospital stay	Across 4 centres = 19.7 days (range 1-78)	14 days (IQR 13-15)	-	6.49 (1.99)	-	1.55 (10.71)	-	-	17 days (SD 2.71 days)
No. of outpatients	-	Median = 264	-	Mean = 3.22 (0.11)	-	Mean = 3.25 (0.09)	-	-	NR
% patients in day care centre	-	17.3% (excluding phototherapy)	-	-	-	-	-	-	NR
Mean Work Productivity and Activity Impairment score	-	-	-	-	-	-	-	-	At admission = 68.7%
Applicability in England	Applicable	Applicable	Applicable		Applicable		Applicable		Applicable

IQR = interquartile range; SLR= systematic literature review; SD = standard deviation; SE = standard error; UK = United Kingdom

Table 83: Summary of cost data identified from SLR

Reference	**Fonia *et al*. 2010[146]**		**Agius *et al*. 2014[194]**	**Schaefer *et al*. 2015[191]**
Type of analysis	Retrospective observational study		Opportunistic evaluation of virtual review (Abstract)	Observational (Abstract)
Study population	Adult patients (≥ 18 years) with plaque psoriasis who had been initiated on biologic therapy		Psoriasis patients	Patients with plaque or erythrodermic psoriasis from 107 hospital stays across 9 hospitals
Country of study	UK		UK	UK
Date of study	-		2012	-
Intervention	Biologics: adalimumab, infliximab, efalizumab, etanercept		-	-
Patient age (mean)	47.3 years		50 years	45.5 years
Data source; currency; year	The NHS Reference Costs and the British National Formulary; £; 2008		NR; £; NR	Not reported
Cost data	*Mean cost per patient 12 months before biologic initiation £ (SE)*	*Mean cost per patient 12 months after biologic initiation £ (SE)*	*Mean cost cross the study group*	*Mean cost across all enrolled patients £ (SD)*
Adalimumab	-	405.3 (SE 190.6)	-	-
Infliximab	-	2633 (SE 535.40)	-	-
Efalizumab	-	464.8 (SE 209.5)	-	-
Etanercept	-	6920.1 (SE 619.9)	-	-
Total biologics	-	10423.3 (SE 370.4)	-	-
Acitretin	81.0 (SE 20.3)	10.1 (SE 7.7)	-	-
Ciclosporin	628.9 (SE 97.5)	212.5 (SE 67.7)	-	-
Fumaric acid ester	509.5 (SE 150.6)	43.8 (SE 25.7)	-	-
Hydroxycarbamide	3.6 (SE 1.8)	-	-	-
Methotrexate	15.15 (SE 3.4)	11.9 (SE 6.2)	-	-
Mycophenolate mofetil	10.8 (SE 7.2)	278.2 (SE 70.9)	-	-
Total systemic drugs	1249.4 (SE 179.5)	278.2 (SE 70.9)	-	-
Amoxicillin	0.05 (SE 0.05)	-	-	-

Augmentin	0.05 (SE 0.05)	0.1 (SE 0.10)	-	-
Ciprofloxacin	-	0.03 (SE 0.03)	-	-
Erythromycin	0.2 (SE 0.20)	-	-	-
Flucloxacillin	0.74 (SE 0.74)	4.63 (SE 2.96)	-	-
Hydrocortisone	-	0.28 (SE 0.28)	-	-
Prednisolone	0.15 (SE 0.12)	0.18 (SE .17)	-	-
Rifinah 300	-	0.28 (SE 0.28)	-	-
Total supportive drugs	1.14 (SE 0.77)	5.50 (SE 3.29)	-	-
Total drug cost per patient	1250.5 (SE 781.3)	10707.0 (SE 396.2)	-	-
Phototherapy	770.8 (SE 336.0)	74.5 (SE 74.5)	-	-
Inpatient admissions	1887.7 (SE 578.4)	451.8 (SE 206.3)	-	Hospital stay = 4875 (SD 3096)
A&E visits	2.26 (SE 2.26)	3.39 (SE 2.52)	-	-
Outpatient visits	232.1 (SE 8.0)	234.0 (SE 6.8)	-	-
Day ward admission	63.8 (SE 22.9)	510.6 (SE 98.1)	-	-
Total hospital cost	2956.7 (SE 758.8)	1274.3 (SE 240.2)	-	-
Travel	-	-	41.76 (range 2.5 – 325)	-
Applicability in England	Applicable	Applicable	Applicable	Applicable

A&E = accident and emergency ; NHS = National Health Service; NR = not reported; SLR= systematic literature review; SD = standard deviation; SE = standard error; UK = United Kingdom

5.5.2 Intervention and comparators' costs and resource use

Drug acquisition cost

Drug acquisition costs have been derived from the online version of MIMS. The drug unit costs are presented in Table 84. A confidential simple discount patient access scheme (PAS) has been agreed and approved by Patient Access Scheme Liaison Unit (PASLU)/Department of Health and this price for ixekizumab is used in the current analysis.

Secukinumab was recommended for use in patients with moderate to severe psoriasis by NICE under a PAS that applied a confidential simple price discount to the list price. The base case analysis uses the list price for secukinumab. Ustekinumab was approved for use in patients with plaque psoriasis by NICE under a PAS in which the higher dose of 90 mg needed for people who weigh more than 100 kg was provided at the same total cost as the lower dose of 45 mg for people who weigh 100 kg or less. The PAS for the ustekinumab 90 mg dose is included in the base case analysis. Infliximab has weight-based dosing; baseline weight of all patients in the UNCOVER trial programme were used to calculate a weighted average of 91.56 kg. [15]

A common evidence base was assumed in the NMA for biosimilar therapies and their branded counterparts, therefore the use of biosimilar therapy prices would result in a more conservative estimate of the cost-effectiveness of ixekizumab. Biosimilar infliximab was launched in the UK in February 2015[195] and biosimilar etanercept became available in the UK in February 2016.[175] In the base case analysis, biosimilar prices are used for both infliximab and etanercept.

Table 84: Drug acquisition costs

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (induction period)	Total annual cost (maintenance)	Source
Ixekizumab	1	80mg	[redacted]	[redacted]	[redacted]	[redacted]	PAS price
Adalimumab (Humira)	2	40 mg/0.8ml	£704.28	£352.14	£3,521.40	£9,155.64	MIMS, June 2016 [196]
Etanercept (Enbrel)	4	50 mg	£715.00	£178.75	£2,145.00	£9,295.00	MIMS, June 2016 [196]
Biosimilar etanercept (Benepali)	4	50 mg	£656.00	£164.00	£1,968.00	£8,528.00	MIMS, June 2016 [196]
Infliximab (Remicade)	1	100 mg	£419.62	£1,921.02*	£5,763.06*	£12,486.63*	MIMS, June 2016 [196]
Biosimilar infliximab (Remsima)	1	100 mg	£377.66	£1,728.93*	£5,186.78*	£11,238.03*	MIMS, June 2016 [196]
Secukinumab (Cosentyx)	2	150 mg	£1218.78	£1,218.78	£8,531.46	£15,844.14	MIMS, June 2016 [196]
Ustekinumab 45 mg (Stelara)	1	45 mg	£2,147.00	£2,147.00	£4,294.00	£9,303.67	MIMS, June 2016 [196]
Ustekinumab 90 mg (Stelara)	1	90 mg	£2,147.00	£2,147.00	£4,294.00	£9,303.67	MIMS, June 2016 [196]; NICE TA 180[69]

MIMS = Monthly Index of Medical Specialities; PAS = Patient Access Scheme

*Infliximab dose based on a baseline weight of 91.56 kg

Drug administration cost

All therapies of interest are administered as an SC injection with the exception of infliximab which is administered via intravenous (IV) infusion.

Patients who received SC injections incurred administration costs only for nurse training for self-administration in the induction period and no further administration costs in the maintenance period. Based on revisions by the ERG for the secukinumab submission, training for self-administration of SC injections is assumed to consist of three one-hour training sessions. Patients who received infliximab received an IV infusion cost three times in the induction period and an average of 6.5 times each year they remain on treatment.

The cost of administration was obtained from the PSSRU Unit Costs of Health and Social Care 2015 and the NHS Reference Costs 2014-15.[197,198]

Table 85: Drug administration cost

Administration method	Admin cost	Admin: induction period	Annual admin: maintenance	Total cost: induction period	Total annual cost	Source
SC self-injection: three 1-hour nurse training sessions	£36.00	3	0	£108.00	£0.00	PSSRU, Unit Costs of Health and Social Care 2015, Nurse (GP practice), wage cost per hour [197]
IV infusion, outpatient procedure	£97.08	3	6.5	£291.24	£631.02	NHS Reference Cost 2014-2015, Outpatient Procedure (Currency Code: WF01A, "Non-Admitted Face to Face Attendance, Follow-up". Dermatology).[198]

GP = general practitioner; IV = intravenous; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; SC = subcutaneous

Monitoring

Costs for monitoring during treatment have been obtained from the NHS Reference Costs[198] and all resource use estimates are taken from the NICE clinical guideline 153.[8]

Table 86: Costs for administration and monitoring of treatment

Resource	Price	Reference	Cost year
Physician visit (Specialist)(Consultant Led Outpatient Attendances)	£101.58	Physician (Specialist) - NHS Reference Cost 2014-2015, "Consultant Led Outpatient Attendances", service code 330 in Dermatology	2014-2015
Full blood count (FBC)	£3.01	NHS Reference Cost 2014-2015 (National schedule of reference costs: the main schedule), Currency Code: DAPS05 (Haematology)	2014-2015
Test for urea & electrolytes (U&E)	£1.19	NHS Reference Cost 2014-2015, Currency Code: DAPS04 (Clinical Biochemistry)	2014-2015
Liver function test (LFT)	£1.19	NHS Reference Cost 2014-2015, Currency Code: DAPS04 (Clinical Biochemistry)	2014-2015

FBC = full blood count; LFT = liver function test; NHS = National Health Service; U&E = urea and electrolytes test

Resource use is stratified by SC and IV administration and by induction and maintenance periods in the UK setting as per the costing template accompanying CG153.[8] The frequency of physician visits and monitoring tests for ixekizumab is assumed equivalent to resource use rates for other SC administered biologic treatments.

Table 87: Resource use for SC and IV administration of therapies in induction and maintenance

Treatment period	Physician visits	FBC	LFT	U&E
SC administration				
Induction	2	2	2	2
Maintenance (annual)	4	4	4	4
IV administration				
Induction	1	3	3	3
Maintenance (annual)	0	4	4	4

FBC = full blood count; IV = intravenous; LFT = liver function test; NHS = National Health Service; SC = subcutaneous; U&E = urea and electrolytes test

Best supportive care

The cost of BSC is based on Fonia *et al*. (2010)[146], which was identified in the literature review as the most recent full publication on cost and resource use in patients with moderate to severe psoriasis in the UK. Fonia *et al* (2010) was also recommended by the ERGs as a more plausible estimate of BSC resource use in the final appraisal determination for secukinumab and for apremilast.[144,145] In this retrospective UK cohort study, the authors describe the impact of biologic therapy introduction in moderate to severe psoriasis patients

on the use of medical resources and costs. Data on hospital resource use and drug usage were collected 12 months prior to and 6 months following the initiation of biologic treatment.

The annual cost of BSC is estimated from the sum of drug cost and the cost of inpatient admissions and outpatient care over the 12 months before treatment initiation to reflect costs for how moderate to severe patients are managed without biologic treatment. The mean cost of inpatient admissions and outpatient care captures inpatient admissions, Intensive Care Unit (ICU) admissions, High Dependency Unit admissions, accident and emergency (A&E) visits, outpatient visits, day ward admissions and phototherapy. Prices were inflated from 2008 prices in the publication to 2015 for use in the model. BSC costs are converted to a monthly cost and applied each cycle.

Table 88: Best supportive care cost estimates (Fonia *et al* 2010)[146]

Parameter	Cost	Cost applied per model cycle
Drug cost	£1,250.50	
Inpatient admissions and outpatient care	£2,956.70	
Total annual cost (2014-15)	£5,082.22	£423.52

Non-responder cost

A cost for non-responders is applied to the induction period following discontinuation from treatment, reflecting that patients typically have higher disease activity and therefore worse health after failure to respond to treatment. Based on the recommendations from the ERG in the final appraisal determination for apremilast, this cost is set at £225 per 28-day cycle[144] reflecting the cost incurred 12 months before a patient starts a biologic treatment (£2,956.70) minus outpatient visits (£232.10) reported by Fonia *et al*.[146], as a proxy of management without biologics.

In the current model, the mean cost of £2,724.60 is inflated to 2015 prices and converted into a monthly cost of £274.27, which is assigned per cycle when a patient fails treatment. This cost is only applied during the next subsequent induction periods in the sequence, and is not applied during the active therapy maintenance period, BSC 'induction' period and BSC post-'induction' period.

This cost is only applied to patients who have failed to respond to a prior biologic, i.e. patients who are biologic experienced at the start of the model or who have been treated with a biologic during the course of the model.

5.5.3 Health-state unit costs and resource use

Cost categories associated with each PASI response health state are presented in Table 89.

Table 89: List of health states and associated costs in the economic model

Health states	Item	Value	Reference
PASI<50 PASI 50-74 PASI 75-89 PASI 90-99 PASI 100	*Treatment costs*		
	Ixekizumab	[redacted]	PAS price
	Adalimumab	£352.14 per dose	MIMS, June 2016 [196]
	Biosimilar etanercept	£164.00 per 50 mg dose	MIMS, June 2016 [196]
	Biosimilar infliximab	£1,728.93 per dose	MIMS, June 2016 [196]
	Secukinumab	£1,218.78 per dose	MIMS, June 2016 [196]
	Ustekinumab 45 mg	£2,147.00	MIMS, June 2016 [196]
	Ustekinumab 90 mg	£2,147.00	MIMS, June 2016 [196]
	Administration costs		
	Nurse training for SC administration	£36.00 per hour of nurse time	PSSRU, Unit Costs of Health and Social Care 2015, Nurse (GP practice), wage cost per hour [197]
	IV infusion	£97.08 per administration	NHS Reference Cost 2014-2015, Outpatient Procedure (Currency Code: WF01A, "Non-Admitted Face to Face Attendance, Follow-up". Dermatology).[198]
	Monitoring costs		
	Physician visit costs	£101.58 per visit	Physician (Specialist) - NHS Reference Cost 2014-2015, "Consultant Led Outpatient Attendances", service code 330 in Dermatology
	FBC	£3.01 per test	NHS Reference Cost 2014-2015, Currency Code: DAPS05 (Haematology) [198]
	LFT	£1.19 per test	NHS Reference Cost 2014-2015, Currency Code: DAPS04 (Clinical Biochemistry)
	U&E	£1.19 per test	NHS Reference Cost 2014-2015, Currency Code: DAPS04 (Clinical Biochemistry)
	BSC costs		
	Drug costs, and inpatient and outpatient admissions	£5,082.22	Fonia *et al* (2010) [146]
PASI<50 PASI 50-74 (active therapy induction period only)	Non responders costs	£274.27 per cycle	Fonia *et al* (2010); NICE 2015 TA368 FAD [67,146]

BSC = best supportive care; FBC = full blood count; IV = intravenous; LFT = liver function test; NHS = National Health Service; PASI = Psoriasis Area and Severity Index; SC = subcutaneous; U&E = urea and electrolytes test

5.5.4 Adverse reaction unit costs and resource use

AE costs are not modelled in the base case analysis due to lack of information for event rates for certain biologics and due to the fact that the contribution of AEs to the overall cost

is relatively minor. AEs and their associated costs are included only in a scenario analysis and are described in further detail in Section 5.8.3.

5.5.5 Miscellaneous unit costs and resource use

No other healthcare resources were modelled in the analysis.

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 Summary of base-case de novo analysis inputs

The cost-effectiveness analysis presented has been carried out in line with the NICE reference case. The model takes an NHS/PSS perspective with a lifetime time horizon.

Health effects are measured in QALYs, which in turn are based on EQ-5D-5L responses collected in the trials informing the efficacy of ixekizumab. Costs and health effects are discounted at 3.5% p.a. Cost-effectiveness results are reported as incremental cost-utility ratios (ICUR) in a fully incremental analysis.

Table 90: Summary of variables applied in the economic model

	Variable	Value	SE	Lower 95% CI or CrI	Upper 95% CI or CrI	Reference to section in submission
Model settings	Discount rate (costs)	3.5%	N/A	N/A	N/A	Section 5.2.2
	Discount rate (benefits)	3.5%	N/A	N/A	N/A	Section 5.2.2
Patient characteristics	Age	45	N/A	N/A	N/A	Section 5.2.2
	Weight	91.56 kg	N/A	N/A	N/A	Section 4.5.4
	Male	67.8%	N/A	N/A	N/A	Section 5.3.3
Response rates: adalimumab	PASI 50	77.8%	N/A	68.9%	85.5%	Section 4.9.14
	PASI 75	57.5%	N/A	46.4%	68.2%	Section 4.9.14
	PASI 90	31.7%	N/A	22.3%	42.2%	Section 4.9.14
	PASI 100	10.0%	N/A	5.7%	15.6%	Section 4.9.14
Response rates: etanercept 50 mg QW	PASI 50	63.9%	N/A	52.8%	74.3%	Section 4.9.14
	PASI 75	41.3%	N/A	30.3%	52.8%	Section 4.9.14
	PASI 90	18.9%	N/A	11.8%	27.5%	Section 4.9.14
	PASI 100	4.6%	N/A	2.3%	7.9%	Section 4.9.14
Response rates: infliximab	PASI 50	92.8%	N/A	88.1%	96.1%	Section 4.9.14
	PASI 75	81.1%	N/A	72.6%	88.1%	Section 4.9.14
	PASI 90	58.7%	N/A	47.2%	69.4%	Section 4.9.14
	PASI 100	27.8%	N/A	18.7%	38.0%	Section 4.9.14
Response rates: ixekizumab Q2W	PASI 50	[redacted]	N/A	[redacted]	[redacted]	Section 4.9.14
	PASI 75	[redacted]	N/A	[redacted]	[redacted]	Section 4.9.14
	PASI 90	[redacted]	N/A	[redacted]	[redacted]	Section 4.9.14

	Variable	Value	SE	Lower 95% CI or CrI	Upper 95% CI or CrI	Reference to section in submission
	PASI 100	[redacted]	N/A	[redacted]	[redacted]	Section 4.9.14
Response rates: secukinumab	PASI 50	93.2%	N/A	89.5%	96.1%	Section 4.9.14
	PASI 75	81.8%	N/A	74.9%	88.1%	Section 4.9.14
	PASI 90	59.6%	N/A	50.0%	69.3%	Section 4.9.14
	PASI 100	28.6%	N/A	20.7%	37.9%	Section 4.9.14
Response rates: ustekinumab 45 mg	PASI 50	87.1%	N/A	81.4%	91.7%	Section 4.9.14
	PASI 75	71.0%	N/A	62.2%	78.8%	Section 4.9.14
	PASI 90	45.6%	N/A	36.0%	55.2%	Section 4.9.14
	PASI 100	17.9%	N/A	12.0%	24.7%	Section 4.9.14
Response rates: ustekinumab 90 mg	PASI 50	89.6%	N/A	84.2%	93.7%	Section 4.9.14
	PASI 75	75.1%	N/A	66.2%	82.7%	Section 4.9.14
	PASI 90	50.6%	N/A	40.1%	60.7%	Section 4.9.14
	PASI 100	21.4%	N/A	14.3%	29.5%	Section 4.9.14
BSC	PASI 50	13.7%	N/A	10.1%	17.9%	Section 4.9.14
	PASI 75	4.7%	N/A	3.1%	6.6%	Section 4.9.14
	PASI 90	1.0%	N/A	0.6%	1.5%	Section 4.9.14
	PASI 100	0.1%	N/A	0.0%	0.1%	Section 4.9.14
Change from baseline EQ-5D-5L (baseline-adjusted, DLQI>10)	PASI<50	0.012	0.006	N/A	N/A	Section 5.4.5
	PASI 50	0.100	0.010	N/A	N/A	Section 5.4.5
	PASI 75	0.131	0.008	N/A	N/A	Section 5.4.5
	PASI 90	0.144	0.007	N/A	N/A	Section 5.4.5
	PASI 100	0.153	0.007	N/A	N/A	Section 5.4.5
Drop-out rate		20%	NR	NR	NR	Section 5.2.4
Drug costs (list price)	Ixekizumab Q2W	[redacted]	N/A	N/A	N/A	Sections 2.3 and Section 5.5.2
	Adalimumab	£704.28	N/A	N/A	N/A	Section 5.5.2
	Biosimilar etanercept 50 mg	£656.00	N/A	N/A	N/A	Section 5.5.2
	Biosimilar infliximab	£377.66	N/A	N/A	N/A	Section 5.5.2
	Ustekinumab 45 mg	£2,147.00	N/A	N/A	N/A	Section 5.5.2
	Ustekinumab 90 mg	£2,147.00	N/A	N/A	N/A	Section 5.5.2
	Secukinumab	£1,218.78	N/A	N/A	N/A	Section 5.5.2
BSC cost		£5,082.22	779.74	N/A	N/A	Section 5.5.2
Monitoring costs	Cost of FBC	£3.01	NR	NR	NR	Section 5.5.2
	Cost of LFT	£1.19	NR	NR	NR	Section 5.5.2
	Cost of U&E	£1.19	NR	NR	NR	Section 5.5.2
	Cost of self-admin training	£36.00	NR	NR	NR	Section 5.5.2
	Cost of physician visit for IV	£97.08	NR	NR	NR	Section 5.5.2
	Cost of office visit	£101.58	NR	NR	NR	Section 5.5.2

	Variable	Value	SE	Lower 95% CI or CrI	Upper 95% CI or CrI	Reference to section in submission
Non-responder cost		£274.27 per cycle	NR	NR	NR	Section 5.5.2
Resource use: physician visits	IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, - Induction period	2	NR	NR	NR	Section 5.5.2
	IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, - maintenance (annually)	4	NR	NR	NR	Section 5.5.2
	INF – physician visits: induction period (10 weeks)	1	NR	NR	NR	Section 5.5.2
	INF – physician visits: maintenance (annually)	0	NR	NR	NR	Section 5.5.2
Drug administration	Number of self-admin training hours (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	3	NR	NR	NR	Section 5.5.2
	Number of IV infusions (INF) – induction period	3	NR	NR	NR	Section 5.5.2
	Number of IV infusions (INF) – maintenance	6.5	NR	NR	NR	Section 5.5.2
Monitoring frequency – induction period	Number of FBC (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	NR	NR	NR	Section 5.5.2
	Number of LFT (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	NR	NR	NR	Section 5.5.2
	Number of U&E (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	NR	NR	NR	Section 5.5.2
	Number of FBC (INF)	3	NR	NR	NR	Section 5.5.2
	Number of LFT (INF)	3	NR	NR	NR	Section 5.5.2
	Number of U&E (INF)	3	NR	NR	NR	Section 5.5.2
Monitoring frequency – maintenance	Number of FBC (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	NR	NR	NR	Section 5.5.2
	Number of LFT (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	NR	NR	NR	Section 5.5.2
	Number of U&E (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	NR	NR	NR	Section 5.5.2

ADA = adalimumab; BSC = best supportive care; CI = confidence interval; CrI = credible interval; DLQI = Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life – 5 Dimensions, 5 levels; ETN = etanercept; FBC = full blood count; INF = infliximab; IXE = ixekizumab; IV = intravenous; LFT = liver function test; N/A = not applicable; NR = not reported; PASI = Psoriasis Area and Severity Index; QW = once weekly; Q2W = every 2 weeks; SC = subcutaneous; SE = standard error; SEC = secukinumab; UST = ustekinumab

5.6.2 Assumptions

Utility gain

In the base case analysis, no utility gains are accrued in the induction period of any treatment. Instead, utility gains are experienced only when patients continue treatment into the maintenance period.

The model includes the functionality to incorporate two alternative methods of assigning induction period utilities: i) applying an instantaneous health utility gain and ii) applying health utility gain linearly each model cycle during the induction period, which acts as a bridge between the instantaneous gain approach and the 'no gain in induction' approach. As it is not possible to use different methods for assigning health utilities in treatment sequences, the choice in approach to assigning health utility gains is identical for all lines within a treatment sequence.

As ixekizumab is likely associated with a higher weighted average utility gain in the induction period due to the rapid onset of response in patients who achieve a PASI 75 threshold or more and higher proportion of patients achieving PASI 75 response or higher, the approach assuming no gain in the induction period provides is likely to be a more conservative estimate of the HRQoL gains associated with ixekizumab. This approach is therefore used in the base case and the instantaneous gain approach is applied in a sensitivity analysis.

Adverse events

As discussed in Sections 5.4.4 and 5.5.4, adverse event costs and HRQoL impact were not modelled in the base case analysis. The cost impact of adverse events is modelled in a scenario analysis and the adverse events align with those included in the secukinumab submission [68]: non-melanoma skin cancer, malignancies other than non-melanoma skin cancer and severe infections.

Maintenance of response

Patients are assumed to maintain the level of response they attained at the end of the induction period throughout the maintenance period.

Discontinuation

A constant annual discontinuation rate of 20% is applied on a cyclical basis to all patients on active therapy in the maintenance period to capture discontinuation due to any cause, such as loss of efficacy or adverse events. This is in line with all previous NICE TAs for biologic treatments in psoriasis[68-70,72,139] and is supported by data from BADBIR[14] with a 53% drug survival rate after three years for patients receiving adalimumab, etanercept, infliximab and ustekinumab. Similarly, Gniadecki 2015[163], a large Danish study on drug survival, notes that the discontinuation rate among biologically treated patients appears to happen at a constant rate over the treatment period.

No disease progression

As psoriasis is associated with an unpredictable natural history, no underlying disease progression has been assumed in the model. Infliximab is recommended for patients with very severe psoriasis defined as PASI≥20 and DLQI>18. In the model, infliximab is assumed to be a common third-line treatment across all intervention and comparator sequences. This assumption is made on the basis that a treatment with rapid onset of action may be preferred in the final line of active therapy rather than on the basis of disease severity progression.

5.7 *Base-case results*

5.7.1 Base-case incremental cost effectiveness analysis results

A summary of base case cost-effectiveness results is presented in Table 91 for patients who have not responded to prior systemic therapy. ICERs are presented for a fully incremental analysis and pairwise analyses for each comparator sequence versus the ixekizumab sequence.

Etanercept sequence 1C is the referent comparator sequence in the fully incremental analysis. Ixekizumab sequence 1A is the only comparator sequence on the cost-effectiveness frontier and is associated with an ICER of £33,858/QALY versus the referent comparator sequence. Ixekizumab sequence 1A dominates secukinumab sequence 1G and extendedly dominates all other treatment sequences.

When compared pairwise to each treatment sequence other than the referent, ixekizumab sequence 1A is associated with ICERs ranging from £4,300/QALY versus infliximab sequence 1D to £19,202/QALY versus adalimumab sequence 1B.

Table 91: Base-case results (Biologic-naïve patients with prior systemic failure, PASI >10 and DLQI ≥ 10)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
1C	ETN 50 mg weekly	UST 90 mg	INF	BSC	£144,635	1.27	Referent	Referent	Referent	£33,858
1F	UST45 mg	ADA	INF	BSC	£148,218	1.30	£3,582.91	0.04	Extendedly dominated	£18,278
1B	ADA	UST 90 mg	INF	BSC	£148,350	1.32	£3,714.86	0.05	Extendedly dominated	£19,202
1G	UST 90 mg	ADA	INF	BSC	£148,719	1.32	£4,083.20	0.06	Extendedly dominated	£16,763
1D	INF	UST 90 mg	ADA	BSC	£150,350	1.33	£5,714.25	0.06	Extendedly dominated	£4,300
1A	IXE	UST 90 mg	INF	BSC	£150,889	1.45	£6,253.65	0.18	£33,858	N/A
1E	SEC	UST 90 mg	INF	BSC	£177,101	1.42	£32,465.66	0.15	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; DLQI = Dermatology Life Quality Index; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

5.7.2 Clinical outcomes from the model

PASI rates reported in each of the UNCOVER trials and PASI rates used in the model are presented in Table 92. As stated in Section 5.3.2, PASI response rates from the NMA were applied in the model as transition probabilities for treatment continuation from induction to maintenance without any adjustments. The NMA utilised the direct evidence from the UNCOVER trial programme as well as indirect evidence from other biologic treatments, therefore the PASI response rates are not expected to align exactly with the observed response rates from the UNCOVER trials.

Table 92: Summary of clinical outcomes in model compared with clinical data

Outcome	UNCOVER-1	UNCOVER-2	UNCOVER-3	Model
Ixekizumab Q2W	*N=433*	*N=351*	*N=385*	
PASI 50	93.8%	94.9%	93.8%	[redacted]
PASI 75	89.1%	89.7%	87.3%	[redacted]
PASI 90	70.9%	70.7%	68.1%	[redacted]
PASI 100	35.3%	40.5%	37.7%	[redacted]
Etanercept	*N/A*	*N=358*	*N=382*	
PASI 50	N/A	62.8%	78.0%	63.9%
PASI 75	N/A	41.6%	53.4%	41.3%
PASI 90	N/A	18.7%	25.7%	18.9%
PASI 100	N/A	5.3%	7.3%	4.6%
BSC	*N=431*	*N=168*	*N=193*	
PASI 50	11.6%	6.5%	15.5%	13.7%
PASI 75	3.9%	2.4%	7.3%	4.7%
PASI 90	0.5%	0.6%	3.1%	1.0%
PASI 100	0.0%	0.6%	0.0%	0.1%

BSC = best supportive care; N/A = not applicable; PASI = Psoriasis Area and Severity Index; Q2W = every 2 weeks

Source: **UNCOVER-1:** PASI 50, PASI 75, PASI 90, PASI 100: CSR RHAZ, Table RHAZ 11.10; **UNCOVER-2:** PASI 50, PASI 75, PASI 90, PASI 100: CSR RHBA (36 Wk), Table RHBA 11.23; **UNCOVER-3:** PASI 50, PASI 75, PASI 90, PASI 100: CSR RHBC, Table RHBC 11.19

The proportion of the patient cohort in each health state and cumulative discounted QALY traces are provided in Appendix 15 for BSC as standalone psoriasis management, Sequences 1A-F.

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Disaggregated QALY gains and incremental costs are disaggregated by health state in Table 93 and Table 94. Costs are disaggregated by resource use category in Table 95.

Table 93: Summary of QALY gain by health state

Health state	QALY intervention (1A)	QALY comparator (1B-G)	Increment	Absolute increment	% absolute increment
	1A: IXE sequence	*1B: ADA sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.36	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.28	[redacted]	[redacted]	[redacted]
Total	**1.45**	**1.32**	**0.13**	**0.28**	**100%**
	1A: IXE sequence	*1C: ETN sequence*			
PASI<50	[redacted]	0.27	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.35	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.36	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.25	[redacted]	[redacted]	[redacted]
Total	**1.45**	**1.27**	**0.18**	**0.33**	**100%**
	1A: IXE sequence	*1D: INF sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.35	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.29	[redacted]	[redacted]	[redacted]
Total	**1.45**	**1.33**	**0.13**	**0.25**	**100%**
	1A: IXE sequence	*1E: SEC sequence*			
PASI<50	[redacted]	0.25	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.34	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.43	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.37	[redacted]	[redacted]	[redacted]
Total	**1.45**	**1.42**	**0.03**	**0.10**	**100%**
	1A: IXE sequence	*1F: UST45 mg sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.36	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.26	[redacted]	[redacted]	[redacted]
Total	**1.45**	**1.30**	**0.15**	**0.30**	**100%**

	1A: IXE sequence	*1G: UST90 mg sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.36	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.28	[redacted]	[redacted]	[redacted]
Total	**1.45**	**1.32**	**0.13**	**0.27**	**100%**

Table 94: Summary of costs by health state

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
	1A: IXE sequence	*1B: ADA sequence*			
PASI<50	[redacted]	£53,685	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,471	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£30,952	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£32,793	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£23,449	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£148,350**	**£2,539**	**£22,672**	**100.00%**
	1A: IXE sequence	*1C: ETN sequence*			
PASI<50	[redacted]	£55,976	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,492	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£29,442	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£30,026	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£21,700	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£144,635**	**£6,254**	**£27,991**	**100.00%**
	1A: IXE sequence	*1D: INF sequence*			
PASI<50	[redacted]	£53,697	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,494	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£30,602	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£33,539	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£25,018	[redacted]	[redacted]	[redacted]
Total	[redacted]	**£150,350**	**£539**	**£20,043**	**100.00%**
	1A: IXE sequence	*1E: SEC sequence*			
PASI<50	[redacted]	£50,588	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,342	[redacted]	[redacted]	[redacted]

PASI 75-90	[redacted]	£35,437	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£44,944	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£38,790	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£177,101**	**-£26,212**	**£26,212**	**100.00%**
	1A: IXE sequence	*1F: UST 45 mg sequence*			
PASI<50	[redacted]	£54,421	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,672	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£31,280	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£32,429	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£22,417	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£148,218**	**£2,671**	**£25,335**	**100.00%**
	1A: IXE sequence	*1G: UST 90 mg sequence*			
PASI<50	[redacted]	£53,770	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,531	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£30,761	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£32,903	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£23,754	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£148,719**	**£2,170**	**£22,213**	**100.00%**

ADA = adalimumab; ETN = etanercept; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; SEC = secukinumab; UST = ustekinumab.

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 95: Summary of predicted resource use by category of cost

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
	1A: IXE sequence	*1B: ADA sequence*			
Treatment costs	[redacted]	£82,185	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£1,958	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,377	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£187	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,373	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,270	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£148,350**	**£2,539**	**£11,648**	**100.00%**
	1A: IXE sequence	*1C: ETN sequence*			
Treatment costs	[redacted]	£75,935	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£2,015	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,169	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£178	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,411	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£62,928	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£144,635**	**£6,254**	**£20,867**	**100.00%**
	1A: IXE sequence	*1D: INF sequence*			
Treatment costs	[redacted]	£83,873	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£2,389	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,100	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£188	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,530	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,270	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£150,350**	**£539**	**£10,824**	**100.00%**
	1A: IXE sequence	*1E: SEC sequence*			
Treatment costs	[redacted]	£113,989	[redacted]	[redacted]	[redacted]
Administration	[redacted]	£1,888	[redacted]	[redacted]	[redacted]

costs					
Physician visit costs	[redacted]	£2,706	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£202	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,323	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£56,992	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£177,101**	**-£26,212**	**£26,423**	**100.00%**
	1A: IXE sequence	*1F: UST45 mg sequence*			
Treatment costs	[redacted]	£81,253	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£1,969	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,322	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£184	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,601	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,890	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£148,218**	**£2,671**	**£13,496**	**100.00%**
	1A: IXE sequence	*1G: UST90 mg sequence*			
Treatment costs	[redacted]	£82,338	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£1,956	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,378	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£187	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,590	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,270	[redacted]	[redacted]	[redacted]
Total	**£150,889**	**£148,719**	**£2,170**	**£11,709**	**100.00%**

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; SEC = secukinumab; UST = ustekinumab

5.8 *Sensitivity analyses*

5.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken with 1,000 model simulations. A full list of all parameters included in the probabilistic sensitivity analyses is presented in Table 96 below. Mean values and their standard error are also presented, and standard errors are calculated from confidence intervals, where available, and two times the standard normal deviate of 1.96, according to Equation 5, as described in the Cochrane Handbook.[199]

Equation 5 – Calculation of standard error from confidence interval

$$se = \frac{(upper\ limit - lower\ limit)}{3.92}$$

In the absence of data on the variability around the sampling distribution of mean values, the standard error is assumed to be equal to the mean value divided by 4.

Utilities are assumed to be normally distributed as many variables are reasonably described by this type of distribution. The normal distribution is bell-shaped as it is symmetrical around the mean; the size of the bell depends on the standard deviation, e.g. it is small and narrow for small standard deviations.

Annual discontinuation rate and adverse event rates are assumed to be beta distributed as values range between 0 and 1. Based off the mean ($\bar{x}$) and standard error (SE), each α and β is calculated based on the following set of equations (Equation 6):

Equation 6 – Calculation of alpha and beta for beta distributed parameters

$$\alpha = \bar{x} * \left(\frac{\bar{x} * (1 - \bar{x})}{se^2}\right) - 1$$

$$\beta = (1 - \bar{x}) * \left(\frac{\bar{x} * (1 - \bar{x})}{se^2}\right) - 1$$

A gamma distribution is assumed for all other parameters that can range between zero and infinity. Calculation of each α and β are based on Equation 7:

Equation 7 Calculation of alpha and beta for gamma distributed parameters

$$\alpha = \left(\frac{\bar{x}}{s}\right)^2$$

$$\beta = \frac{s^2}{\bar{x}}$$

Table 96: PSA inputs

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
Utilities	Utility gain PASI<50	0.012	0.006	Normal distribution	N/A
	Utility gain PASI 50-74	0.100	0.010	Normal distribution	N/A
	Utility gain PASI 75-89	0.131	0.008	Normal distribution	N/A
	Utility gain PASI 90-99	0.144	0.007	Normal distribution	N/A
	Utility gain PASI 100	0.153	0.007	Normal distribution	N/A
Discontinuation rate	Annual discontinuation rate	0.20	0.05	Beta	Assumption SE=mean/4
Resource use: physician visits	IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC - Induction period	2	0.5	Beta	Assumption SE=mean/4
	IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC - maintenance (annually)	4	1	Gamma	Assumption SE=mean/4
	INF – physician visits: induction period (10 weeks)	1	0.25	Gamma	Assumption SE=mean/4
	INF – physician visits: maintenance (annually)	0	0	Gamma	Assumption SE=mean/4
Monitoring frequency – induction period	Number of FBC (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	0.50	Gamma	Assumption SE=mean/4
	Number of LFT (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	0.50	Gamma	Assumption SE=mean/4
	Number of U&E (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	0.50	Gamma	Assumption SE=mean/4
	Number of FBC (INF)	3	0.75	Gamma	Assumption SE=mean/4
	Number of LFT (INF)	3	0.75	Gamma	Assumption SE=mean/4
	Number of U&E (INF)	3	0.75	Gamma	Assumption SE=mean/4
Monitoring frequency – maintenance	Number of FBC (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	1	Gamma	Assumption SE=mean/4

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
	Number of LFT (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	1	Gamma	Assumption SE=mean/4
	Number of U&E (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	1	Gamma	Assumption SE=mean/4
BSC cost		£5,082.22	779.74	Gamma	Combined SE from Fonia et al (2010) [146]
Monitoring costs	Cost of FBC	£3.01	0.75	Gamma	Assumption SE=mean/4
	Cost of LFT	£1.19	0.30	Gamma	Assumption SE=mean/4
	Cost of U&E	£1.19	0.30	Gamma	Assumption SE=mean/4
	Cost of self-admin training	£36.00	9.00	Gamma	Assumption SE=mean/4
	Cost of physician visit for IV	£97.08	24.27	Gamma	Assumption SE=mean/4
	Cost of office visit to physician	£101.58	25.40	Gamma	Assumption SE=mean/4
BSC efficacy (response rates: placebo)	PASI 50	13.7%	(10.1%, 17.9%)	CODA	N/A
	PASI 75	4.7%	(3.1%, 6.6%)	CODA	N/A
	PASI 90	1.0%	(0.6%, 1.5%)	CODA	N/A
	PASI 100	0.1%	(0.0%, 0.1%)	CODA	N/A
Response rates: ixekizumab Q2W	PASI 50	96.6%	(94.3%, 98.3%)	CODA	N/A
	PASI 75	89.5%	(84.1%, 93.7%)	CODA	N/A
	PASI 90	72.2%	(62.9%, 80.5%)	CODA	N/A
	PASI 100	41.3%	(31.3%, 51.8%)	CODA	N/A
Response rates: adalimumab	PASI 50	77.8%	(68.9%, 85.5%)	CODA	N/A
	PASI 75	57.5%	(46.4%, 68.2%)	CODA	N/A
	PASI 90	31.7%	(22.3%, 42.2%)	CODA	N/A
	PASI 100	10.0%	(5.7%, 15.6%)	CODA	N/A
Response rates: etanercept 50 mg QW	PASI 50	63.9%	(52.8%, 74.3%)	CODA	N/A
	PASI 75	41.3%	(30.3%, 52.8%)	CODA	N/A
	PASI 90	18.9%	(11.8%, 27.5%)	CODA	N/A
	PASI 100	4.6%	(2.3%, 7.9%)	CODA	N/A
Response	PASI 50	92.8%	(88.1%,	CODA	N/A

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
rates: infliximab			96.1%)		
	PASI 75	81.1%	(72.6%, 88.1%)	CODA	N/A
	PASI 90	58.7%	(47.2%, 69.4%)	CODA	N/A
	PASI 100	27.8%	(18.7%, 38.0%)	CODA	N/A
Response rates: ustekinumab 45 mg	PASI 50	87.1%	(81.4%, 91.7%)	CODA	N/A
	PASI 75	71.0%	(62.2%, 78.8%)	CODA	N/A
	PASI 90	45.6%	(36.0%, 55.2%)	CODA	N/A
	PASI 100	17.9%	(12.0%, 24.7%)	CODA	N/A
Response rates: ustekinumab 90 mg	PASI 50	89.6%	(84.2%, 93.7%)	CODA	N/A
	PASI 75	75.1%	(66.2%, 82.7%)	CODA	N/A
	PASI 90	50.6%	(40.1%, 60.7%)	CODA	N/A
	PASI 100	21.4%	(14.3%, 29.5%)	CODA	N/A
Response rates: secukinumab	PASI 50	93.2%	(89.5%, 96.1%)	CODA	N/A
	PASI 75	81.8%	(74.9%, 88.1%)	CODA	N/A
	PASI 90	59.6%	(50.0%, 69.3%)	CODA	N/A
	PASI 100	28.6%	(20.7%, 37.9%)	CODA	N/A

ADA = adalimumab; BSC = best supportive care;CI = confidence interval; CODA = Convergence Diagnostic and Output Analysis; CrI = credible interval; DLQI = Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life – 5 Dimensions, 5 levels; ETN = etanercept; FBC = full blood count; INF = infliximab; IXE = ixekizumab; IV = intravenous; LFT = liver function test; N/A = not applicable; NMSC = non-melanoma skin cancer; NR = not reported; PASI = Psoriasis Area and Severity Index; QW = once weekly; Q2W = every 2 weeks; SC = subcutaneous; SE = standard error; SEC = secukinumab; UST = ustekinumab

A summary of the probabilistic results is presented in Table 97. Ixekizumab sequence 1A dominates secukinumab sequence 1E, extendedly dominates all other sequences and is associated with an ICER of £32,815 versus the referent treatment sequence, etanercept sequence 1C.

Table 97: Probabilistic results

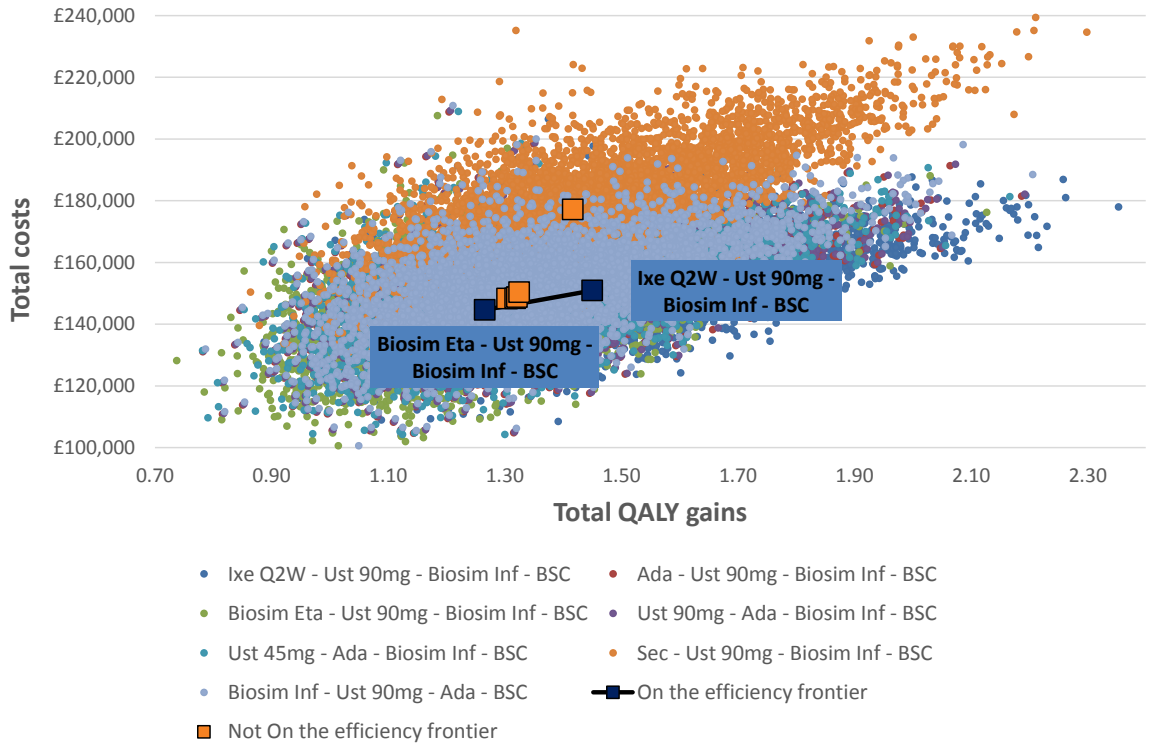
Comparator sequence	Total costs	Total QALY gain	ICER (cost/QALY)
1C: ETN sequence	£145,400	1.30	Referent
1F: UST 45 mg sequence	£149,050	1.34	Extendedly dominated
1B: ADA sequence	£149,174	1.35	Extendedly dominated

1G: UST 90 mg sequence	£149,555	1.35	Extendedly dominated
1D: INF sequence	£151,391	1.36	Extendedly dominated
1A: IXE sequence	£151,575	1.49	£32,815
1E: SEC sequence	£179,042	1.45	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

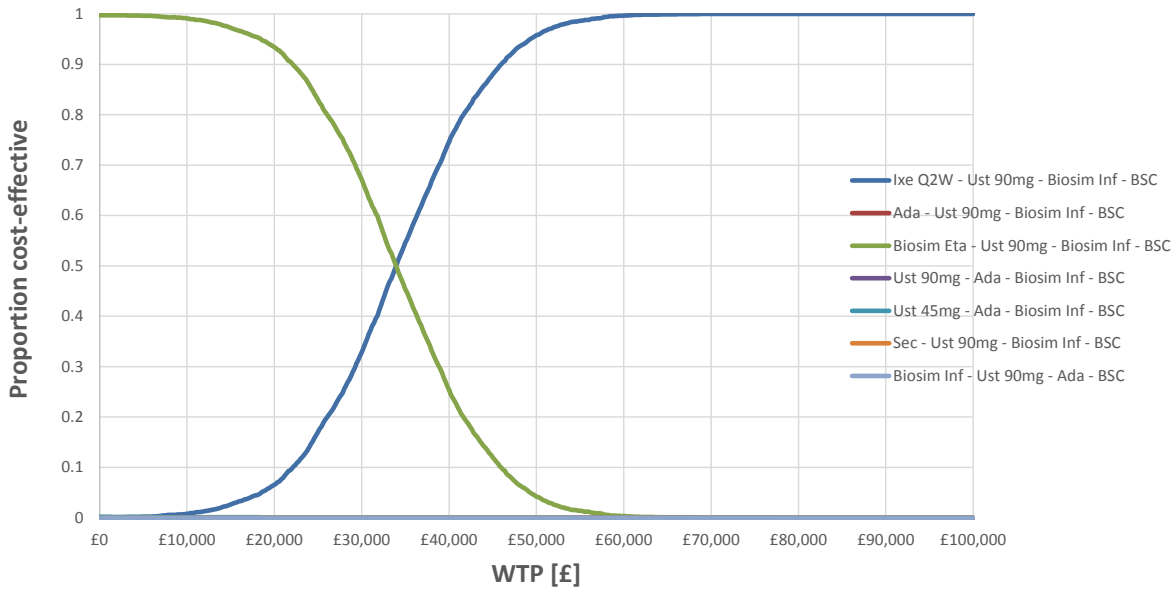
A graphical depiction of the simulations is presented in Figure 40, demonstrating that sequences 1A and 1C are the only two treatment sequences that lie on the frontier. The cost-effectiveness acceptability curves (CEAC) and cost-effectiveness acceptability frontier (CEAF) are presented in Figure 41 and Figure 42, respectively. Sequences 1A and 1C are the treatment sequences with the greatest probability of being cost-effective over a willingness to pay threshold range of £0 to £34,000 for etanercept sequence 1C and over £34,000 for ixekizumab sequence 1A and the highest NMB over these ranges.

Figure 40: CE plane



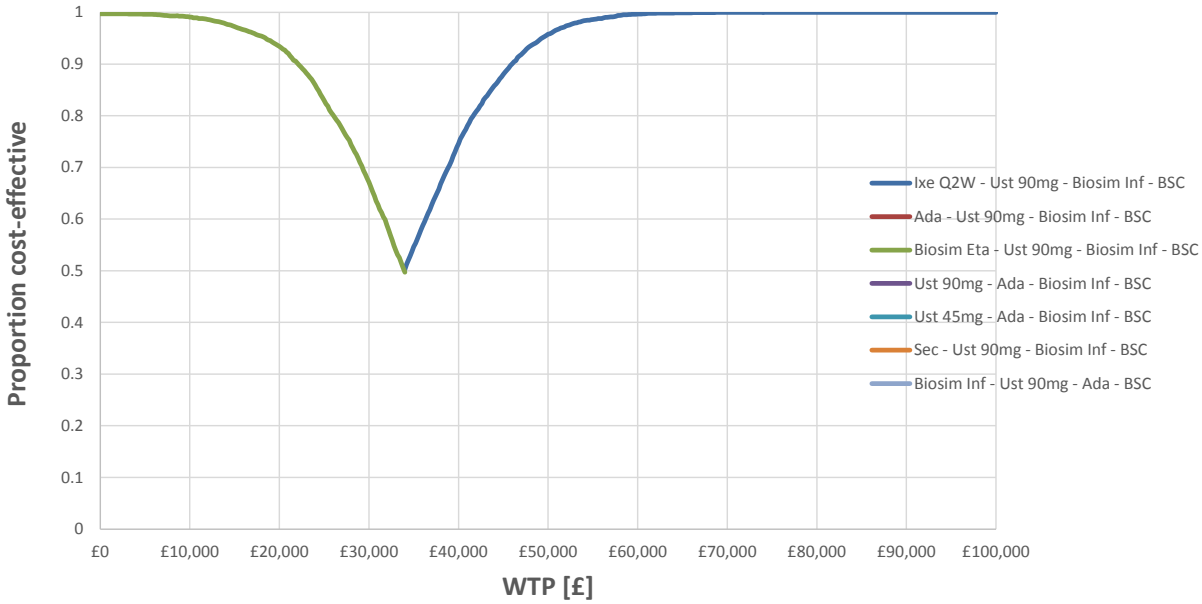
ADA = adalimumab; BSC = best supportive care; CE = cost-effectiveness; ETN = etanercept; INF = infliximab; IXE = ixekizumab; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Figure 41: CEAC



ADA = adalimumab; BSC = best supportive care; CEAC = cost-effectiveness acceptability curves; ETN = etanercept; INF = infliximab; IXE = ixekizumab; SEC = secukinumab; UST = ustekinumab; WTP = willingness to pay

Figure 42: CEAF



ADA = adalimumab; BSC = best supportive care; CEAF = cost-effectiveness acceptability frontier; ETN = etanercept; INF = infliximab; IXE = ixekizumab; SEC = secukinumab; UST = ustekinumab; WTP = willingness to pay

5.8.2 Deterministic sensitivity analysis

One-way sensitivity analyses (OWSA) were undertaken to assess the impact of key variables on the model outcomes. The annual discontinuation rate is varied between the upper and lower limits of the 95% confidence interval and for other parameters, values were varied by either plus or minus 20% from the base-case value or by plus or minus one unit.

The parameters varied in the deterministic sensitivity analyses (DSA) are presented in Table 98.

Table 98: DSA inputs

Category	Parameter	Mean	Lower bound	Upper bound	Comment
Discount	Discount rate QALYS	3.5%	0%	5%	Assumption
	Discount rate costs	3.5%	0%	5%	Assumption
	Annual discontinuation rate	0.20	0.047	0.428	Woolacott *et al*. (2006)
	Annual cost of BSC (Fonia)	£5,082.22	£4,065.78	£6,098.66	±20% of mean value
Drug costs (pack cost)	Ixekizumab Q2W	[redacted]	[redacted]	[redacted]	±20% of mean value
	Adalimumab	£704.28	£563.42	£845.14	±20% of mean value
	Biosimilar etanercept 50 mg	£656.00	£524.80	£787.20	±20% of mean value
	Infliximab	£377.66	£302.13	£453.19	±20% of mean value
	Ustekinumab 45 mg	£2,147.00	1717.6	2576.4	±20% of mean value
	Ustekinumab 90 mg	£2,147.00	1717.6	2576.4	±20% of mean value
	Secukinumab	£1,218.78	975.0	1462.5	±20% of mean value

Category	Parameter	Mean	Lower bound	Upper bound	Comment
Monitoring costs	Cost of full blood count	£3.01	2.4	3.6	±20% of mean value
	Cost of liver function test	£1.19	1.0	1.4	±20% of mean value
	Cost of urea and electrolytes test	£1.19	1.0	1.4	±20% of mean value
	Cost of self-admin training	£36.00	28.8	43.2	±20% of mean value
	Cost of physician visit for IV	£97.08	77.7	116.5	±20% of mean value
	Cost of office visit to physician	£101.58	81.3	121.9	±20% of mean value
Resource use: physician visits	IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC - Induction period	2	1	3	±1 visit (assumption)
	IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC - maintenance (annually)	4	3	5	±1 visit (assumption)
	INF – physician visits: induction period (10 weeks)	1	0	2	±1 visit (assumption)
	INF – physician visits: maintenance (annually)	0	0	1	±1 visit (assumption)
Drug administration	Number of self-admin training hours (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	3	2	4	±1 hour of training (assumption)
	Number of IV infusions (INF) – induction period	3	2	4	±1 infusion (assumption)
	Number of IV infusions (INF) – maintenance	6.5	5.5	7.5	±1 infusion (assumption)
Monitoring frequency – induction period	Number of FBC (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	1	3	±1 test (assumption)
	Number of LFT (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	1	3	±1 test (assumption)
	Number of U&E (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC)	2	1	3	±1 test (assumption)
	Number of FBC (INF)	3	2	4	±1 test (assumption)
	Number of LFT (INF)	3	2	4	±1 test (assumption)
	Number of U&E (INF)	3	2	4	±1 test (assumption)
Monitoring frequency – maintenance	Number of FBC (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	3	5	±1 test (assumption)
	Number of LFT (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	3	5	±1 test (assumption)
	Number of U&E (IXE Q2W, ADA, ETN 50 mg, UST 45 mg, UST 90 mg, SEC, INF)	4	3	5	±1 test (assumption)
BSC efficacy (response	PASI 50	13.7%	10.1%	17.9%	95% CrI, CODA
	PASI 75	4.7%	3.1%	6.6%	95% CrI, CODA

Category	Parameter	Mean	Lower bound	Upper bound	Comment
rates: placebo)	PASI 90	1.0%	0.6%	1.5%	95% CrI, CODA
	PASI 100	0.1%	0.0%	0.1%	95% CrI, CODA
Response rates: ixekizumab Q2W	PASI 50	[redacted]	[redacted]	[redacted]	95% CrI, CODA
	PASI 75	[redacted]	[redacted]	[redacted]	95% CrI, CODA
	PASI 90	[redacted]	[redacted]	[redacted]	95% CrI, CODA
	PASI 100	[redacted]	[redacted]	[redacted]	95% CrI, CODA
Response rates: adalimumab	PASI 50	77.8%	68.9%	85.5%	95% CrI, CODA
	PASI 75	57.5%	46.4%	68.2%	95% CrI, CODA
	PASI 90	31.7%	22.3%	42.2%	95% CrI, CODA
	PASI 100	10.0%	5.7%	15.6%	95% CrI, CODA
Response rates: etanercept 50 mg QW	PASI 50	63.9%	52.8%	74.3%	95% CrI, CODA
	PASI 75	41.3%	30.3%	52.8%	95% CrI, CODA
	PASI 90	18.9%	11.8%	27.5%	95% CrI, CODA
	PASI 100	4.6%	2.3%	7.9%	95% CrI, CODA
Response rates: infliximab	PASI 50	92.8%	88.1%	96.1%	95% CrI, CODA
	PASI 75	81.1%	72.6%	88.1%	95% CrI, CODA
	PASI 90	58.7%	47.2%	69.4%	95% CrI, CODA
	PASI 100	27.8%	18.7%	38.0%	95% CrI, CODA
Response rates: ustekinumab 45 mg	PASI 50	87.1%	81.4%	91.7%	95% CrI, CODA
	PASI 75	71.0%	62.2%	78.8%	95% CrI, CODA
	PASI 90	45.6%	36.0%	55.2%	95% CrI, CODA
	PASI 100	17.9%	12.0%	24.7%	95% CrI, CODA
Response rates: ustekinumab 90 mg	PASI 50	89.6%	84.2%	93.7%	95% CrI, CODA
	PASI 75	75.1%	66.2%	82.7%	95% CrI, CODA
	PASI 90	50.6%	40.1%	60.7%	95% CrI, CODA
	PASI 100	21.4%	14.3%	29.5%	95% CrI, CODA
Response rates: secukinumab	PASI 50	93.2%	89.5%	96.1%	95% CrI, CODA
	PASI 75	81.8%	74.9%	88.1%	95% CrI, CODA
	PASI 90	59.6%	50.0%	69.3%	95% CrI, CODA
	PASI 100	28.6%	20.7%	37.9%	95% CrI, CODA

ADA = adalimumab; BSC = best supportive care;CI = confidence interval; CODA = Convergence Diagnostic and Output Analysis; CrI = credible interval; DLQI = Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life – 5 Dimensions, 5 levels; ETN = etanercept; FBC = full blood count; INF = infliximab; IXE = ixekizumab; IV = intravenous; LFT = liver function test; N/A = not applicable; NMSC = non-melanoma skin cancer; NR = not reported; PASI = Psoriasis Area and Severity Index; QW = once weekly; Q2W = every 2 weeks; SC = subcutaneous; SE = standard error; SEC = secukinumab; UST = ustekinumab

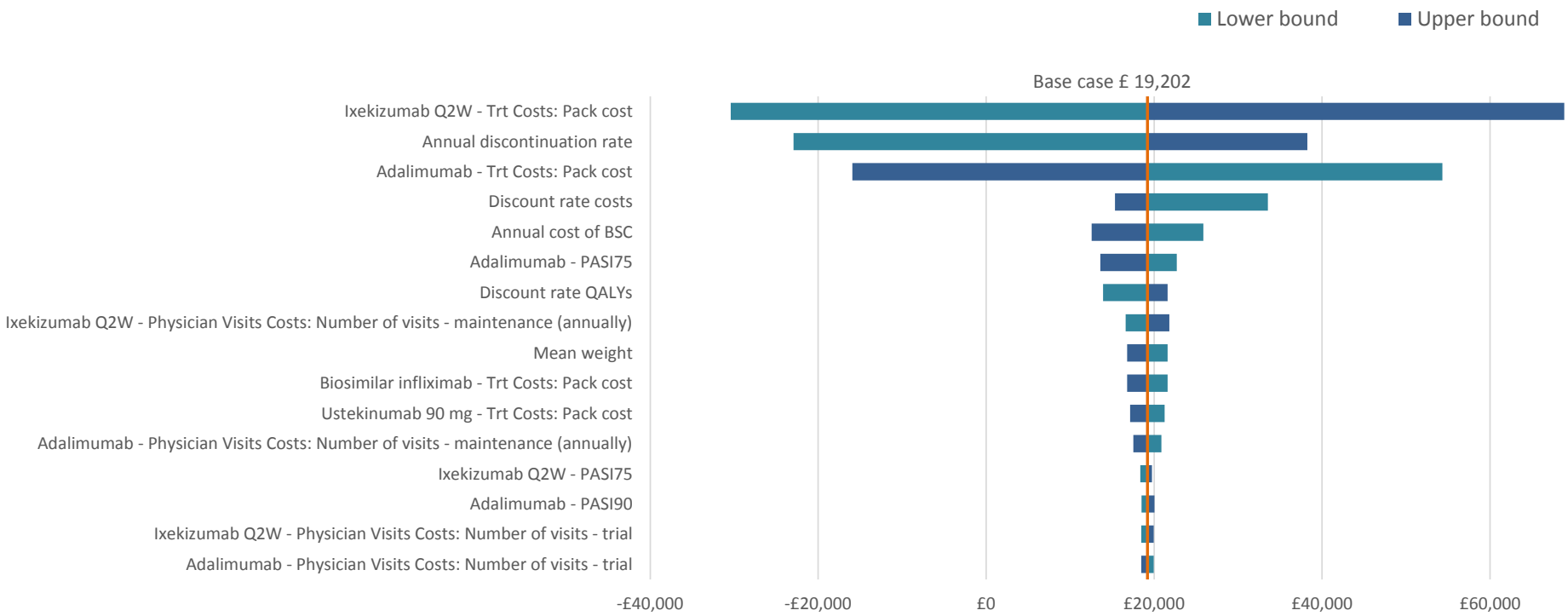
Summary of DSA results

The OWSA results for ixekizumab sequence 1A versus adalimumab sequence 1B, etanercept 50 mg sequence 1C, infliximab sequence 1D, secukinumab sequence 1E, and ustekinumab 90 mg sequence 1F are presented in Tornado diagrams in Figure 43, Figure 44, Figure 45, Figure 46 and Figure 47, respectively.

Common drivers of the ICERs across pairwise comparisons that contributed the most to the results are pack costs, discount rates on costs and QALYs, and the annual discontinuation rate. The latter three are particularly relevant in the context of the treatment sequencing approach as although many sequences share common treatments later in the sequence, the initial PASI response rates affect the timing of downstream consequences. Consequently, over a lifetime horizon, varying maintenance treatment discontinuation rates and discount rates for costs and QALYs in a treatment sequencing approach can amplify small initial differences in incremental results.

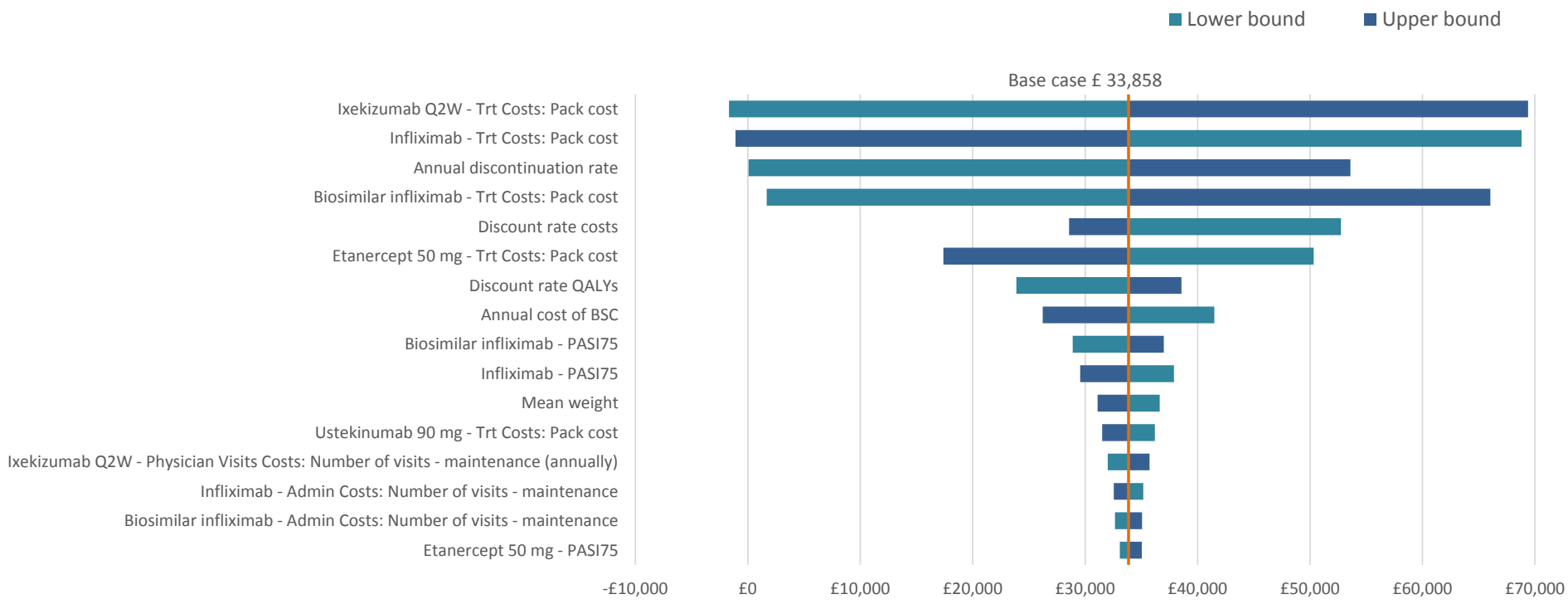
Ixekizumab sequence 1A dominates secukinumab sequence 1E in the base case analysis and this dominance persists in each of the DSAs. The pairwise comparison with secukinumab sequence 1E differs from the other pairwise DSAs in that PASI 75 response rates for both ixekizumab and secukinumab are the two largest drivers of the cost-effectiveness results whereas response rates are not as significant for other pairwise comparisons.

Figure 43: Tornado diagram: ixekizumab sequence versus adalimumab sequence



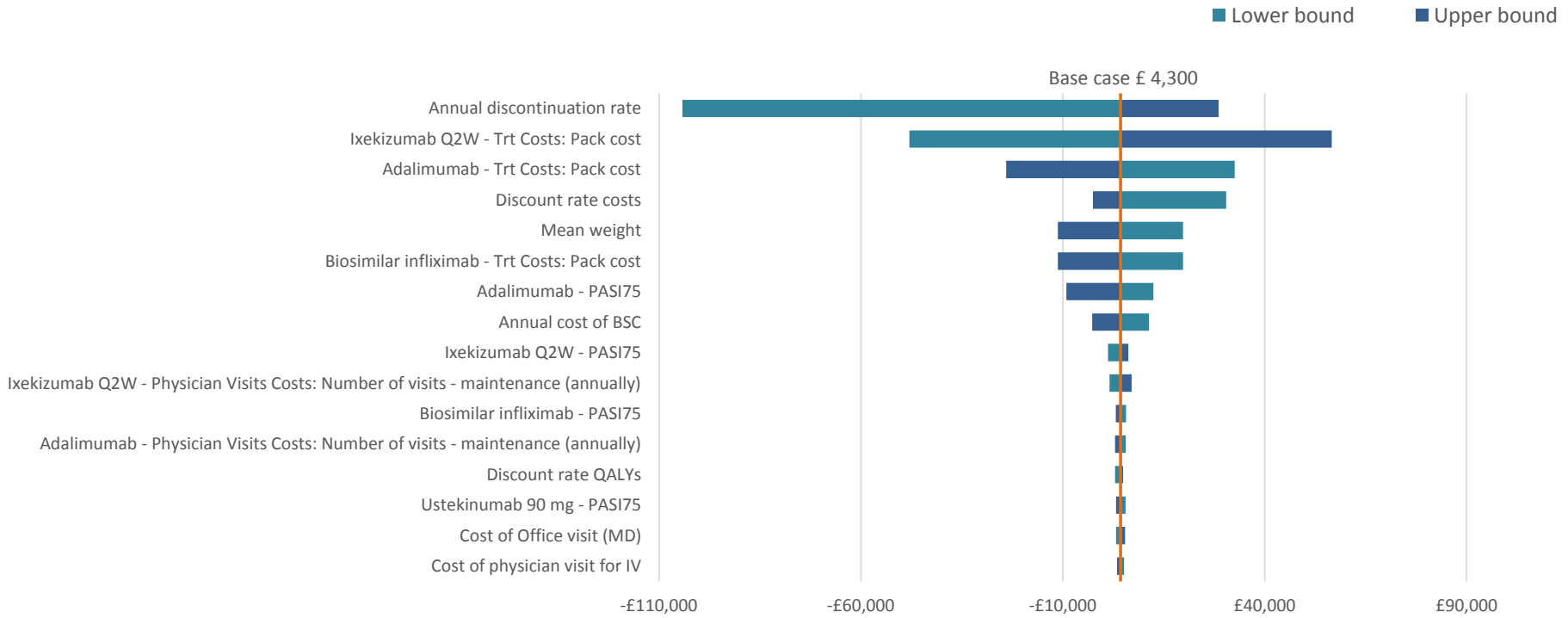
ADA = adalimumab; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; Trt = treatment; UST = ustekinumab

Figure 44: Tornado diagram: ixekizumab sequence versus etanercept sequence



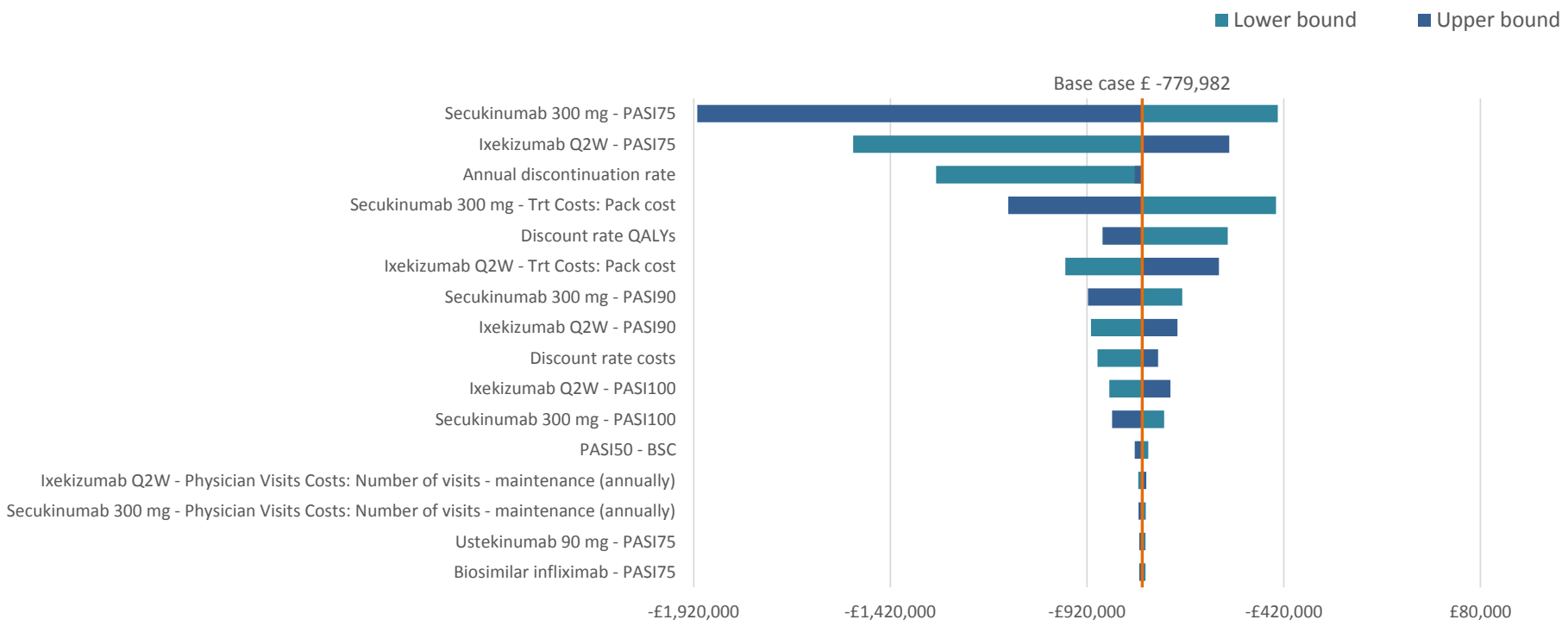
BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; Trt = treatment; UST = ustekinumab

Figure 45: Tornado diagram: ixekizumab sequence versus infliximab sequence



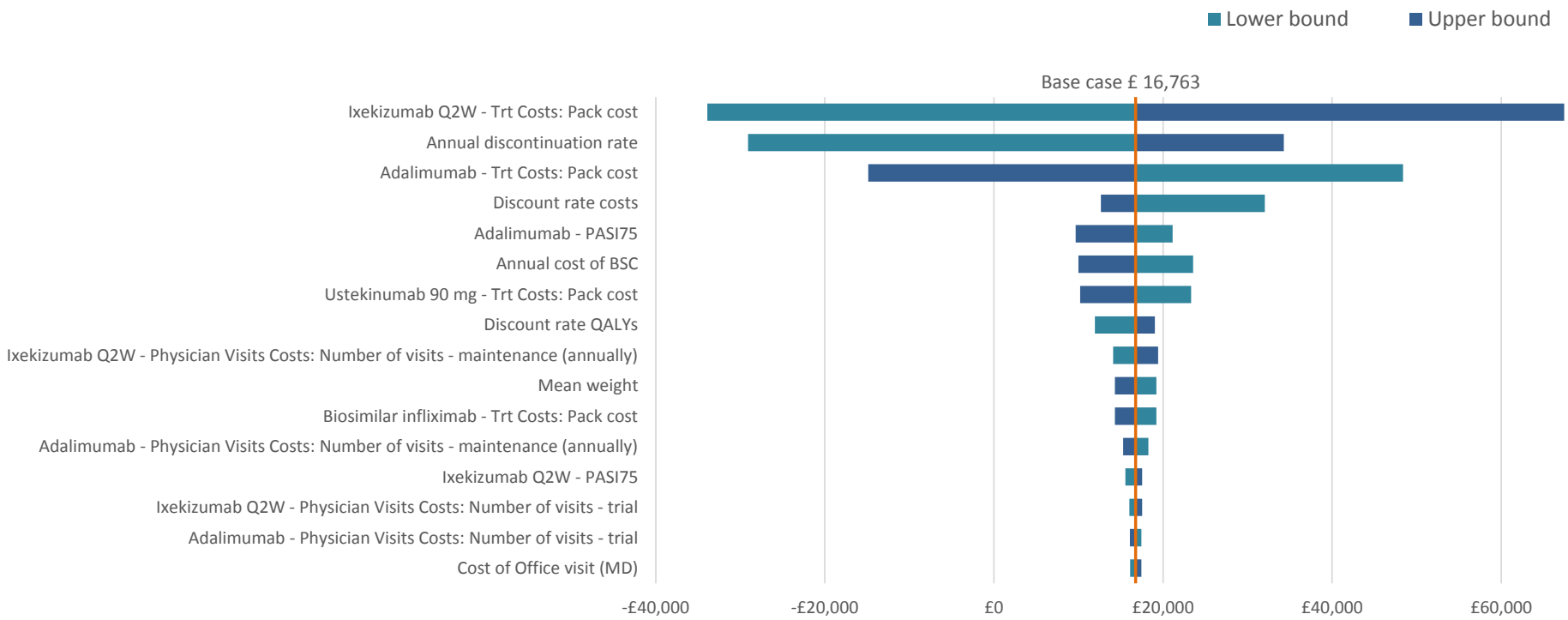
ADA = adalimumab; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; Trt = treatment; UST = ustekinumab

Figure 46: Tornado diagram: ixekizumab sequence versus secukinumab sequence



BSC = best supportive care; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; SEC = secukinumab; Trt = treatment; UST = ustekinumab

Figure 47: Tornado diagram: ixekizumab sequence versus ustekinumab 90 mg sequence



ADA = adalimumab; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; Trt = treatment; UST = ustekinumab

5.8.3 Scenario analysis

The structural uncertainty was explored by assessing the change in results using alternative functional forms, assumptions or sources for key input parameters. Each scenario is described in further detail below.

Prior failure on or contraindication to TNF-alpha inhibitor

Adalimumab had the largest market share of 54.9% in 2014 as a first-line therapy for psoriasis [161] and therefore is used as a common first-line therapy across the sequences. The treatment sequences in Table 99 assume that an alternative mechanism of action follows failure on a first-line TNF-α inhibitor. For ease of comparison across comparator sequences, infliximab is assumed to be a third-line biologic (Section 5.2.3).

Table 99: Intervention and comparators as second-line in treatment sequence

Sequence	1st Line	2nd Line	3rd Line	4th Line
2A	Adalimumab	Ixekizumab	Infliximab	BSC
2B	Adalimumab	Secukinumab	Infliximab	BSC
2C	Adalimumab	Ustekinumab 45 mg	Infliximab	BSC
2D	Adalimumab	Ustekinumab 90 mg	Infliximab	BSC

BSC = best supportive care

Sequence 2A with ixekizumab as second-line therapy is the referent comparator in this scenario analysis with the lowest costs and highest total QALY gain, thereby dominating all other sequences.

Table 100: Scenario analysis: ixekizumab in patients with inadequate response to prior biologic therapy

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
2A: IXE sequence	£147,612	1.38	Referent	Referent	Referent	N/A
2C: UST 45 mg sequence	£147,842	1.30	£230	-0.08	Dominated	Dominated
2D: UST90 mg sequence	£148,350	1.32	£738	-0.06	Dominated	Dominated
2B: SEC sequence	£171,192	1.35	£23,580	-0.03	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Single treatment comparator

A fully incremental analysis was undertaken using single treatment comparators followed by BSC. This is presented in Table 101. Ixekizumab as a single treatment is associated with the highest total QALY gain. The ICER for ixekizumab versus etanercept 50 mg is £39,563/QALY and ixekizumab dominates ustekinumab 90 mg, infliximab and secukinumab and extendedly dominates adalimumab and ustekinumab 45 mg.

Table 101: Scenario analysis: single treatment comparators

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
Etanercept 50 mg	£107,405	0.67	Referent	Referent	Referent	£39,563
Adalimumab	£112,198	0.74	£4,793	0.07	Extendedly dominated	£26,963
Ustekinumab 45 mg	£116,083	0.81	£8,678	0.14	Extendedly dominated	£4,814
Ixekizumab Q2W	£116,539	0.90	£9,134	0.23	£39,563	N/A
Ustekinumab 90 mg	£116,807	0.83	£9,402	0.16	Dominated	Dominated
Infliximab	£125,419	0.86	£18,014	0.19	Dominated	Dominated
Secukinumab 300 mg	£142,295	0.86	£34,890	0.19	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; Q2W = every 2 weeks; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Conventional systemic therapy

Ixekizumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.[200] Patients are eligible for conventional systemic therapy if their psoriasis has not been controlled with topical therapy; has had a significant impact on physical, psychological or social wellbeing; and is extensive (BSA>10% or PASI>10) or is localised with significant functional impairment and/or high-levels of distress or for which phototherapy has been ineffective, cannot be used or has resulted in rapid relapse.[65]

Ixekizumab as a single treatment is compared to methotrexate, ciclosporin and BSC in a scenario analysis using PASI response rates from NMA scenario analysis 2 (Section 4.9.14). It is assumed that when patients discontinue from ixekizumab, methotrexate or ciclosporin, they proceed to BSC. Methotrexate is associated with an additional monitoring cost of liver biopsy and PIIINP (amino-terminal propeptide of type III procollagen), and ciclosporin is associated with an additional monitoring cost of glomerular filtration rate testing. As both therapies are administered orally, no administration cost is incurred.

Table 102: Additional monitoring costs

Monitoring	Induction frequency	Maintenance frequency	Cost	Source
Liver biopsy	0.012	0.04	£716.83	Costing template accompanying CG153. [8] National schedule of reference costs 2014-15, Percutaneous Punch Biopsy of Lesion of Liver, 19 years and over. (currency code: YG11A) [198]
PIIINP	0	4	£25.29	Costing template accompanying CG153. [8]
Glomerular filtration rate test	0	1	£1.19	Costing template accompanying CG153. [8] NHS Reference Cost 2014-2015, Currency Code: DAPS04 (Clinical Biochemistry). [198] Note: A blood test for creatinine is used to estimate glomerular filtration rate (GFR)

Ixekizumab is associated with an ICER of £65,468/QALY relative to the referent treatment, methotrexate. Methotrexate dominates ciclosporin followed by BSC and BSC alone.

Table 103: Scenario analysis: ixekizumab versus conventional systemic therapy

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
Methotrexate	£95,425	0.60	Referent	Referent	Referent	£65,468
Ciclosporin	£97,925	0.58	£2,488	-0.01	Dominated	£55,231
BSC	£100,380	0.52	£4,943	-0.08	Dominated	£40,506
Ixekizumab Q2W	£116,517	0.92	£21,092	0.32	£65,468	N/A

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; IXE = ixekizumab; N/A = not applicable; Q2W = every 2 weeks; QALYs = quality-adjusted life years

Model time horizon

A time horizon of 10 years is used in a scenario analysis with treatment sequences. This aligns the model with time horizons used in previous submissions in psoriasis.

Ixekizumab sequence 1A is associated with an ICER of £24,216/QALY versus etanercept sequence 1C, the referent comparator, which is lower than the base case ICER for this comparison. Ustekinumab 45 mg sequence 1F is dominated by adalimumab sequence 1B. Ixekizumab sequence 1A either dominates or extendedly dominates all other comparator sequences.

Table 104: Scenario analysis: 10 year time horizon

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£77,246	0.81	Referent	Referent	Referent	£24,216
1B: ADA sequence	£79,559	0.84	£2,313	0.03	Extendedly dominated	£5,610

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1F: UST45 mg sequence	£79,787	0.83	£2,541	0.02	Dominated	£2,815
1G: UST 90 mg sequence	£80,000	0.84	£2,754	0.03	Extendedly dominated	£646
1A: IXE sequence	£80,054	0.92	£2,808	0.12	£24,216	N/A
1D: INF sequence	£83,309	0.85	£6,063	0.04	Dominated	Dominated
1E: SEC sequence	£104,993	0.90	£27,747	0.09	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Effect modification

To account for a potentially decreased efficacy in patients previously treated with biologics for psoriasis, an effect modification is applied in a scenario analysis that affects both treatment response and persistence with biologics in responders.

In a Danish study [163], prior (primary or secondary) failure of a biologic treatment was shown to be a significant negative predictor of drug survival (i.e. time to discontinuation). Using data collected from a Cox regression model, a forward Wald method was used to calculate an odds ratio of drug survival for biologic naïve vs. previously biologic exposed patients. The resulting odds ratio of 1.24 is set as the base case effect modifying value and is used to increase the drop-out rate and decrease treatment response of the non-naïve population. It is applied to both primary (treatment failure in the induction period) and secondary failures.

The result of the effect modifier is twofold given that the odds ratio of 1.24 is applied both to the discontinuation rate and PASI response rates. In the model, this modifier decreases efficacy by dividing response (e.g. PASI 50 = 95%) by the effect modifier (thus, 95% / 1.24 = 76.6%).

This results in fewer patients achieving response at the end of the induction period and moving to the maintenance state, thus overall achieving lower health utility gain. Additionally, the monthly drop out probability of 1.84% is multiplied by 1.24, increasing the monthly drop out probability to 2.28% per cycle, resulting in more patients discontinuing treatment in each maintenance cycle.

This effect modification can be assigned to: (i) any biologic treatments; or (ii) to TNFα inhibitors only. In this scenario analysis, the effect modification is applied to all biologic treatments and will begin from the second-line of treatment onwards.

Similar to the base case, ixekizumab sequence 1A is the only treatment in addition to the referent etanercept sequence 1C, which lies on the cost-effectiveness frontier. Although applying effect modification lowers both total costs and total QALYs for all sequences, the incremental QALYs for ixekizumab sequence 1A versus the referent are lower and incremental costs are higher relative to the base case, resulting in a higher ICER for ixekizumab sequence 1A versus etanercept sequence 1C. Similarly, pairwise ICERs for ixekizumab sequence 1A versus adalimumab sequence 1B, and ustekinumab sequences 1F and 1G are higher relative to the base case pairwise ICERs for these comparisons.

Table 105: Scenario analysis: effect modification

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£134,937	1.05	Referent	Referent	Referent	£38,034
1B: ADA sequence	£138,426	1.10	£3,488	0.05	Extendedly dominated	£23,940
1F: UST45 mg sequence	£138,768	1.10	£3,831	0.05	Dominated	£20,974
1G: UST 90 mg sequence	£139,232	1.11	£4,294	0.06	Extendedly dominated	£19,500
1A: IXE sequence	£141,260	1.22	£6,322	0.17	£38,034	N/A
1D: INF sequence	£141,351	1.12	£6,413	0.07	Dominated	Dominated
1E: SEC sequence	£163,488	1.19	£28,551	0.14	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Branded prices

Using the higher branded prices of etanercept and infliximab results in both a lower fully incremental ICER for ixekizumab sequence 1A versus the referent etanercept sequence 1C and lower pairwise ICERs for ixekizumab sequence 1A versus adalimumab sequence 1B and ustekinumab sequences 1F and 1G relative to the base case in which biosimilar etanercept and infliximab prices are used.

The higher branded price of infliximab alters the relative ranking of comparators in the fully incremental analysis relative to the base case since infliximab is a common third-line biologic treatment across all sequences except infliximab sequence 1D. In contrast to the base case, in which sequence 1D is extendedly dominated by sequence 1A, the use of branded infliximab price results in sequence 1A dominating 1D.

Table 106: Scenario analysis: branded prices

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£149,588	1.27	Referent	Referent	Referent	£24,923
1F: UST 45 mg sequence	£151,722	1.30	£2,134	0.04	Extendedly dominated	£16,898
1B: ADA sequence	£151,829	1.32	£2,241	0.05	Extendedly dominated	£17,864
1G: UST 90 mg sequence	£152,198	1.32	£2,610	0.06	Extendedly dominated	£15,397
1A: IXE sequence	£154,191	1.45	£4,603	0.18	£24,923	N/A
1D: INF sequence	£154,732	1.33	£5,144	0.06	Dominated	Dominated
1E: SEC sequence	£180,448	1.42	£30,860	0.15	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Utility gain assignment

When health utility gain is assigned instantaneously, treatment response is allocated during the treatment induction period based on PASI stratification at the end of the induction period i.e., the benefit from the treatment is assumed to begin accruing as soon as treatment is commenced. This method includes utility for both responders and non-responders and uses the distribution of patients across PASI response rates at the end of the induction period and assigns health utility gain from the first cycle of the induction period. This is estimated as follows:

Equation 8 – Health utility improvement during induction period for responders and non-responders -instantaneous gain

$$\mathbf{u_t} = [\mathbf{u_{00}} \times \left(\mathbf{1} - \mathbf{p_{trt}^{PASI50}}\right) + \mathbf{u_{50}} \times \left(\mathbf{p_{trt}^{PASI50}} - \mathbf{p_{trt}^{PASI75}}\right) + \mathbf{u_{75}} \times \left(\mathbf{p_{trt}^{PASI75}} - \mathbf{p_{trt}^{PASI90}}\right) + \mathbf{u_{90}} \times \left(\mathbf{p_{trt}^{PASI90}} - \mathbf{p_{trt}^{PASI100}}\right) + \mathbf{u_{100}} \times \left(\mathbf{p_{trt}^{PASI100}}\right)]$$

u_t : health utility in induction period; u_{xx} : health utility improvement in patients who achieve ΔPASIXX; p : proportion achieving different levels of PASI response

u_t : health utility in induction period; u_{xx} : health utility improvement in patients who achieve ΔPASIXX; p : proportion achieving different levels of PASI response

As the model allows for flexibility of induction period duration amongst the comparators, when utilities are assigned only in the maintenance period as per the base case, patients receiving the comparator with the shortest induction period transition to the maintenance state and begin accruing utilities ahead of a treatment that has a longer induction period. The method for allocating utility gain instantaneously can account for this unbalance;

however it may not be realistic to assume that patients see benefits from treatment immediately.

Assigning instantaneous health utility gains does not have a major impact on the incremental results. The relative ranking of comparators remains unchanged. The ICER for ixekizumab sequence 1A versus the referent etanercept sequence 1C is slightly lower relative to the base case but pairwise ICERs for all other comparator sequences are slightly higher. Secukinumab sequence 1E remains dominated by sequence 1A.

Table 107: Scenario analysis: instantaneous health utility gain in induction period

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£144,635	1.34	Referent	Referent	Referent	£32,337
1F: UST45 mg sequence	£148,218	1.39	£3,583	0.05	Extendedly dominated	£18,398
1B: ADA sequence	£148,350	1.41	£3,715	0.06	Extendedly dominated	£19,605
1G: UST 90 mg sequence	£148,719	1.41	£4,083	0.07	Extendedly dominated	£16,974
1D: INF sequence	£150,350	1.41	£5,714	0.07	Extendedly dominated	£4,313
1A: IXE sequence	£150,889	1.54	£6,254	0.19	£32,337	N/A
1E: SEC sequence	£177,101	1.50	£32,466	0.16	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Adverse events

Following the approach used in the secukinumab NICE submission [68], the following serious AEs requiring hospitalisation are included in a scenario analysis: non-melanoma skin cancer, malignancy other than non-melanoma skin cancer, and severe infections.

Rates per patient year for the three categories are presented in Table 108. Rates for non-melanoma skin cancer and malignancy other than NMSC for adalimumab and ustekinumab were obtained from their SmPC, in addition to the severe infections rate for ustekinumab.[155,156] Severe infection rates for adalimumab, etanercept, infliximab and secukinumab were obtained from Dixon *et al.* [201] As rates for non-melanoma skin cancer or malignancies other than NMSC were not found, an average rate of the other biologic treatments is used as a proxy. For infliximab, rates for non-melanoma skin cancer and

malignancies other than NMSC were obtained from Reich *et al.*[202] The AE rates for ixekizumab were obtained from the ixekizumab phase 3 RCTs.

Table 108: AE rates

Treatment	Non-melanoma skin cancer (rate/patient year)	Malignancies other than NMSC (rate/patient year)	Severe infections (rate/patient year)	Reference:
Ixekizumab Q2W	0.007	0.004	0.019	Gordon 2016 [15]
Adalimumab	0.0097	0.0098	0.0519	SmPC; Dixon (2006) [155,201]
Etanercept 50 mg	0.0354	0.00093	0.0513	Enbrel product information; Dixon (2006) [201,203]
Infliximab	0.005	0	0.0552	Reich (2015); Dixon (2006) [201,202]
Secukinumab	0.0070	0.0040	0.015	Infection: SmPC [158]; NMSC and other malignancies: assumed equal to ixekizumab Q2W
Ustekinumab 45 mg	0.0065	0.0016	0.01	SmPC [156]
Ustekinumab 90 mg	0.0065	0.0016	0.01	SmPC [156]

AE = adverse event; NMSC = non-melanoma skin cancer; Q2W = every 2 weeks; SmPC = summary of product characteristics

Costs were obtained from the National Schedule of Reference Costs for the year 2013-2014 (Table 109). Costs for severe infection are considered to be a simple average of six types of infection: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection, and urinary tract infection. Similarly, the cost of malignancy other than non-melanoma skin cancer represents a simple average cost of lymphoma and melanoma. Wherever several codes were applicable, weighted averages were calculated. Table 110 displays the total annual cost of adverse events by biologic treatment.

Table 109: Costs associated with AEs in the economic model

Adverse reactions	AE	Cost	Average cost	Reference in submission
NMSC		£2,461.59	£2,461.59	National Schedule of Reference Costs Year 2014-15 : JC42A [198]
Malignancy other than NMSC:	Lymphoma (hospital costs)	£1,942.39	£2,201.99	National Schedule of Reference Costs Year 2014-15 : SA31A-F [198]
	Melanoma (hospital costs)	£2,461.59		National Schedule of Reference Costs Year 2014-15 : JC42A [198]
Severe Infection:	Sepsis	£2,149.02	£2,602.93	National Schedule of Reference Costs Year 2014-15 : WJ05A-B; WJ06A-J [198]

Adverse reactions	AE	Cost	Average cost	Reference in submission
	Tuberculosis	£2,570.71		National Schedule of Reference Costs Year 2014-15 : DZ14F-J [198]
	Pneumonia	£2,066.42		National Schedule of Reference Costs Year 2014-15 : DZ23H-N [198]
	Skin and soft tissue infection	£3,453.45		National Schedule of Reference Costs Year 2014-15 : JD07A-D [198]
	Bone and joint infection	£3,550.54		National Schedule of Reference Costs Year 2014-15 : HD25D-H [198]
	Urinary tract infection	£1,827.46		National Schedule of Reference Costs Year 2014-15 : LA04H-S [198]

AE = adverse event; NMSC = non-melanoma skin cancer

Table 110: Costs of AEs per year

Treatment	Malignancies other than NMSC	NMSC	Severe infections	Total annual cost
Ixekizumab Q2W	£17.23	£8.81	£49.46	£75.49
Adalimumab	£23.88	£21.58	£135.09	£180.55
Etanercept 50 mg	£87.14	£2.05	£133.53	£222.72
Infliximab	£12.31	£0.00	£143.68	£155.99
Secukinumab	£17.23	£8.81	£39.04	£65.08
Ustekinumab 45 mg	£16.00	£3.52	£26.03	£45.55
Ustekinumab 90 mg	£16.00	£3.52	£26.03	£45.55

AE = adverse event; NMSC = non-melanoma skin cancer; Q2W = every 2 weeks

Incorporating the cost of AEs does not change the relative ranking of sequences in the fully incremental analysis but does increase incremental costs for adalimumab sequence 1B and infliximab sequence 1D versus the referent, etanercept sequence 1C, compared to the base case. Although etanercept is associated with the highest annual cost associated with AEs, the lower PASI 75 response rates associated with etanercept relative to other treatments result in a greater proportion of patients discontinuing treatment and proceeding sooner to BSC, which is associated with zero AE costs. Pairwise ICERs for ixekizumab sequence 1A are lower for all comparator treatment sequences relative to the base case.

Table 111: Scenario analysis: adverse events

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£145,588	1.27	Referent	Referent	Referent	£32,932
1F: UST45 mg sequence	£149,162	1.30	£3,573	0.04	Extendedly dominated	£17,174

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1B: ADA sequence	£149,335	1.32	£3,746	0.05	Extendedly dominated	£17,670
1G: UST 90 mg sequence	£149,663	1.32	£4,075	0.06	Extendedly dominated	£15,506
1D: INF sequence	£151,331	1.33	£5,742	0.06	Extendedly dominated	£2,713
1A: IXE sequence	£151,671	1.45	£6,083	0.18	£32,932	N/A
1E: SEC sequence	£177,833	1.42	£32,245	0.15	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

PASI response criteria

In this scenario analysis, a different PASI response threshold is used as the basis of treatment continuation: i) PASI 50 or ii) PASI 90.

The stricter criterion for treatment continuation, PASI 90, preserves the relative ranking of treatment sequences of the base case but results in higher fully incremental and pairwise ICERs for ixekizumab sequence 1A relative to the base case. The more relaxed criterion for treatment continuation, PASI 50, results in a different ordering of comparators on the basis of total cost, and lower fully incremental and pairwise ICERs for ixekizumab sequence 1A.

Table 112: Scenario analysis: PASI 50 treatment continuation rule

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£150,659	1.36	Referent	Referent	Referent	£30,146
1B: ADA sequence	£154,534	1.41	£3,876	0.05	Extendedly dominated	£6,895
1F: UST45 mg sequence	£154,701	1.40	£4,043	0.04	Dominated	£4,928
1G: UST 90 mg sequence	£154,976	1.41	£4,318	0.05	Extendedly dominated	£2,855
1A: IXE sequence	£155,267	1.52	£4,608	0.15	£30,146	N/A
1D: INF sequence	£157,284	1.42	£6,626	0.06	Dominated	Dominated
1E: SEC sequence	£185,065	1.49	£34,406	0.13	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Table 113: Scenario analysis: PASI 90 treatment continuation rule

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1C: ETN sequence	£134,362	1.04	Referent	Referent	Referent	£35,506
1E: UST45 mg sequence	£137,012	1.07	£2,650	0.03	Extendedly dominated	£26,536
1B: ADA sequence	£137,393	1.09	£3,031	0.05	Extendedly dominated	£27,252
1F: UST 90 mg sequence	£137,688	1.09	£3,326	0.05	Extendedly dominated	£25,776
1D: INF sequence	£138,457	1.09	£4,094	0.05	Extendedly dominated	£21,504
1A: IXE sequence	£141,945	1.25	£7,583	0.21	£35,506	N/A
1G: SEC sequence	£161,257	1.20	£26,895	0.16	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Alternative utility sources

PASI response state-specific utility gains are sourced from previous submissions of biologic therapies in the treatment of moderate to severe psoriasis. Using HRQoL data from all patients in the UNCOVER trial programme results in the highest fully incremental and pairwise ICERs for ixekizumab sequence 1A relative to the base case. Utilities associated with PASI response from patients with 4th quartile DLQI from the York model resulted in the lowest ICERs for sequence 1A relative to the base case.

Table 114: Alternative sources of utility gains associated with PASI response thresholds

Health Utility	PASI<50	PASI 50	PASI 75	PASI 90	PASI 100
IXE 5L - All patients (baseline adj.)	0.005	0.071	0.083	0.102	0.104
IXE 5L - DLQI>10 (baseline unadj.)	0.029	0.094	0.130	0.139	0.141
IXE 5L - EQ-PSO bolt-on, DLQI>10	0.021	0.117	0.141	0.148	0.198
York - 4th DLQI	0.120	0.290	0.380	0.410	0.410
SEC - DLQI>10	0.109	0.193	0.226	0.264	0.264

Adj. = adjusted for baseline EQ-5D-5L; DLQI = Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life – 5 dimensions, 5 levels; EQ-PSO = EQ-5D psoriasis bolt-on; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; SEC = secukinumab; unadj. = unadjusted for baseline EQ-5D-5L

Table 115: Scenario analysis: utility sources

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
IXE 5L - All patients (baseline adj)						
1C: ETN sequence	£144,635	0.82	Referent	Referent	Referent	£47,235
1E: UST45 mg sequence	£148,218	0.85	£3,583	0.03	Extendedly dominated	£25,460
1B: ADA sequence	£148,350	0.86	£3,715	0.04	Extendedly dominated	£26,749
1F: UST 90 mg sequence	£148,719	0.86	£4,083	0.04	Extendedly dominated	£23,366
1D: INF sequence	£150,350	0.87	£5,714	0.04	Extendedly dominated	£6,003
1A: IXE sequence	£150,889	0.95	£6,254	0.13	£47,235	N/A
1G: SEC sequence	£177,101	0.93	£32,466	0.11	Dominated	Dominated
IXE 5L - DLQI>10						
1C: ETN sequence	£144,635	1.40	Referent	Referent	Referent	£42,158
1E: UST45 mg sequence	£148,218	1.43	£3,583	0.03	Extendedly dominated	£22,834
1B: ADA sequence	£148,350	1.44	£3,715	0.04	Extendedly dominated	£23,951
1F: UST 90 mg sequence	£148,719	1.45	£4,083	0.04	Extendedly dominated	£20,931
1D: INF sequence	£150,350	1.45	£5,714	0.05	Extendedly dominated	£5,366
1A: IXE sequence	£150,889	1.55	£6,254	0.15	£42,158	N/A
1G: SEC sequence	£177,101	1.52	£32,466	0.12	Dominated	Dominated
IXE 5L - EQ-PSO (UNCOVER-3), DLQI>10						
1C: ETN sequence	£144,635	1.50	Referent	Referent	Referent	£27,615
1E: UST45 mg sequence	£148,218	1.54	£3,583	0.04	Extendedly dominated	£14,273
1B: ADA sequence	£148,350	1.55	£3,715	0.06	Extendedly dominated	£14,904
1F: UST 90 mg sequence	£148,719	1.56	£4,083	0.06	Extendedly dominated	£13,045
1D: INF	£150,350	1.56	£5,714	0.07	Extendedly	£3,377

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
sequence					dominated	
1A: IXE sequence	£150,889	1.72	£6,254	0.23	£27,615	N/A
1G: SEC sequence	£177,101	1.67	£32,466	0.18	Dominated	Dominated
York - 4th DLQI						
1C: ETN sequence	£144,635	4.48	Referent	Referent	Referent	£16,109
1E: UST45 mg sequence	£148,218	4.56	£3,583	0.08	Extendedly dominated	£8,644
1B: ADA sequence	£148,350	4.59	£3,715	0.11	Extendedly dominated	£9,038
1F: UST 90 mg sequence	£148,719	4.59	£4,083	0.11	Extendedly dominated	£7,916
1D: INF sequence	£150,350	4.60	£5,714	0.12	Extendedly dominated	£2,035
1A: IXE sequence	£150,889	4.87	£6,254	0.39	£16,109	N/A
1G: SEC sequence	£177,101	4.80	£32,466	0.32	Dominated	Dominated
SEC - DLQI>10						
1C: ETN sequence	£144,635	3.17	Referent	Referent	Referent	£28,633
1E: UST45 mg sequence	£148,218	3.21	£3,583	0.04	Extendedly dominated	£14,840
1B: ADA sequence	£148,350	3.23	£3,715	0.05	Extendedly dominated	£15,401
1F: UST 90 mg sequence	£148,719	3.23	£4,083	0.06	Extendedly dominated	£13,563
1D: INF sequence	£150,350	3.24	£5,714	0.07	Extendedly dominated	£3,524
1A: IXE sequence	£150,889	3.39	£6,254	0.22	£28,633	N/A
1G: SEC sequence	£177,101	3.35	£32,466	0.18	Dominated	Dominated

ADA = adalimumab; adj. = adjusted for baseline EQ-5D-5L; BSC = best supportive care; DLQI = Dermatology Life Quality Index; 5L = European Quality of Life – 5 dimensions, 5 levels; EQ-PSO = EQ-5D psoriasis bolt-on; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; unadj. = unadjusted for baseline EQ-5D-5L; UST = ustekinumab

BSC cost

An alternative cost option for BSC is CG153 [8], published in October 2012. In conjunction with recommendations, a costing tool was also developed to aid different organizations in

the UK plan for the financial implications of implementing the clinical guidelines for psoriasis. The costing tool used current clinical practice, published information, available data and expert opinion to populate the inputs.

When costed according to CG153, BSC is estimated to comprise of a combination of methotrexate and ciclosporin treatment, as well as day care centre, narrow-band ultraviolet B (NBUVB), and inpatient care (hospital admissions) for high and 'very high need' patients. During the advisory board convened to validate the conceptual model, the consensus among the advisors was that CG153 was not reflective of the current treatment practice for psoriasis as it is unlikely that patients are hospitalized for the estimated 20.8 days, therefore Fonia *et al* (2010) [146] was used in the base case. However, it could be argued that the costs of BSC from CG153 are applicable when modelling a sequence of multiple biologics, given that access to more than 4 biologics is limited and that these patients may be likely to incur greater costs than those determined by Fonia et al.

Table 116: BSC costs derived from CG153 [8]

Medication	**Proportion treated**	**Annual treatment cost**		**Annual overall cost**
Treatment costs:				
Methotrexate	0.45	£ 28.98		£ 13.04
Ciclosporin	0.45	£ 1,765.40		£ 794.43
No drug	0.1	£ 0.00		£ 0.00
Monitoring costs:				
Methotrexate	0.45	£ 166.67		£ 75.00
Ciclosporin	0.45	£ 22.75		£ 10.24
No drug	0.1	5 annual outpatient visits, total cost £ 507.90 annually		£ 50.79
	Proportion treated	**Annual resource cost**	**Unit cost of treatment**	**Annual overall cost**
Other treatment:				
Day care center	1	5	£ 389.06	£1,945.50
NBUVB	0.16	1 course (24 sessions)	£1,943.70	£310.99
Inpatient care:				
High need	0.82	20.8 days (1 admission)	£303.13	£5,170.19
Very high need	0.18	53.04 (2.55 admissions)	£303.13	£2,894.04
		Total annual overall cost		£10,320.52
		Total annual cost (inflated to 2015)		£11,257.14

BSC = best supportive care; CG153 = Clinical Guidelines 153; NBUVB = narrow band ultraviolet B

When the cost of BSC is based on CG153, ixekizumab sequence 1A is associated with the highest total QALYs and lowest costs of all the treatment sequences, thereby dominating all

other treatment sequences. BSC is associated with significant costs and time to BSC is delayed in sequence 1A relative to other treatment sequences.

Table 117: Scenario analysis: BSC cost, CG153

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
1A: IXE sequence	£567,904	1.45	Referent	Referent	Referent	N/A
1B: ADA sequence	£598,092	1.32	£30,188	-0.13	Dominated	Dominated
1F: UST 90 mg sequence	£598,460	1.32	£30,557	-0.13	Dominated	Dominated
1D: INF sequence	£600,091	1.33	£32,188	-0.13	Dominated	Dominated
1G: SEC sequence	£602,433	1.42	£34,529	-0.03	Dominated	Dominated
1E: UST45 mg sequence	£602,574	1.30	£34,671	-0.15	Dominated	Dominated
1C: ETN sequence	£614,170	1.27	£46,267	-0.18	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; CG153 = Clinical Guidelines 153; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

BSC efficacy

Response rates were reported according to baseline PASI in Woods *et al* (2008) [193] and were used as alternative sources for BSC:

- 0% of patient attain PASI 50, PASI 75, PASI 90 and PASI 100
- 65% of patients achieve PASI 50 and 0% achieve PASI 75, PASI 90 and PASI 100
- 83% of patients achieve PASI 50 and 0% achieve PASI 75, PASI 90 and PASI 100

Increasing the efficacy of BSC beyond the PASI response rates associated with placebo in the NMA results in higher ICERs for ixekizumab sequence 1A in the fully incremental analysis and pairwise comparison. Greater BSC efficacy increases the QALY gains associated with each treatment sequences; however, as patients receiving other comparator sequences spend a longer time in the BSC treatment state than patients receiving ixekizumab sequence 1A, the incremental QALY gain for sequence 1A is lower relative to the base case.

Conversely, when PASI 50 is set to zero for BSC, below the response rate estimated in the NMA, the ICERs for sequence 1A in the fully incremental analysis and pairwise comparisons

is lower relative to the base case due to the lower QALY gains incurred in the BSC treatment state for comparator treatment sequence relative to the base case.

Table 118: Scenario analysis: BSC efficacy

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs comparator
0% of patients attain PASI 50-100						
1C: ETN sequence	£144,635	1.10	Referent	Referent	Referent	£30,738
1E: UST45 mg sequence	£148,218	1.14	£3,583	0.04	Extendedly dominated	£16,750
1B: ADA sequence	£148,350	1.16	£3,715	0.06	Extendedly dominated	£17,643
1F: UST 90 mg sequence	£148,719	1.16	£4,083	0.06	Extendedly dominated	£15,376
1D: INF sequence	£150,350	1.17	£5,714	0.07	Extendedly dominated	£3,933
1A: IXE sequence	£150,889	1.30	£6,254	0.20	£30,738	N/A
1G: SEC sequence	£177,101	1.27	£32,466	0.17	Dominated	Dominated
65% of patients attain PASI 50; 0% achieve PASI 75-100						
1C: ETN sequence	£144,635	1.80	Referent	Referent	Referent	£50,047
1E: UST45 mg sequence	£148,218	1.82	£3,583	0.02	Extendedly dominated	£25,770
1B: ADA sequence	£148,350	1.83	£3,715	0.03	Extendedly dominated	£26,728
1F: UST 90 mg sequence	£148,719	1.83	£4,083	0.03	Extendedly dominated	£23,528
1D: INF sequence	£150,350	1.83	£5,714	0.04	Extendedly dominated	£6,114
1A: IXE sequence	£150,889	1.92	£6,254	0.12	£50,047	N/A
1G: SEC sequence	£177,101	1.90	£32,466	0.10	Dominated	Dominated
83% of patients attain PASI 50; 0% achieve PASI 75-100						
1C: ETN sequence	£144,635	1.99	Referent	Referent	Referent	£60,586
1E: UST45 mg sequence	£148,218	2.01	£3,583	0.02	Extendedly dominated	£30,286
1B: ADA sequence	£148,350	2.01	£3,715	0.02	Extendedly dominated	£31,173

1F: UST 90 mg sequence	£148,719	2.01	£4,083	0.02	Extendedly dominated	£27,577
1D: INF sequence	£150,350	2.02	£5,714	0.03	Extendedly dominated	£7,223
1A: IXE sequence	£150,889	2.09	£6,254	0.10	£60,586	N/A
1G: SEC sequence	£177,101	2.07	£32,466	0.08	Dominated	Dominated

ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

5.8.4 Summary of sensitivity analyses results

The sensitivity analyses were conducted to indicate which key parameters and assumptions had the greatest impact on the results. The DSAs demonstrated that there were some common factors across the pairwise comparisons that had the greatest impact on the implications for cost-effectiveness: treatment acquisition costs, discontinuation rate and discounting of costs and QALYs. With the exception of these parameters, ICERs were generally robust to variation in parameters. The efficiency frontier in the PSA was in accordance with the base case deterministic efficiency frontier with only etanercept sequence 1C and ixekizumab sequence 1A on the frontier. The mean probabilistic ICER for sequence 1A versus sequence 1C was lower than the deterministic base case ICER.

Scenarios that modelled alternatives to the base case treatment sequencing approach were ixekizumab as second-line therapy in a treatment sequence versus biologics other than TNF-α inhibitors; ixekizumab versus other biologics as single treatment comparators; and ixekizumab followed by BSC versus conventional systemic therapies followed by BSC. Ixekizumab as second-line therapy in patients with prior failure on or contraindication to a TNF-α inhibitor dominated treatment strategies in which ustekinumab 45 mg, ustekinumab 90 mg and secukinumab occupied the same position in the sequence. In a comparison of single treatments, ixekizumab was associated with an ICER of £39,563 versus the referent etanercept. However, pairwise comparisons demonstrated that ixekizumab was associated with ICERs of £4,814/QALY versus ustekinumab 45 mg and £26,963/QALY versus adalimumab, and dominated other single biologic treatments. Ixekizumab versus conventional systemics was associated with the highest QALY gains; however, compared to the referent, methotrexate, the ICER was £65,432/QALY.

Scenario analyses that tested key assumptions while continuing to compare ixekizumab as a first line biologic therapy to other biologics retained the same treatments on the efficiency frontier as the base case with some differences in which treatments were dominated or extendedly dominated. A number of scenarios applied assumptions or parameter values

from previous technology appraisals of biologic therapies: these were a model time horizon of 10 years, alternative utility data sources from the York model and secukinumab submission [68,71], and a definition of BSC based on CG153. Each of these resulted in an ICER for ixekizumab sequence 1A that was below £30,000/QALY and in the case of the CG153-based cost of BSC, this resulted in ixekizumab sequence 1A dominating the other treatment strategies.

5.9 *Subgroup analysis*

The base case economic evaluation considers a population with moderate to severe psoriasis defined as PASI≥10 and DLQI>10. The PASI score eligibility criterion in the trials was PASI>12 with no restriction related to DLQI. Due to limited availability of PASI response rates by baseline DLQI score from the NMA, PASI response rates are representative of the ITT population in the trial. Data presented in Section 4.7.6 show that for ixekizumab, at least, that the efficacy data in this population is congruent with the overall ITT population.

EQ-5D-5L data were dichotomised by DLQI≤10 and DLQI>10. An interaction model was run to explore whether there was a significant interaction between PASI score and baseline DLQI. A statistically significant interaction ($p<0.0001$) was indicated for DLQI≤10 and DLQI>10, which supported using DLQI>10 as the main analysis approach.

The subgroup of patients with DLQI≤10 would not be of interest for the decision problem as these patients would not be eligible for the systemic biological therapies approved for use in the UK.

Lastly, the key point of note with respect to sub-groups is that the data provided in Table 44 (Section **Error! Reference source not found.**) presented various sub-groups where ixekizumab efficacy was consistent regardless of baseline patient characteristics, therefore exploration of cost-effectiveness by clinically defined sub-groups was not warranted.

5.10 *Validation*

5.10.1 Validation of the de novo cost-effectiveness analysis

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision-Making (SMDM) Joint Task Force for Modelling Good Research Practices describes model validity simply, as “how well the model reproduces reality”. [204] The guidelines define the following 5 elements of model validation:

1. Face validity: experts evaluate model structure, data sources, assumptions, results, e.g., consultation with clinical advisors before and (perhaps) after model development

2. Verification or internal validity: check accuracy of coding, e.g., “quality control” checks

3. Cross validity: comparison of results with other models analysing the same problem

4. External validity: comparing model results with real-world results

5. Predictive validity: comparing model results with prospectively observed events

Face validity of the conceptual model was checked in an advisory board with clinical and health economic experts. Revisions to the conceptual model were made on the basis of feedback from the advisory board and subsequently incorporated in the model development.

The model was developed by an external consultancy and internal validation was undertaken by another external consultancy. The model was checked by the second consultancy from an overall health economics and outcomes research (HEOR) perspective and to quality control the programming of the model to identify errors or omissions. A cell-by-cell technical validation of the model was carried out and the VBA code was checked.

Replicating comparisons from previous submissions may be one way of checking cross-validity. However, differences in discount rates, time horizon, treatment sequencing and utility values between submissions, the expansion of the evidence base for biologic treatments and the confidential PAS price for secukinumab makes the cross-validation of base case ICERs between previous submissions difficult.

A trial of ixekizumab versus ustekinumab is currently underway (NCT02561806). Although EQ-5D-5L data and PASI response rates from this trial are not currently available, predictive validity could be assessed by comparing the ICER for ixekizumab versus ustekinumab from the model, as and when it can be updated with the head-to-head trial data, to the ICER as it is with currently available indirect evidence. Similarly, long term observational studies have not been carried out for ixekizumab, therefore external validity of real world clinical effectiveness is difficult to assess.

5.10.2 Data

A hierarchy of evidence in the estimation of parameters is outlined in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 13.[205] The five data elements described in the TSD are clinical effect sizes, baseline clinical data, resource use, unit costs and health utilities. As noted in Table 119, the sources informing these parameters in the model are ranked highly as 1+, 1 or 2.

Table 119: Hierarchy of evidence (NICE DSU TSD 13)

Parameters	Rank	TSD 13 description	Evidence used to inform model
Clinical effect sizes	1+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes	✓ - Section 4.9
	1	Single RCT with direct comparison between comparator therapies, measuring final outcomes	
	2+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring surrogate outcomes* Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy	
	2	Single RCT with direct comparison between comparator therapies, measuring surrogate outcomes* Single placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy	
	3+	Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring surrogate outcomes*	
	3	Single placebo-controlled RCTs with similar trial populations, measuring surrogate outcomes* for each individual therapy	
	4	Case-control or cohort studies	
	5	Non-analytic studies, for example, case reports, case series	
	6	Expert opinion	
Baseline clinical data	1	Case series or analysis of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest	
	2	Recent case series or analysis of reliable administrative databases covering patients solely from the jurisdiction of interest	✓ - Human Mortality Database, Section 5.2.2
	3	Recent case series or analysis of reliable administrative databases covering patients solely from another jurisdiction	
	4	Old case series or analysis of reliable administrative databases. Estimates from RCTs	
	5	Estimates from previously published economic analyses: unsourced	
	6	Expert opinion	
Resource use	1	Prospective data collection or analysis of reliable administrative data from same jurisdiction for specific study	
	2	Recently published results of prospective data collection or recent analysis of reliable administrative data – same jurisdiction	✓ -Fonia *et al* 2010, Section 5.5.2; costing template accompanying CG153
	3	Unsourced data from previous economic evaluations – same jurisdiction	
	4	Recently published results of prospective data collection or recent analysis of reliable administrative data – different	

Parameters	Rank	TSD 13 description	Evidence used to inform model
		jurisdiction	
	5	Unsourced data from previous economic evaluation – different jurisdiction	
	6	Expert opinion	
Unit costs	1	Cost calculations based on reliable databases or data sources conducted for specific study –same jurisdiction	✓ - PSSRU, MIMS, NHS reference costs, Section 5.5.2
	2	Recently published cost calculations based on reliable databases or data sources – same jurisdiction	✓ - Fonia *et al* 2010, Section 5.5.2
	3	Unsourced data from previous economic evaluation – same jurisdiction	
	4	Recently published cost calculations based on reliable databases or data sources – different jurisdiction	
	5	Unsourced data from previous economic evaluation – different jurisdiction	
	6	Expert opinion	
Utilities	1	Direct utility assessment for the specific study from a sample: of the general population with knowledge of the disease(s) of interest of patients with the disease(s) of interest Indirect utility assessment from specific study from patient sample with disease(s) of interest: using tool validated for the patient population	✓ - UNCOVER trial programme, Section 5.4.1
	2	Indirect utility assessment from a patient sample with disease(s) of interest: using a tool not validated for the patient population	
	3	Direct utility assessment from a previous study from a sample of the general population with knowledge of the disease(s) of interest of patients with the disease(s) of interest Indirect utility assessment from specific study from patient sample with disease(s) of interest: using tool validated for the patient population	
	4	Unsourced utility data from previous study – method of elicitation unknown	
	5	Patient preference values obtained from a visual analogue scale	
	6	Delphi panels, expert opinion	

CG153 = Clinical Guidelines 153; DSU = Decision Support Unit; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit; RCT = randomised controlled trial; TSD = Technical Support Document

5.11 *Interpretation and conclusions of economic evidence*

While a number of cost-effectiveness models have been developed to assess biologics in psoriasis, only one of which has modelled treatment sequences, the current cost-effectiveness analysis builds on the strengths of previous models and is the first to include data for ixekizumab, take a treatment sequencing approach in a fully incremental analysis framework and include PASI 100, complete clearance of symptoms, as a health state with a corresponding directly elicited utility value.

Some of the criticisms raised in ERG reports for previous submissions for biologics were addressed in the development of the current model, namely the treatment sequencing approach, which is better reflects clinical practice in the UK.[68,150-152] While official guidance was not available on the ordering of treatments within a sequence, the rationale for the ordering selected in the base case was based on market shares in second-line therapy, switching between mechanism of action and ease of comparison in having common treatments across the sequences.

In light of the treatment sequencing approach, a lifetime time horizon was assumed and age-dependent, gender-weighted mortality risk was incorporated. In the absence of robust data to the contrary, mortality risk was assumed to be equivalent across the sequences, as modelled in the secukinumab submission model. Despite this similarity in modelling survival between the models, due to the confidential PAS discount of secukinumab, it is difficult to compare predicted ICERs between the submissions.

The flexibility of the model in allowing different positions for treatments was tested in the scenario analysis assessing ixekizumab as a second-line therapy versus ustekinumab 45 mg, ustekinumab 90 mg and secukinumab in patients who had inadequate response or contraindication to a previous TNF-α inhibitor. The ixekizumab sequence dominated the other treatment sequences, demonstrating that ixekizumab may be a cost-effective option for patients at this later point in the clinical pathway (Figure 5).

However, when compared as a single treatment followed by BSC to methotrexate and ciclosporin, while ixekizumab was the only treatment other than the referent to lie on the frontier, the ICER relative to methotrexate was higher than the upper range of willingness to pay thresholds commonly accepted by NICE. For patients who are eligible to receive conventional systemic therapy, ixekizumab may therefore not be a cost-effective treatment option.

HRQoL was directly elicited from patients using the EQ-5D-5L instrument in the UNCOVER trial programme and the EQ-PSO bolt-on measure in UNCOVER-3. Valuation using five

rather than three dimensions, as in previous submissions, has generated a narrower range of utility values associated with PASI response categories for a population with more severe DLQI, even with the bolt-on measure. It could be argued that this is a strength of the current analysis as it allows for a more nuanced valuation of HRQoL.

One limitation of the model is that it assumes that efficacy estimates at 12 weeks, which were obtained from the NMA, are maintained throughout the model horizon, with patients dropping out of the maintenance phase at an annual rate of 20%. With the lack of real-world evidence, it is unclear how realistic this assumption is or if patients would experience eventual effect weaning. However, in addition to this method being used in previous model submissions, it is reasonable to assume that the relatively high annual dropout rate would capture those patients who discontinue use due to loss of efficacy, a notion that is also supported by European real-world evidence.[14,163] Efficacy for BSC was assumed to be equal to the efficacy of placebo that was obtained from the NMA. Given that the patients who are treated with BSC in the model have failed previous treatment modalities (both conventional systemic and biologic), it is arguable that efficacy would be low and that placebo efficacy is a reasonable estimate. However, the lack of underlying data makes the efficacy estimate uncertain.

Similarly, the cost of BSC is uncertain reflecting the dearth of data on the composition of BSC. In the scenario analysis where the impact of BSC cost was explored and the cost of BSC was set to £11,257 according to CG153, approximately double the cost used in the base case, ixekizumab was cost saving in comparison to the base case setting.

It is difficult to compare results from this economic evaluation with other published submissions. The current submission is based on the York model structure and draws on learnings from that and subsequent submissions. Overall, the current analysis is associated with more conservative assumptions than previous submissions, such as the lower cost estimate for BSC from Fonia *et al* (2010), a narrower and lower range of health state utility gains, splitting the PASI 90 health state into PASI 90-99 and PASI 100, and the use of a lifetime time horizon. Further analyses that could be carried out to enhance the robustness of the results would be to incorporate data from the head to head trial of ixekizumab versus ustekinumab.

The final notable conclusion that can be drawn from the cost-effectiveness analyses presented is that ixekizumab is a cost-effective option for the treatment of patients with moderate to severe psoriasis relative to treatments that are already approved by NICE for both the biologic-naïve and biologic experienced patient population.

6 Assessment of factors relevant to the NHS and other parties

Summary of budget impact analysis

- A budget impact analysis was developed to assess the cost impact of ixekizumab in the five years after its introduction in the market for biologics in the treatment of moderate to severe psoriasis in England and Wales.
- The number of patients eligible to receive biologics was derived from the Office for National Statistics' population projections for England and Wales over the period 2017 to 2021, and estimates of psoriasis prevalence and the proportion of patients eligible to receive a biologic used in the costing template accompanying CG153. The estimated number of patients eligible to receive biologics ranged from 21,243 in 2017 to 21,768 in 2021.
- Estimated market shares for biologics were applied to the total eligible population, with the exception of secukinumab which has been approved in the UK under a confidential PAS discount and was therefore excluded from the BIM. The expected future market share of ixekizumab was assumed to displace market shares of other biologics to a similar extent.
- An annual discontinuation rate of 20%, which has been frequently used in previous economic evaluations of biologics in the treatment of moderate to severe psoriasis, was used to break down the total numbers receiving each therapy into patients initiating treatment and patients continuing treatment from the previous year.
- Annual administration and acquisition costs per patient differ in the first year of initiating treatment and subsequent years due to differences in induction period dosing and maintenance therapy dosing.
- First year costs and subsequent year costs were multiplied by the number of new starters and continuing patients to calculate the budget impact in each year. The total budget impact of ixekizumab over 2017 to 2021 was estimated to be a cost increase of £596,329.

6.2 *Population*

The targeted patient population for the budget impact model is the prevalence of patients with moderate to severe psoriasis in England and Wales who are eligible to receive biologic therapies. The inputs that inform the calculation of the eligible patient population in the current year, 2016, and over a five year time horizon from 2017 to 2021 are presented in Table 120.

Projected population numbers were obtained from the Office for National Statistics over the years 2016 to 2021 for the working age and pension populations in England and Wales. The prevalence of psoriasis in the UK was obtained from CG153 and is estimated to be around 1.3% to 2.2%.[8] A midpoint estimate of 1.75% was applied to the general population. The proportion of patients estimated to have been treated with a biologic is 2.55%.[8]

Table 120: Eligible adult patient population, England and Wales

Parameter	Value	2017	2018	2019	2020	2021	Source
Adult population, England		45,039,185	45,325,400	45,607,580	45,898,521	46,190,923	Office for National Statistics, 2014-based national population projections (England summary) [206]
Adult population, Wales		2,563,180	2,569,264	2,575,200	2,581,373	2,588,257	Office for National Statistics, 2014-based national population projections (Wales summary) [207]
Adult population, England and Wales		47,602,365	47,894,664	48,182,780	48,479,894	48,779,180	Calculation
Psoriasis prevalence	1.75%	833,041	838,157	843,199	848,398	853,636	NICE CG153 [8]
% currently treated with biologics	2.55%	21,243	21,373	21,502	21,634	21,768	NICE CG153 [8]

CG153 = Clinical Guidelines 153; NICE = National Institute for Health and Care Excellence

6.3 *Current and anticipated treatment practice*

Biologic systemic therapies currently approved for use in the UK, with the exception of secukinumab, are included as single treatment options in the BI. Secukinumab was approved in the UK in May 2015 under a confidential PAS discount. As secukinumab has not been established in the UK market for as long as other approved biologics and using the list price would result in an overestimate of costs associated with secukinumab, it is excluded from the BIM.

Market shares for all other treatments are provided in Table 121. These were based on 2014 market share data prior to the positive NICE recommendation for secukinumab. [161] These are multiplied by the number of biologic-eligible patients in Table 120 to arrive at the total numbers of patients receiving each treatment.

All patients in the first year of the BIM, 2017, are assumed to be new starters, incurring costs specific to the first year of initiating treatment. Subsequently, a discontinuation rate of 20% is applied and the 80% of patients who continue treatment comprise the 'continuing patients' population in the subsequent year. The number of new starters grows year on year due to projected population growth in England and Wales.

Table 121: Market shares and numbers of patients receiving currently approved biologics except secukinumab

Biologic therapy	Market share	2017	2018	2019	2020	2021
Total population						
Adalimumab	54.9%	11,662	11,734	11,804	11,877	11,950
Etanercept	13.8%	2,931	2,949	2,967	2,986	3,004
Infliximab	6.5%	1,381	1,389	1,398	1,406	1,415
Ustekinumab	24.8%	5,268	5,301	5,332	5,365	5,398
Continuing patients						
Adalimumab	N/A	0	9,330	9,387	9,443	9,502
Etanercept	N/A	0	2,345	2,360	2,374	2,388
Infliximab	N/A	0	1,105	1,111	1,118	1,125
Ustekinumab	N/A	0	4,215	4,240	4,266	4,292
New starters						
Adalimumab	N/A	11,662	2,404	2,417	2,434	2,449
Etanercept	N/A	2,931	604	608	612	616
Infliximab	N/A	1,381	285	286	288	290
Ustekinumab	N/A	5,268	1,086	1,092	1,099	1,106

N/A = not applicable

Projected market shares for ixekizumab in the biologic market over the next five years is presented in Table 122 alongside expected market shares of other comparators following displacement by ixekizumab and patient numbers. As in Table 121, the total patient numbers are divided into new starters and continuing patients.

Table 122: Anticipated market share of ixekizumab and future market share of other treatments

Biologic therapy	2017	2018	2019	2020	2021
Market shares					
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total population					
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing patients					
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New starters					
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 *Costs*

Cost and resource use categories considered in the BIM are acquisition and administration cost as described in Section 5.5.2. These are based on pack prices from MIMS and unit costs from the PSSRU Unit Costs of Health and Social Care 2015.[196,197] Based on the dosing regimen, total annual doses in the first year of initiating treatment and subsequent years are presented in Table 123.

Table 123: Number of doses in treatment periods and each year of treatment

Biologic therapy	Induction doses	Maintenance doses	First year doses	Subsequent year doses
Ixekizumab	8	10	18	13
Adalimumab	8	20	28	26
Etanercept	24	40	64	52
Infliximab	3	5	8	7
Ustekinumab	7	10	17	13

The cost per dose presented in Table 84 is multiplied by the number of doses in the first and subsequent years of treatment. Costs presented in Table 85 for SC and IV administration are used to calculate costs in the first year of treatment and subsequent years of treatment. These are presented in Table 124.

Table 124: Acquisition and administration costs per patient

Biologic therapy	First year	Subsequent year
Ixekizumab	[redacted]	[redacted]
Adalimumab	£9,968	£9,156
Etanercept	£10,604	£8,528
Infliximab	£14,523	£11,800
Ustekinumab	£10,793	£9,232

6.5 *Anticipated budget impact*

The projected cost of the biologic market without and with ixekizumab and the budget impact of ixekizumab over the period 2017-2021 are presented in Table 125.

Ixekizumab is associated with a total budget increase of £596,329 across the five years. Ixekizumab is associated with the second highest cost in the first year of initiating therapy and as such, there is a positive budget impact as ixekizumab displaces market shares of other therapies. The cost saving in the final year is due to the increasing number of patients who are receiving ixekizumab maintenance therapy in subsequent years since initiation as ixekizumab is associated with the lowest subsequent year cost compared to other biologics.

Table 125: Anticipated cost of biologic market without and with ixekizumab and budget impact, 2017-2021

Biologic therapy	2017	2018	2019	2020	2021
Without ixekizumab					
Adalimumab	£116,247,507	£109,382,963	£110,040,023	£110,719,723	£111,403,295
Etanercept	£31,085,336	£26,407,623	£26,565,874	£26,730,428	£26,895,480
Infliximab	£20,053,507	£17,168,618	£17,271,522	£17,378,482	£17,485,787

Biologic therapy	2017	2018	2019	2020	2021
Ustekinumab	£56,861,574	£50,630,367	£50,934,119	£51,249,197	£51,565,625
With ixekizumab					
Ixekizumab	£612,742	£2,745,760	£8,150,252	£16,516,676	£21,879,051
Adalimumab	£115,956,888	£108,033,462	£105,952,130	£102,207,462	£99,599,266
Etanercept	£31,007,623	£26,053,863	£25,506,202	£24,556,319	£23,953,777
Infliximab	£20,003,373	£16,940,071	£16,586,353	£15,971,168	£15,578,029
Ustekinumab	£56,719,420	£49,977,452	£48,968,383	£47,188,741	£46,008,917
Budget impact	£52,122	£161,037	£351,781	£362,536	-£331,147
Total budget impact	£596,329				

6.6 *Discussion*

The estimated budget impact does not capture potential savings for ixekizumab over the other biologics in terms of less time spent in BSC following discontinuation and lower overall non-responder costs. Monitoring costs were not included in the BIM as the budget impact was expected to be small in this category; nevertheless, there would be a slight saving for ixekizumab as an SC therapy over infliximab, which as an IV therapy is associated with more physician visits and tests.

A main limitation of the BIM is that its purpose is to provide an instantaneous overview of costs in each year, therefore the treatment sequence approach used in the cost-effectiveness analysis is not modelled in the BIM as the sequencing approach relies more on modelling the time dimension. This may exclude potential cost savings associated with the better PASI response of ixekizumab delaying entry to more expensive treatment states. In addition, secukinumab is excluded from the BI analysis. As the PAS discount for secukinumab is confidential, using the list price of secukinumab would result in a greatly overestimated cost-saving for ixekizumab.

7 References

1. European Medicines Agency. Taltz - Summary of product characteristics 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003943/WC500205804.pdf.
2. Clark RA. Resident memory T cells in human health and disease. Sci Transl Med. 2015;7(269):269rv1.
3. Witte E, Kokolakis G, Witte K, Philipp S, Doecke WD, Babel N, et al. IL-19 is a component of the pathogenetic IL-23/IL-17 cascade in psoriasis. J Invest Dermatol. 2014;134(11):2757-67.
4. Kim J, Krueger JG. The immunopathogenesis of psoriasis. Dermatol Clin. 2015;33(1):13-23.
5. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Arch Dermatol. 2005;141(12):1537-41.
6. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc. 2004;9(2):136-9.
7. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64 Suppl 2:ii18-23; discussion ii4-5.
8. National Institute for Health and Care Excellence. The assessment and management of psoriasis. NICE guidelines [CG153]. 2012.
9. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. J Am Acad Dermatol. 2014;70(5):871-81 e1-30.
10. Augustin M, Reich K, Glaeske G, Schaefer I, Radtke M. Co-morbidity and age-related prevalence of psoriasis: Analysis of health insurance data in Germany. Acta Derm Venereol. 2010;90(2):147-51.
11. Sato R, Milligan G, Molta C, Singh A. Health-related quality of life and healthcare resource use in European patients with plaque psoriasis: an association independent of observed disease severity. Clin Exp Dermatol. 2011;36(1):24-8.
12. Feldman SR, Burudpakdee C, Gala S, Nanavaty M, Mallya UG. The economic burden of psoriasis: a systematic literature review. Expert Rev Pharmacoecon Outcomes Res. 2014;14(5):685-705.
13. National Institute for Health and Care Excellence. Costing statement: Secukinumab for treating moderate to severe plaque psoriasis [TA350]. 2015.
14. Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.
15. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. N Engl J Med. 2016.

16. Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541-51.
17. Revicki D CD, Viswanathan H, et al. Improvement in patient reported symptoms and health related quality of life associated with achieving Psoriasis Area and Severity Index 100. Journal of the American Academy of Dermatology. 2013;68(4):AB202.
18. Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. J Eur Acad Dermatol Venereol. 2014;28(3):333-7.
19. Torbica A, Fattore G, Ayala F. Eliciting preferences to inform patient-centred policies: the case of psoriasis. Pharmacoeconomics. 2014;32(2):209-23.
20. Eli Lilly and Company Limited. UNCOVER-3 (RHBC) - Week 108 data. Data on file. 2016.
21. Eli Lilly and Company Limited. UNCOVER-1 (RHAZ) - Clinical Study Report (CSR). Data on file. 2016.
22. Eli Lilly and Company Limited. UNCOVER-2 (RHBA) - Clinical Study Report (CSR). Data on file. 2016.
23. Eli Lilly and Company Limited. UNCOVER-3 (RHBC) - Clinical Study Report (CSR). Data on file. 2016.
24. Bagel JD, K.C.; Bukhalo, M.; et al.,. Ease of use and confidence with auto-injector to administer ixekizumab in a phase 3 trial evaluated with Subcutaneous Administration Assessment Questionnaire (SQAAQ). American Academy of Dermatology; 2016; Washington, DC, United States.
25. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826-50.
26. Reich A, Welz-Kubiak K, Rams L. Apprehension of the disease by patients suffering from psoriasis. Postepy Dermatol Alergol. 2014;31(5):289-93.
27. Heidenreich R, Rocken M, Ghoreschi K. Angiogenesis drives psoriasis pathogenesis. Int J Exp Pathol. 2009;90(3):232-48.
28. Bergboer JG, Zeeuwen PL, Schalkwijk J. Genetics of psoriasis: evidence for epistatic interaction between skin barrier abnormalities and immune deviation. J Invest Dermatol. 2012;132(10):2320-31.
29. Di Meglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. Immunity. 2011;35(6):857-69.
30. Kunz S, Wolk K, Witte E, Witte K, Doecke WD, Volk HD, et al. Interleukin (IL)-19, IL-20 and IL-24 are produced by and act on keratinocytes and are distinct from classical ILs. Exp Dermatol. 2006;15(12):991-1004.
31. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. Arch Dermatol. 2010;146(8):891-5.
32. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013;2(2):e000062.

33. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med. 2011;124(8):775 e1-6.
34. Ahlehoff O, Skov L, Gislason G, Gniadecki R, Iversen L, Bryld LE, et al. Cardiovascular outcomes and systemic anti-inflammatory drugs in patients with severe psoriasis: 5-year follow-up of a Danish nationwide cohort. J Eur Acad Dermatol Venereol. 2015;29(6):1128-34.
35. Young Park J, Hyun Rim J, Beom Choe Y, Il Youn J. Facial psoriasis: comparison of patients with and without facial involvement. J Am Acad Dermatol. 2004;50(4):582-4.
36. Reich A, Hrehorow E, Szepietowski JC. Pruritus is an important factor negatively influencing the well-being of psoriatic patients. Acta Derm Venereol. 2010;90(3):257-63.
37. Augustin M, Kruger K, Radtke MA, Schwippl I, Reich K. Disease severity, quality of life and health care in plaque-type psoriasis: a multicenter cross-sectional study in Germany. Dermatology. 2008;216(4):366-72.
38. Meyer N, Paul C, Feneron D, Bardoulat I, Thiriet C, Camara C, et al. Psoriasis: an epidemiological evaluation of disease burden in 590 patients. J Eur Acad Dermatol Venereol. 2010;24(9):1075-82.
39. Korman NJ, Zhao Y, Li Y, Liao M, Tran MH. Clinical symptoms and self-reported disease severity among patients with psoriasis - Implications for psoriasis management. J Dermatolog Treat. 2015;26(6):514-9.
40. Globe D, Bayliss MS, Harrison DJ. The impact of itch symptoms in psoriasis: results from physician interviews and patient focus groups. Health Qual Life Outcomes. 2009;7:62.
41. Amatya B, Nordlind K. Focus groups in Swedish psoriatic patients with pruritus. J Dermatol. 2008;35(1):1-5.
42. Stinco G, Trevisan G, Piccirillo F, Pezzetta S, Errichetti E, di Meo N, et al. Pruritus in chronic plaque psoriasis: a questionnaire-based study of 230 Italian patients. Acta Dermatovenerol Croat. 2014;22(2):122-8.
43. Baker CS, Foley PA, Braue A. Psoriasis uncovered--measuring burden of disease impact in a survey of Australians with psoriasis. Australas J Dermatol. 2013;54 Suppl 1:1-6.
44. Lynde CW, Poulin Y, Guenther L, Jackson C. The burden of psoriasis in Canada: insights from the pSoriasis Knowledge IN Canada (SKIN) survey. J Cutan Med Surg. 2009;13(5):235-52.
45. Bundy C, Borthwick M, McAteer H, Cordingley L, Howells L, Bristow P, et al. Psoriasis: snapshots of the unspoken: using novel methods to explore patients' personal models of psoriasis and the impact on well-being. Br J Dermatol. 2014;171(4):825-31.
46. Brazzelli V, Carugno A, Alborghetti A, Grasso V, Cananzi R, Fornara L, et al. Prevalence, severity and clinical features of psoriasis in fingernails and toenails in adult patients: Italian experience. J Eur Acad Dermatol Venereol. 2012;26(11):1354-9.
47. Canpolat F, Cemil BC, Eskioglu F, Akis HK. Is facial involvement a sign of severe psoriasis? Eur J Dermatol. 2008;18(2):169-71.
48. Salonen SH. The EUROPSO psoriasis patient study: Treatment history and satisfaction reported by 17,990 members of european psoriasis patient associations 2003. Available from: http://www.europso.eu/media/archive2/europso_survey_en.pdf.

49. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris - Update 2015 - Short version - EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29(12):2277-94.
50. Levin AA, Gottlieb AB, Au SC. A comparison of psoriasis drug failure rates and reasons for discontinuation in biologics vs conventional systemic therapies. J Drugs Dermatol. 2014;13(7):848-53.
51. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66.
52. van de Kerkhof PC, Reich K, Kavanaugh A, Bachelez H, Barker J, Girolomoni G, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. J Eur Acad Dermatol Venereol. 2015;29(10):2002-10.
53. National Institute for Health and Care Excellence. DMARDs Scenario: Methotrexate. 2015. Available from: http://cks.nice.org.uk/dmards#!scenario:8.
54. Crowley J. Scalp psoriasis: an overview of the disease and available therapies. J Drugs Dermatol. 2010;9(8):912-8.
55. Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. Br J Dermatol. 2014;170(2):398-407.
56. Klaassen KM, van de Kerkhof PC, Pasch MC. Nail Psoriasis, the unknown burden of disease. J Eur Acad Dermatol Venereol. 2014;28(12):1690-5.
57. Okun MK, A; Signorovitch, J; Yang, M; Sundaram, M. Nail psoriasis significantly impairs health-related quality of life among patients with chronic plaque psoriasis. Journal of the American Academy of Dermatology. 2014;70(5):AB177.
58. Ortonne JP, Chimenti S, Reich K, Gniadecki R, Sprogel P, Unnebrink K, et al. Efficacy and safety of adalimumab in patients with psoriasis previously treated with anti-tumour necrosis factor agents: subanalysis of BELIEVE. J Eur Acad Dermatol Venereol. 2011;25(9):1012-20.
59. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. JAMA Dermatol. 2013;149(10):1180-5.
60. Schaarschmidt ML, Schmieder A, Umar N, Terris D, Goebeler M, Goerdt S, et al. Patient preferences for psoriasis treatments: process characteristics can outweigh outcome attributes. Arch Dermatol. 2011;147(11):1285-94.
61. Office for National Statistics. Population projections by the Office for National Statistics (England and Wales) 2014. Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/bulletins/nationalpopulationprojections/2015-10-29.
62. Health & Social Care Information Centre. Hospital episode statistics for England. Inpatient statistics, 2014-2015 2015. Available from: http://www.hscic.gov.uk/searchcatalogue?productid=18030&q=title%3a%22Provisional+Monthly+Hospital+Episode+Statistics%22&sort=Relevance&size=10&page=2#top.

63. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007;143(12):1493-9.
64. Office for National Statistics. Deaths Registered in England and Wales 2014. Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables.
65. National Institute for Health and Care Excellence. Psoriasis. NICE quality standard [QS40]. 2013.
66. National Institute for Health and Care Excellence. Grenz rays therapy for inflammatory skin conditions. NICE interventional procedure guidance [IPG236]. 2007.
67. National Institute for Health and Care Excellence. Apremilast for treating moderate to severe plaque psoriasis [TA368]. 2015.
68. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis [TA350]. 2015.
69. National Institute for Health and Care Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis [TA180]. 2009.
70. National Institute for Health and Care Excellence. Adalimumab for the treatment of adults with psoriasis [TA146]. 2008.
71. National Institute for Health and Care Excellence. Etanercept and efalizumab for the treatment of adults with psoriasis [TA103]. 2006.
72. National Institute for Health and Care Excellence. Infliximab for the treatment of adults with psoriasis [TA134]. 2008.
73. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987-1019.
74. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012;366(13):1190-9.
75. Gordon KB, Kimball AB, Chau D, Viswanathan HN, Li J, Revicki DA, et al. Impact of brodalumab treatment on psoriasis symptoms and health-related quality of life: use of a novel patient-reported outcome measure, the Psoriasis Symptom Inventory. Br J Dermatol. 2014;170(3):705-15.
76. Zhu B, Edson-Heredia E, Guo J, Maeda-Chubachi T, Shen W, Kimball AB. Itching is a significant problem and a mediator between disease severity and quality of life for patients with psoriasis: results from a randomized controlled trial. Br J Dermatol. 2014;171(5):1215-9.
77. Gordon KB, Leonardi CL, Lebwohl M, Blauvelt A, Cameron GS, Braun D, et al. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. J Am Acad Dermatol. 2014;71(6):1176-82.
78. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis (Supplementary Appendix). N Engl J Med. 2016.
79. Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials (Supplementary appendix). Lancet. 2015;386(9993):541-51.

80. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis 2004. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf Accessed March 2016.
81. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.
82. Kimball ABK, R.; Nikai, E; et al.,. Impact of ixekizumab on psoriasis itch severity and other patient reported outcomes: results from UNCOVER-1. 24th European Academy of Dermatology and Venereology Congress 2015; Copenhagen, Denmark.
83. Augustin MG, K.; Nikai, E.; et al., . The Impact of Ixekizumab Treatment on Health-Related Quality of Life in Patients with Moderate-to-Severe Psoriasis: Results from UNCOVER-1. 24th European Academy of Dermatology and Venereology Congress 2015; Copenhagen, Denmark.
84. Eli Lilly and Company Limited. UNCOVER-2 (RHBA) - Clinical Section of HTA Toolkit. Data on file. 2016.
85. Eli Lilly and Company Limited. UNCOVER-3 (RHBC) - Clinical Section of HTA Toolkit. Data on file 2016.
86. ELi Lilly and Company Limited. Primary Psoriasis Placebo-controlled Integrated Analysis Set. ITT population. Selected subgroups - Data on file. 2016.
87. Papp KW, J., Puig, L.; et al.,. Ixekizumab Shows Efficacy and Safety in Patients Who Failed Bi-weekly Etanercept Therapy: Analysis From UNCOVER-2, a Phase 3 Randomized Clinical Trial in Psoriasis. . American Academy of Dermatology; 2016; Washington, DC, United States.
88. Lacour JPD, Y.; Zhang, L. Efficacy of ixekizumab in patients with and without previous experience with biologic therapies: results from UNCOVER-2, a phase 3 trial in patients with plaque psoriasis. World Congres of Dermatology 2015; Vancouver, Canada.
89. Eli Lilly and Company Limited. Psoriasis Placebo- and Active-controlled Integrated Analysis Set (UNCOVER-2 and UNCOVER-3). ITT population. Data on file. 2016.
90. Eli Lilly and Company Limited. Primary Psoriasis Placebo-controlled Integrated Analysis Set. ITT population. Previous biologic use - Data on file. 2016.
91. Eli Lilly and Company Limited. Primary Psoriasis Placebo-controlled Integrated Analysis Set. ITT population. Patients elgibile for biologic use - Data on file. 2016.
92. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006;55(4):598-606.
93. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol. 2008;58(1):106-15.
94. Asahina A, Nakagawa H, Etoh T, Ohtsuki M, Adalimumab MSG. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. J Dermatol. 2010;37(4):299-310.

95. Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis. N Engl J Med. 2015;373(2):136-44.
96. Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. Circ Cardiovasc Imaging. 2013;6(1):83-90.
97. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003;349(21):2014-22.
98. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005;152(6):1304-12.
99. van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol. 2008;159(5):1177-85.
100. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003;139(12):1627-32; discussion 32.
101. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet. 2005;366(9494):1367-74.
102. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2004;51(4):534-42.
103. Torii H, Nakagawa H, Japanese Infliximab Study i. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010;59(1):40-9.
104. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007;56(1):31 e1-15.
105. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet. 2001;357(9271):1842-7.
106. Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. Chin Med J (Engl). 2012;125(11):1845-51.
107. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38.
108. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015;172(2):484-93.

109. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015;29(6):1082-90.
110. Thaci D, Blauvelt A, Reich K, Tsai TF, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol. 2015;73(3):400-9.
111. Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, Shen YK, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci. 2011;63(3):154-63.
112. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665-74.
113. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371(9625):1675-84.
114. Zhu X, Zheng M, Song M, Shen YK, Chan D, Szapary PO, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). J Drugs Dermatol. 2013;12(2):166-74.
115. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010;362(2):118-28.
116. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study G. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2012;39(3):242-52.
117. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. N Engl J Med. 2015;373(14):1318-28.
118. Strohal R, Puig L, Chouela E, Tsai TF, Melin J, Freundlich B, et al. The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). J Dermatolog Treat. 2013;24(3):169-78.
119. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet. 2006;367(9504):29-35.
120. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet. 2015;386(9993):552-61.
121. Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind,

placebo-controlled study of etanercept. J Am Acad Dermatol. 2012;67(1):86-92.
122. Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol. 2011;165(3):661-8.
123. Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol. 2011;165(3):652-60.
124. Meffert H, Brautigam M, Farber L, Weidinger G. Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile. Acta Derm Venereol. 1997;77(2):137-41.
125. Barker J, Hoffmann M, Wozel G, Ortonne JP, Zheng H, van Hoogstraten H, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol. 2011;165(5):1109-17.
126. European Medicines Agency. Secukinumab EPAR 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf.
127. ClinicalTrials.gov. A 52-week multicentre, randomised, blinded, parallel-group study comparing the efficacy and safety of ixekizumab with ustekinumab in patients with moderate-to-severe plaque psoriasis (NCT02561806) 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02561806?term=rhbs&rank=11.
128. ClinicalTrials.gov. A multicentre, randomised, double-blind study comparing the efficacy and safety of ixekizumab dosing regimens in patients with moderate-to-severe plaque psoriasis 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02513550?term=rhbp&rank=1.
129. Colombo GL, Di Matteo S, Peris K, Fargnoli MC, Esposito M, Mazzotta A, et al. A cost-utility analysis of etanercept for the treatment of moderate-to-severe psoriasis in Italy. Clinicoecon Outcomes Res. 2009;1:53-9.
130. Heinen-Kammerer T, Daniel D, Stratmann L, Rychlik R, Boehncke WH. Cost-effectiveness of psoriasis therapy with etanercept in Germany. J Dtsch Dermatol Ges. 2007;5(9):762-8.
131. Knight C, Mauskopf J, Ekelund M, Singh A, Yang S, Boggs R. Cost-effectiveness of treatment with etanercept for psoriasis in Sweden. Eur J Health Econ. 2012;13(2):145-56.
132. Pan F, Brazier NC, Shear NH, Jivraj F, Schenkel B, Brown R. Cost utility analysis based on a head-to-head Phase 3 trial comparing ustekinumab and etanercept in patients with moderate-to-severe plaque psoriasis: a Canadian perspective. Value Health. 2011;14(5):652-6.
133. Anis AH, Bansback N, Sizto S, Gupta SR, Willian MK, Feldman SR. Economic evaluation of biologic therapies for the treatment of moderate to severe psoriasis in the United States. J Dermatolog Treat. 2011;22(2):65-74.
134. Sawyer LM, Wonderling D, Jackson K, Murphy R, Samarasekera EJ, Smith CH. Biological therapies for the treatment of severe psoriasis in patients with

previous exposure to biological therapy: a cost-effectiveness analysis. Pharmacoeconomics. 2015;33(2):163-77.
135. Villacorta R, Hay JW, Messali A. Cost effectiveness of moderate to severe psoriasis therapy with etanercept and ustekinumab in the United States. Pharmacoeconomics. 2013;31(9):823-39.
136. Lloyd A, Reeves P, Conway P, Reynolds A, Baxter G. Economic evaluation of etanercept in the management of chronic plaque psoriasis. Br J Dermatol. 2009;160(2):380-6.
137. Sizto S, Bansback N, Feldman SR, Willian MK, Anis AH. Economic evaluation of systemic therapies for moderate to severe psoriasis. Br J Dermatol. 2009;160(6):1264-72.
138. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.
139. Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technol Assess. 2006;10(46):1-233, i-iv.
140. Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology. 2009;219(3):209-18.
141. Loveman E, Turner D, Hartwell D, Cooper K, Clegg A. Infliximab for the treatment of adults with psoriasis. Health Technol Assess. 2009;13 Suppl 1:55-60.
142. Turner D, Picot J, Cooper K, Loveman E. Adalimumab for the treatment of psoriasis. Health Technol Assess. 2009;13 Suppl 2:49-54.
143. Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A. Ustekinumab for the treatment of moderate to severe psoriasis. Health Technol Assess. 2009;13 Suppl 3:61-6.
144. Wade RH, S; Yang, H; Harden, M; Palmer, S; Woolacott, N,. Apremilast for treating moderate to severe plaque psoriasis 2015. Available from: https://www.nice.org.uk/guidance/TA368/documents/psoriasis-plaque-moderate-to-severe-apremilast-id679-committee-papers-4.
145. Cummins ES, N; Cruickshank, M; Fraser, C; Ormerod, A; Brazzelli, M. Secukinumab for treating moderate to severe plaque psoriasis 2015. Available from: https://www.nice.org.uk/guidance/TA350/documents/secukinumab-for-treating-moderate-to-severe-plaque-psoriasis-committee-papers2.
146. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. Br J Dermatol. 2010;163(4):807-16.
147. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1-10.
148. Eli Lilly and Company Limited. Clinical Section of HTA Toolkit for Pooled Studies. Data on file. 2015.
149. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013.
150. Kerdel F, Zaiac M. An evolution in switching therapy for psoriasis patients who fail to meet treatment goals. Dermatol Ther. 2015;28(6):390-403.

151. Pan Mersey Area Prescribing Committee. Sequential use of biological agents in the management of psoriasis 2013. Available from: http://www.panmerseyapc.nhs.uk/guidelines/documents/G13.pdf.
152. New Therapies Subgroup (Greater Manchester Medicines Management Group). The sequential use of biologic agents in the treatment of chronic or plaque psoriasis for those patients fulfilling NICE criteria for a biologic 2015. Available from: http://gmmmg.nhs.uk/docs/nts/NTS%20Biologic%20Agents%20-%20Sequential%20use%20in%20Psoriasis%200715.pdf.
153. Xin S. Markov modelling in healthcare economic evaluations. Chin J Evid-based Med. 2007;7(10):750-6.
154. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. Pharmacoeconomics. 1998;13(4):397-409.
155. Electronic Medicines Compendium. Summary of Product Characteristics: Humira 40 mg/0.8 ml pre-filled syringe and pre-filled pen 2016. Available from: https://www.medicines.org.uk/emc/medicine/21201.
156. Electronic Medicines Compendium. Summary of Product Characteristics: Stelara 45 mg solution for injection 2016. Available from: https://www.medicines.org.uk/emc/medicine/21425.
157. Electronic Medicines Compendium. Summary of Product Characteristics: Remicade 100mg for concentrate for solution for infusion 2016. Available from: https://www.medicines.org.uk/emc/medicine/3236/SPC/Remicade+100mg+powder+for+concentrate+for+solution+for+infusion/.
158. Electronic Medicines Compendium. Summary of Product Characteristics: Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen 2016. Available from: https://www.medicines.org.uk/emc/medicine/29848.
159. Electronic Medicines Compendium. Summary of Product Characteristics: Enbrel 25 mg powder and solvent for solution for injection 2016. Available from: https://www.medicines.org.uk/emc/medicine/3343.
160. National Clinical Guideline Centre. Psoriasis - Management of psoriasis clinical guideline methods, evidence and recommendations2012. Available from: http://www.nice.org.uk/guidance/cg153/resources/cg153-psoriasis-full-guideline3.
161. Ipsos Healthcare - Therapy Monitor Team. Therapy Monitor Report: EU5. Dermatology (Psoriasis). Study period Q1-2016. Data on file. . 2016.
162. Eedy DJ, Griffiths CE, Chalmers RJ, Ormerod AD, Smith CH, Barker JN, et al. Care of patients with psoriasis: an audit of U.K. services in secondary care. Br J Dermatol. 2009;160(3):557-64.
163. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol. 2015;172(1):244-52.
164. The Human Mortality Database [Internet]. Available from: http://www.mortality.org/.
165. EuroQoL Research Foundation. What is EQ-5D 2016. Available from: http://www.euroqol.org/.
166. Swinburn P, Lloyd A, Boye KS, Edson-Heredia E, Bowman L, Janssen B. Development of a disease-specific version of the EQ-5D-5L for use in patients suffering from psoriasis: lessons learned from a feasibility study in the UK. Value Health. 2013;16(8):1156-62.

167. Shikiar R, Heffernan M, Langley RG, Willian MK, Okun MM, Revicki DA. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. J Dermatolog Treat. 2007;18(1):25-31.
168. Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2008;158(3):549-57.
169. Reich K, Segaert S, Van de Kerkhof P, Durian C, Boussuge MP, Paolozzi L, et al. Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. Dermatology. 2009;219(3):239-49.
170. A Phase 3, Multi Site, Randomized, Double Blind, Placebo Controlled Study Of The Efficacy And Safety Comparing CP- 690,550 And Etanercept In Subjects With Moderate To Severe Chronic Plaque Psoriasis [Internet]. 2010. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01241591.
171. Efficacy and Safety of Subcutaneous Secukinumab (AIN457) for Moderate to Severe Chronic Plaque-type Psoriasis Assessing Different Doses and Dose Regimens (SCULPTURE) [Internet]. 2011. Available from: https://clinicaltrials.gov/ct2/show/NCT01406938.
172. Puig L, Strohal R, Husni ME, Tsai TF, Noppakun N, Szumski A, et al. Cardiometabolic profile, clinical features, quality of life and treatment outcomes in patients with moderate-to-severe psoriasis and psoriatic arthritis. J Dermatolog Treat. 2015;26(1):7-15.
173. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005;125(4):659-64.
174. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.
175. Etanercept biosimilar [Internet]. 2016. Available from: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=6049.
176. Fortune DG, Richards HL, Griffiths CE. Psychologic factors in psoriasis: consequences, mechanisms, and interventions. Dermatol Clin. 2005;23(4):681-94.
177. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. Br J Dermatol. 1995;132(2):236-44.
178. Ginsburg IH. Psychological and psychophysiological aspects of psoriasis. Dermatol Clin. 1995;13(4):793-804.
179. Fortune DG, Main CJ, O'Sullivan TM, Griffiths CE. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. Br J Dermatol. 1997;137(5):755-60.
180. Richards HL, Fortune DG, Griffiths CE, Main CJ. The contribution of perceptions of stigmatisation to disability in patients with psoriasis. J Psychosom Res. 2001;50(1):11-5.

181. Akay A, Pekcanlar A, Bozdag KE, Altintas L, Karaman A. Assessment of depression in subjects with psoriasis vulgaris and lichen planus. J Eur Acad Dermatol Venereol. 2002;16(4):347-52.
182. Pearce DJ, Singh S, Balkrishnan R, Kulkarni A, Fleischer AB, Feldman SR. The negative impact of psoriasis on the workplace. J Dermatolog Treat. 2006;17(1):24-8.
183. Zachariae H, Zachariae R, Blomqvist K, Davidsson S, Molin L, Mork C, et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. Acta Derm Venereol. 2002;82(2):108-13.
184. Mazzotti E, Picardi A, Sampogna F, Sera F, Pasquini P, Abeni D, et al. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. Br J Dermatol. 2003;149(2):318-22.
185. Finlay AY, Salek MS, Haney J, Alefacept Clinical Study G. Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis. Dermatology. 2003;206(4):307-15.
186. Touw CR, Hakkaart-Van Roijen L, Verboom P, Paul C, Rutten FF, Finlay AY. Quality of life and clinical outcome in psoriasis patients using intermittent cyclosporin. Br J Dermatol. 2001;144(5):967-72.
187. Kind PH, G; Macran, S. UK Population Norms for EQ-5D (Discussion Paper 172) 1999. Available from: http://www.york.ac.uk/che/pdf/DP172.pdf.
188. NHS reference costs 2014 to 2015. [Internet]. 2015. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477919/2014-15_Reference_costs_publication.pdf.
189. Department of Health. A simple guide to Payment by Results 2012. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477919/2014-15_Reference_costs_publication.pdf.
190. Consumer Prices Index, Special Aggregate: 06 Health [Internet]. 2016. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/l528.
191. Schaefer C, Mamolo C, Cappelleri JC, Le C, Daniel S, Mallbris L, et al. Disease Burden, Outcomes and Costs Among Adults Admitted To Hospital In The United Kingdom (Uk) Due to Plaque Or Erythrodermic Psoriasis. Value Health. 2015;18(7):A425.
192. Iskandar IY, Ashcroft DM, Warren RB, Yiu ZZ, McElhone K, Lunt M, et al. Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br J Dermatol. 2015;173(2):510-8.
193. Woods AL, Rutter KJ, Gardner LS, Lewis VJ, Saxena S, George SA, et al. Inpatient management of psoriasis: a multicentre service review to establish national admission standards. Br J Dermatol. 2008;158(2):266-72.
194. Agius EF, C; Smith,C. Clinical utility of virtual patient follow-up in a tertiary psoriasis service. British Journal of Dermatology. 2014(171 Suppl. 1).
195. Infliximab biosimilar [Internet]. 2015. Available from: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=5794.
196. Monthly Index of Medical Specialities [Internet]. 2016. Available from: http://www.mims.co.uk/.

197. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2015. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/.
198. NHS reference costs 2014 to 2015. National schedule of reference costs: the main schedule [Internet]. 2015. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.
199. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. In: Higgins JG, S editor.: The Cochrane Collaboration; 2011.
200. European Medicines Agency. Summary of opinion (initial authorisation) - Taltz (ixekizumab) 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003943/WC500202360.pdf.
201. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006;54(8):2368-76.
202. Reich K, Mrowietz U, Radtke MA, Thaci D, Rustenbach SJ, Spehr C, et al. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. Arch Dermatol Res. 2015;307(10):875-83.
203. Amgen. Highlights of prescribing information: Enbrel (R) (etanercept) 2015. Available from: http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf.
204. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. Value Health. 2012;15(6):843-50.
205. NICE Decision Support Unit. Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models 2011. Available from: http://www.nicedsu.org.uk/TSD%2013%20model%20parameters.pdf.
206. Office for National Statistics. Table A1-4, Principal Projection - England Summary 2015. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/tablea14principalprojectionenglandsummary.
207. Office for National Statistics. Table A1-5, Principal Projection - Wales Summary 2015. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/tablea15principalprojectionwalessummary.

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Single technology appraisal

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Dear Company,

The Evidence Review Group, Kleijnen Systematic Reviews Ltd., and the technical team at NICE have looked at the submission received on 8 July from Eli Lilly and Company Limited. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **10 August**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Anna Brett, Technical Lead (anna.brett@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Literature searching

A1. **PRIORITY REQUEST: Appendix 2, table 1** Please confirm if the Ovid search reported here is the correct search. It does not appear to match the search described in section 4.1.1 of the company submission (CS).

- If it is not the correct search please provide all full search strategies for each database used to inform section 4.1.1.
- If it is the correct search, please answer the following questions:
  - Please clarify whether Table 1 reports a full strategy or a search summary only. If this is a summary only, please provide full strategies for each database searched, including number of search results, as in Appendix 11, section 11.1.
  - The Evidence Review Group (ERG) is unclear about the rationale for the Ovid strategy reported in Table 1. It appears to be designed to retrieve data reporting either health-related quality of life (HRQoL) or adverse events only. Please clarify what the search intended to retrieve.
  - Please provide any additional strategies used for identifying papers on randomised controlled trials (RCTs) and non-RCTs for ixekizumab and any relevant indirect or mixed treatment comparators.

A2. **Appendix 2, table 2** In order to aid reproducibility please provide the number of search results for the Clinicaltrials.gov search, as in Appendix 11, section 11.1.

A3. **CS, section 4.1** states that searches were conducted in the following resources: PharmNet.bund, EUCTR, WHO ICTRP, European Medicines Agency (EMA), NICE and SMC. Please provide search dates and full strategies for these resources.

A4. **CS, section 4.11** states that “no relevant non-randomised or non-controlled evidence was identified from the evidence search". Please clarify which searches were used to inform this section.

A5. **CS, section 4.12** does not appear to report how information on adverse events was gathered. Please confirm if the Ovid search reported in Appendix 2, Table 1 was used to inform section 4.12. Please provide details of any other searches used to inform this section.

A6. **Appendix 13, section 13.1** Please clarify the results of the Cochrane search:

- At which points were results exported for review, i.e. beneath line #4 is an unnumbered line reporting an Economic Limit; does this refer to all papers within NHS EED on psoriasis and were they exported at this point?

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- Does line #12 refer to an HRQoL filter added to results for psoriasis across all Cochrane Library databases and were they exported at this point?
- Please confirm if line #13 is intended as a summary of these two sets of results? If this is a search summary, please provide the original full strategy.

References

A7. **Clinical study reports (CSRs)** The table of contents for all 3 CSRs include page numbers higher than the number of pages in the CSR. Please provide the full documents for the 3 UNCOVER trials.

A8. **CSRs** Please provide the CSR for the phase II study (NCT01107457).

PICO

A9. **PRIORITY REQUEST: CS, section 4.10.4** In the trials included in the network meta-analysis, please clarify:

- Is best supportive care (BSC) provided alongside the interventions and the comparators (including placebo)?
- If so, please describe the components of BSC, specifically for patients recruited in the UK and/or similar countries.

A10. **CS, section 4.1.3, table 7** Compared to the decision problem (CS, Table 1), phototherapy with ultraviolet (UVB) radiation seems to be missing from the inclusion criteria for the SLR. Please check and if this is correct please explain why phototherapy with ultraviolet (UVB) radiation has not been included.

Clinical effectiveness results

A11. **PRIORITY REQUEST: CS, section 4.7** The NICE scope defines the population as adults with moderate to severe plaque psoriasis, which is further defined in the comparators section as a) people for whom non-biologic systemic treatment or phototherapy is suitable, and b) people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. By comparing to biologic systemic treatment the company seems to have chosen only to analyse population b) in the clinical effectiveness section. However, this is not explicitly stated.

- Please explain why these two populations were not analysed separately in the clinical effectiveness section.
- Please either justify which of these populations the UNCOVER trials apply to if only one or provide data from each of the UNCOVER trials to show the number of patients in each of these populations as well as summaries of the patient characteristics for each population.

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- Please conduct all analyses (clinical effectiveness and cost effectiveness), also for the other population, i.e. population a) those for whom non-biologic systemic or phototherapy is suitable (including the following comparators: acitretin, ciclosporin, fumaric acid esters, methotrexate and phototherapy with ultraviolet (UVB) radiation).

A12. **CS, section 4.7.2** Please provide a version of Tables 35 and 36 of the CS with results of patients receiving etanercept (induction dosing period) + placebo (maintenance dosing period) and etanercept + ixekizumab 80 mg Q4W, respectively.

Subgroup analysis

A13. **CS, section 4.8** For the subgroup analyses presented, please provide measures of heterogeneity.

Network meta-analysis

A14. **CS, section 4.10** Please provide all datasets used in the NMA analyses (in WinBUGs format) which correspond to the results presented.

Section B: Clarification on cost-effectiveness data

Population and comparators

B1. **PRIORITY REQUEST: CS, section 5** Moderate to severe psoriasis was defined as PASI ≥ 10 and DLQI > 10 (Figure 4). However, the minimum baseline PASI score for enrolment in the UNCOVER trials was 12. NICE CG153 states that severe disease has been defined in NICE technology appraisals as a PASI of ≥ 10 and DLQI > 10.[1] Other authors have defined severe disease as PASI > 12.[2] To estimate utility input for the model, the subgroup of patients with DLQI >10 from the UNCOVER trials was used. For treatment response, the intention-to-treat population was used.

- Please justify how the UNCOVER trials are applicable to the population of moderate to severe psoriasis as opposed to only severe psoriasis.
- Please justify the difference in choice of data (subset) for each of these analyses.
- Please provide an analysis of treatment response and utility gain based on the subgroup of patients with DLQI >10 from the UNCOVER trials.

B2. **PRIORITY REQUEST: CS, section 5.7.1** The heading of Table 91 states: 'base-case results (Biologic-naïve patients with prior systemic failure, PASI >10 and DLQI ≥ 10)'. The treatment response rates used in the economic model are based on the NMA reported in section 4.10. The studies in this NMA included patients who are not biologic naïve, who may not have failed on systemic treatment, and who may not have a DLQI ≥ 10.

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- Please clarify which population is addressed in the base-case analysis, by describing which population the treatment response is based on, and how this relates to the population defined in the scope (moderate to severe plaque psoriasis in adults who are candidates for systemic therapy).
- Please clarify that this is consistent with the population of the UNCOVER trial.

B3. **PRIORITY REQUEST: CS, section 5.7** The NICE scope defines the population as adults with moderate to severe plaque psoriasis, which is further defined in the comparators section as a) people for whom non-biologic systemic treatment or phototherapy is suitable, and b) people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. By comparing to biologic systemic treatment, the company seems to have chosen only to analyse population b) in the cost-effectiveness section. However, this is not explicitly stated. In addition, the population is described as 'biologic naïve', which is only a sub-set of this population.

- Please explain why only one population appears to have been considered (that is, those with prior failure of systemic therapy), and confirm that the inputs for the model (response, utility gain, costs) are based on this specific population.
- If appropriate, please conduct an analysis using only clinical effectiveness data that are from the appropriate subgroup, i.e. for the biologic naïve then only use data from those who are biologic naïve.
- Please conduct all analyses (clinical effectiveness and cost effectiveness), also for the other population, i.e. population a) those for whom non-biologic systemic or phototherapy is suitable (including the following comparators: acitretin, ciclosporin, fumaric acid esters, methotrexate and phototherapy with ultraviolet (UVB) radiation).
- If the company defines the population in terms of biologic experience then please justify how the clinical effectiveness data are most appropriate for the biologic naïve as opposed to the biologic experienced.

B4. **CS, section 5** For the modelling of BSC:

- Please provide a definition of BSC as used in the economic model.
- In the model BSC includes an induction period. Please justify and describe the impact of (removing) this induction period on the model outcomes.

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B5. **CS, section 5.2.3, table 69** Please provide further justification of the treatment sequences used in the economic model:

- Please justify why market share would be an appropriate source to determine the order of biologic treatments in the sequence, and provide sensitivity analyses with alternative order of biologics in the treatment sequences.
- Please justify why treatments are only used once in a treatment sequence.
- Please justify why all treatment sequences consist of three biologics followed by BSC.
- Please confirm that the treatment sequences listed in Table 69 include all sequences used in UK current practice.

Model structure

B6. **PRIORITY REQUEST: CS, section 5.2.2** The model structure is based on health states defined by the response to treatment that is a function of a change in disease state and not absolute disease severity. The transition to the treatment maintenance health state is based on a percentage reduction in PASI score. As a result, patients in the treatment maintenance health state with a response may be heterogeneous in terms of quality of life and costs.

- Please justify the use of relative PASI reduction as opposed to absolute PASI reduction as measure of response. Please also justify the different PASI reduction threshold used (50, 75, 90, 100).
- Please justify the chosen structure by showing that patients with a response are homogeneous in terms of utility gain due to a response and to costs (medical resource use).

Treatment effectiveness

B7. **PRIORITY REQUEST: CS, section 5.2.4** Please justify why the discontinuation rate is equal for all comparators and constant over time.

- Please provide a sensitivity analysis using trial data to inform treatment specific discontinuation rates for the comparators, and the UNCOVER trial data to determine ixekizumab discontinuation rate.
- Please provide scenario analyses using changing treatment discontinuation rates over time.

B8. **CS, section 5.8.3, table 105** The scenario analysis on decreased efficacy in patients previously treated with biologics shows an increase in the ICER of ixekizumab versus etanercept. This seems a plausible scenario as failure of a biologic treatment is indicated to be a significant negative predictor of time to treatment discontinuation.[3]

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- Please justify why this effect is not used to estimate the treatment effect of biologics during the second and subsequent lines in the treatment sequence in the base-case analysis.

Health related quality of life

B9. **PRIORITY REQUEST: CS, section 5.4** Utility gain estimates were determined using linear regression.

- Please justify why PASI response is used to predict utility gain given it is difficult to describe the clinical severity for any specific PASI number (dramatic improvements in patients' appearances can be obtained without reaching the 75% in PASI).[4]
- Please use alternative methods, such as a gamma model (using a log-link) using transformed utility (1-utility) and provide tables with summary statistics for these different methods.
- Please provide in addition to the covariates used in equation 2, analyses with baseline PASI as a covariate, repeat these analyses without adjusting for baseline EQ-5D-5L, and provide summary statistics for these different analyses.
- Please check for interaction between PASI response and baseline EQ-5D-5L to assess whether the assumption of constant utility gain over time is justified.

B10. **CS, section 5.4** Please clarify how the utility gain estimates in Table 80 are determined using the ANOVA results presented in CS Table 70.

B11. **CS, section 5.4.4** Please perform a sensitivity analysis to show the impact of adverse events on both costs and utility on the results of the model.

B12. **CS, section 5.4** 100% PASI reduction is considered as a separate subgroup in the model.

- Please provide PASI response input for the model using 90-100% reduction subgroup (instead of 90-99% and 100% reduction separately), including utility gain.
- Please provide the results of a cost-effectiveness analysis using these model inputs.

B13. **CS, section 5.4.1** For all patients who dropped out before the end of the induction period (week 12), the last EQ-5D-5L value, if collected at the visit prior to drop-out, was used as an estimate for the week 12 value using the last-observation carried forward approach.

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- Please provide information on how many patients the last-observation carried forward approach was used for and at which time points EQ-5D-5L values were taken from.
- Please justify why the last-observation carried forward is a suitable method to handle these missing values.

B14. **CS, section 5.4.5** HRQoL is assumed to be constant over time in the analysis although EQ-5D-3L population norms for the UK general population are shown to decrease with age.

- Please justify why HRQoL is assumed to be constant and show how the HRQoL in the model compares to HRQoL of age-matched general UK population.

Costs

B15. **CS, section 5.5.2** The costs of BSC include inpatient costs, while this does not seem to be the case for the other treatments.

- Please justify why inpatient costs are included for BSC but not for other treatments.
- Please provide a sensitivity analysis using alternative estimates for BSC costs, for example, using BSC costs equal to the estimates provided by Fiona et al. (12 months after initiation of biological therapy instead of 12 months before biological initiation, CS Table 83).[6]

B16. **CS, section 5.5.2** Please clarify how the costs for becoming a non-responder were determined and provide further justification as to why these costs are not already covered by the costs incurred during the induction and maintenance periods.

B17. **CS, section 5.5.2** Please explain how the mean weight from UNCOVER, used to calculate the costs of infliximab, is representative for the population of patients with moderate to severe psoriasis in the UK.

B18. **CS, section 5.5.2** Please use the higher and lower quartiles of the NHS reference costs as inputs for the probabilistic sensitivity analysis and provide the results for this analysis.

B19. **CS, section 5.5.2** Please justify which assumptions the resource use for the induction and maintenance periods are based on (CS Table 87). Please provide the primary source.

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Results

B20. **CS, section 5.7** Please provide a summary of life years gained by health state using the format of Table 93 of the CS.

Excel model

B21. **PRIORITY REQUEST:** The model is programmed in VBA with an Excel user interface. The variables used in the VBA code are not defined, nor linked to the CS report. This severely hampers the transparency of the model.

- Please provide a full list of all parameter names used in the model.
- In addition, for each parameter in this list, provide the name used in the VBA code, the name used in the Excel sheet, cell reference in Excel sheet, a description, the value if applicable, se (standard error) and if applicable the corresponding name/description used in the CS report, as listed in the CS report (summary of variables applied in the economic model). As an example we completed the Table for "inputStartAge" (see Table below).

B22. The model can only calculate the results of ixekizumab versus one comparator at a time. As a consequence, a fully incremental probabilistic analysis with all comparators cannot be performed easily.

- Please adapt the model to make this possible, i.e. by incorporating the possibility to include all comparators simultaneously.

B23. In order to reproduce the results and to increase the transparency of the VBA code and the Excel interface, please explain whether/how the state trace PASI response (columns AI-BD) of the Patient distribution tabs can be calculated by using the 'Transition matrix'-tab.

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Parameter name VBA code	Parameter name Excel sheet	Reference in Excel sheet	Value	Se	Description	CS cross reference	Source
inputStartAge	UIStartAge	Main!D11	45	NA	Baseline age	Tables 66 and 90	baseline in the UNCOVER trials[7]
…							

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References

[1] National Clinical Guideline Centre. *Psoriasis: assessment and management of psoriasis. Clinical Guideline: methods, evidence and recommendations. October 2012. Commissioned by the National Institute for Health and Clinical Excellence [Internet]*. London: National Clinical Guideline Centre, 2012 [accessed 22.7.16] Available from: https://www.nice.org.uk/guidance/cg153/evidence/full-guideline-188351533

[2] Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology* 2005;210(3):194-9.

[3] Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol* 2015;172(1):244-52.

[4] Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *J Am Acad Dermatol* 2004;51(4):563-9.

[5] Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T. How good are clinical severity and outcome measures for psoriasis? Quantitative evaluation in a systematic review. *J Invest Dermatol* 2010;130(4):933-43.

[6] Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. *Br J Dermatol* 2010;163(4):807-16.

[7] Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med* 2016: Epub 2016 Jun 8.

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Single technology appraisal

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Dear Company,

The Evidence Review Group, Kleijnen Systematic Reviews Ltd., and the technical team at NICE have looked at the submission received on 8 July from Eli Lilly and Company Limited. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **10 August**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Anna Brett, Technical Lead (anna.brett@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Literature searching

A1. **PRIORITY REQUEST: Appendix 2, table 1** Please confirm if the Ovid search reported here is the correct search. It does not appear to match the search described in section 4.1.1 of the company submission (CS).

- If it is not the correct search please provide all full search strategies for each database used to inform section 4.1.1.

The search reported in the table is correct and represents the search strategy conducted to inform section 4.1.1. Additional information on the OVID search strategy is provided in Table 1.

- If it is the correct search, please answer the following questions:
  - Please clarify whether Table 1 reports a full strategy or a search summary only. If this is a summary only, please provide full strategies for each database searched, including number of search results, as in Appendix 11, section 11.1.

Due to an oversight from our partner agency that conducted the literature review, it is not possible to provide the full strategies in the format requested. The search strings provided in Table 1 have been re-run but due to likely differences in indexing in the time between the original search and now, numerical differences will be apparent between a new search and the results reported in the PRISMA diagram in the submission. It should be noted, however, that the shortlisted studies populating the network meta-analysis (NMA) are consistent with those included in recent NICE STAs which infers that all relevant evidence has been identified and appropriately incorporated.

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Table 1: OVID search strategy

Search	Search terms
1	Psoriasis.ti,ab
2	(Ixekizumab or acitretin or apremilast or adalimumab or brodalumab or c#closporin* or etanercept or fumaric acid esters or guselkumab or infliximab or methotrexate or namilumab or ponesimod or PUVA or secukinumab or tildrakizumab or tofacitinib or ustekinumab).mp.
3	(PASI or PGA or sPGA or IGA or SF-36 or DLQI or patient global assessment or skin pain VAS or QIDS or EQ-5D or HADS or depression or WPAI or work productivity or productivity or healthcare resource utili#ation or itch or itch VAS or itch NRS).mp.
4	(Infection* or adverse event* or death or malignancy or immunogenicity or injection site reaction* or infusion reaction* or withdrawal* or severe adverse effect* or serious adverse effect* or Treatment-emergent adverse events or cardiovascular event*).mp.
5	3 or 4
6	1 and 2 and 5
7	limit 6 to english language [Limit not valid in Econlit,ACP Journal Club,CDSR,CLCMR,DARE; records were retained]
8	limit 7 to yr="1990 - 2014" [Limit not valid in DARE; records were retained]
9	remove duplicates from 8
10	limit 7 to yr="2014 - 2015" [Limit not valid in DARE; records were retained]
11	remove duplicates from 10
12	9 or 11
13	remove duplicates from 12

- The Evidence Review Group (ERG) is unclear about the rationale for the Ovid strategy reported in Table 1. It appears to be designed to retrieve data reporting either health-related quality of life (HRQoL) or adverse events only. Please clarify what the search intended to retrieve.

The search strategy was not limited to only HRQoL and AEs. Inclusion of the following terms allowed retrieval of data on key clinical efficacy measures: PASI, PGA, sPGA, IGA, itch, itch NRS.

- Please provide any additional strategies used for identifying papers on randomised controlled trials (RCTs) and non-RCTs for ixekizumab and any relevant indirect or mixed treatment comparators.

A review of conference proceedings from 2013 to 2014 was conducted in the original SLR grey literature search. Alongside conference abstracts, key databases relevant to the markets of interest were searched in a structured, non-systematic fashion to provide additional strategic insight and supplementary data. Due to access restrictions and language barriers, certain conference proceedings and databases that were included within the psoriasis grey literature search protocol were reviewed

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separately by Lilly's affiliate teams rather then by the reviewers conducting the search. Details of the conference proceedings searched by can be seen in Table 2.

Table 2: Psoriasis grey literature search for the original SLR

Grey literature	
Key dermatological society conferences	Value in Health Journal/ISPOR (International) Pso: Gene to Clinic
Country-specific databases	Health Quality Ontario (HQO) Ottawa Hospital Research Institute (OHRI) McMaster University Health Forum British Association of Dermatologists (BAD) Australia and New Zealand Clinical Trials Registry (ANZCTR)
Key dermatology conferences	American Academy of Dermatology European Academy of Dermatology and Venereology International Investigative Dermatology Society for Investigative Dermatology World Congress of Dermatology
Country-specific databases	Japanese Medical Research Database (Igaku-Chuo-Zasshi (ICHUSHI))

In addition, a review of conference proceedings of the last 12 months (November 2014 to November 2015) was conducted. The key dermatological society conferences searched were:

- ***American Academy of Dermatology***
- ***European Academy of Dermatology and Venereology (EADV)***
- ***World Congress of Dermatology***

A2. **Appendix 2, table 2** In order to aid reproducibility please provide the number of search results for the Clinicaltrials.gov search, as in Appendix 11, section 11.1.

Using the search terms as described in Appendix 2, table 2 yielded the following results:

For the period 16/10/1994 to 16/10/2014 – 106 relevant studies (original search)

For the period 01/12/2014 to 11/12/2015 – two relevant studies (updated search)

As per the response to A1, this is all the information that can be provided for the clincialtrials.gov search.

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A3. **CS, section 4.1** states that searches were conducted in the following resources: PharmNet.bund, EUCTR, WHO ICTRP, European Medicines Agency (EMA), NICE and SMC. Please provide search dates and full strategies for these resources.

The specific term searched for on the above sites was "psoriasis". These searches were performed in the month of November 2015. Please see response to question A1

A4. **CS, section 4.11** states that "no relevant non-randomised or non-controlled evidence was identified from the evidence search". Please clarify which searches were used to inform this section.

To clarify, the primary aim of the SLR was to populate the NMA and to identify relevant evidence for ixekizumab. Due to the availability of data from three RCTs for ixekizumab and multiple RCTs for other relevant comparators, non-randomised/non-controlled evidence was not actively searched for in the SLR. This should have been made more explicit in the above statement in the submission and is reflected in the exclusion criteria outlined below:

- ***Studies pooling moderate to severe psoriasis results with other comorbidities (e.g. PsA), and not presenting results separately***
- ***Cohort studies***
- ***Cross-sectional studies***
- ***Epidemiological/ecological studies***
- ***Observational studies***
- ***Case-control studies***
- ***Editorials***
- ***Single case reports***
- ***Letters***
- ***Animal studies.***

For completeness, the inclusion criteria from the updated search protocol are shown below:

- ***Clinical trials, including randomised clinical trials and open-label trials, phase II–IV***
- ***Publications presenting un-pooled data relating to moderate to severe psoriasis***
- ***NMAs/MTCs of comparators listed above***
- ***Human studies.***

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A5. **CS, section 4.12** does not appear to report how information on adverse events was gathered. Please confirm if the Ovid search reported in Appendix 2, Table 1 was used to inform section 4.12. Please provide details of any other searches used to inform this section.

The data presented on adverse events in Section 4.12 was collected from the UNCOVER-1, -2 and -3 studies and not from the SLR. Information was taken from journal publications and the CSRs which have been shared with NICE.

A6. **Appendix 13, section 13.1** Please clarify the results of the Cochrane search:

- At which points were results exported for review, i.e. beneath line #4 is an unnumbered line reporting an Economic Limit; does this refer to all papers within NHS EED on psoriasis and were they exported at this point?

This is the original full search terms entered into the Cochrane database. Results from the Cochrane search were all exported on the same date (08/02/2016).

The non-numbered row under line #4 ("Limit: Economic evaluations") refers to the economic evaluation limit applied to the results on line #4 in order to capture all the relevant studies from a broad search. Studies related to economic evaluations were exported at this point.

- Does line #12 refer to an HRQoL filter added to results for psoriasis across all Cochrane Library databases and were they exported at this point?
- Please confirm if line #13 is intended as a summary of these two sets of results? If this is a search summary, please provide the original full strategy.

Line #12 refers to the application of the filter for HRQoL studies in lines #5 to #11 to the psoriasis disease studies identified by line #4. Studies related to HRQoL were exported as this point. Line #13 is not a search strategy line entered into the Cochrane database but a description of the two sets of results (Economic evaluations and HRQoL) combined in line #12.

References

A7. **Clinical study reports (CSRs)** The table of contents for all 3 CSRs include page numbers higher than the number of pages in the CSR. Please provide the full documents for the 3 UNCOVER trials.

Full CSRs for the UNCOVER studies have been sent via encrypted USB to NICE. We believe that all relevant information was provided in the CSRs originally provided as the full reports we have now provided are 20-30,000 pages long and contain individual patient laboratory results, adverse event reports etc. that are unlikely to add any additional pertinent information.

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A8. **CSRs** Please provide the CSR for the phase II study (NCT01107457).

The CSR for the phase II study (NCT01107457) has been sent via encrypted USB to NICE.

PICO

A9. **PRIORITY REQUEST: CS, section 4.10.4** In the trials included in the network meta-analysis, please clarify:

- Is best supportive care (BSC) provided alongside the interventions and the comparators (including placebo)?

BSC, as defined in the economic model, was not allowed in parallel of the intervention(s) in the UNCOVER-1, -2 and -3 studies. We believe that similar trial design is common to all recent and ongoing trials for biologic/non biologic treatments for psoriasis and is therefore consistent with past and more recent NICE appraisals for interventions in psoriasis. Further detail on this aspect of the issue is provided below.

As stated in the submission, the studies evaluated the effectiveness of monotherapy ixekizumab vs monotherapy placebo or monotherapy etanercept.

Concurrent use of the following agents was prohibited in UNCOVER-1:

- ***PUVA, cortico-steroids, methotrexate, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives; or 1, 25 dihydroxy vitamin D3 and analogues or phototherapy or self-treatment with tanning beds or therapeutic sunbathing or topical psoriasis therapy with psoralens within 4 weeks prior to baseline.***
- ***Topical psoriasis treatment (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene) within the previous 2 weeks prior to baseline.***
- ***Concurrent or recent use of any biologic agent within the following washout periods: etanercept <28 days; infliximab, adalimumab, or alefacept <60 days; golimumab <90 days; ustekinumab <8 months; rituximab or efalizumab <12 months; or any other biologic agent <5 half-lives prior to baseline.***
- ***Concurrent or have ever received prior natalizumab or other agents that target alpha-4-integrin.***

Concurrent use of the agents listed above was also prohibited in the UNCOVER-2 and -3 studies, in addition to prior etanercept use being an exclusion.

The use of topical treatments was allowed in specific circumstances (although these were not permitted to be used within 12 hours of a study visit), such as:

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- ***For ethical reasons, some topical treatments are allowed to control symptoms in specific body locations***
- ***Topical steroids were permitted for use limited to the face, axilla, and/or genitalia; non-medicated shampoos (for example, which do not contain corticosteroids, coal tar, or vitamin D3 analogues) will be permitted; emollients that do not contain alpha or beta hydroxyl acids were permitted.***

From publically available literature on the use of parallel interventions in other biologic RCTs including secukinumab, BSC, as defined in the economic model, is not provided alongside the interventions of interest.

According to the ERASURE/FIXTURE protocol, secukinumab was also assessed as a monotherapy option. Table 5-1, P41 of the study protocol indicates the following treatments were prohibited with the wash period recorded in brackets

- ***Alefacept, briakinumab, efalizumab, ustekinumab (6 months)***
- ***Adalimumab, etanercept, infliximab (12 weeks)***
- ***Methotrexate, cyclosporine A, corticosteroids cyclophosphamide (4 weeks)***

The protocol also indicates (P40) topical cortico-steroid of mild or moderate activity was allowed for the face, scalp and genitoanal area during the screening period. But not after the subject has been randomized. Use of topical cortico-steroids was to be recorded on the concomitant medications electronic case report/record form. This is similar to other clinical studies for biologics in psoriasis.

- If so, please describe the components of BSC, specifically for patients recruited in the UK and/or similar countries.

Please refer to the information provided above regarding concomitant therapies. To confirm, UK patients were required to comply with the same restrictions stated.

A10. **CS, section 4.1.3, table 7** Compared to the decision problem (CS, Table 1), phototherapy with ultraviolet (UVB) radiation seems to be missing from the inclusion criteria for the SLR. Please check and if this is correct please explain why phototherapy with ultraviolet (UVB) radiation has not been included.

Please note the inclusion of 'Phototherapy with ultraviolet (UVB) radiation' should not have beeen included in the 'Decision problem addressed in the company submission' column of Table 1 of the CS.

The SLR did not include UVB in the inclusion criteria. The original search strategies were designed before the NICE scope was confirmed and also before the final licensed label was confirmed. As noted in section 3.3.2 of the submission, we expect ixekizumab to occupy a similar position in the treatment pathway to current biologics,

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so it could be argued that the inclusion of UVB is of limited relevance. The following points should also be taken into account:

<u>Second-line options</u>: Current NICE pathway guidance[1] indicates second-line therapies for psoriasis include the phototherapies (broad- or narrow-band ultraviolet B [NB-UVB] light and psoralen plus UVA light [PUVA]. PUVA was included in the inclusion criteria, so a NICE recommended phototherapy was included in the SLR.

<u>Clinical effectiveness</u>: Evidence based recommendations (2012) based on an expert dermatologist panel indicate PUVA is more effective than NB-UVB with response rates of 80% and 70%, respectively.[2]

Both PUVA and UVB are eligible options in the UK. NICE guidelines[3] are consistent with EU recommendation's and indicate PUVA is more effective than NB-UVB for achieving clearance of plaques when both are used twice a week, however, NICE go on to indicate both PUVA and NB-UVB are comparable when PUVA is used twice a week and NB-UVB is given three times a week.[4] NICE guidelines indicate there is a trend towards topical PUVA being more effective than NB-UVB, but this was not statistically significant.[3]

Both PUVA and NB-UVB should be given intermittently, for short-term courses (~30 sessions) with EU recommendations indicating the maximum number of treatments in a life-time for either PUVA or NB-UVB to be 250-300 treatments.[2]

NICE guideline CG153 indicates that following treatment with NB-UVB, most patients relapse; time to relapse is variable. For patients who relapse rapidly, the time, inconvenience, cost incurred when multiple courses of UVB are required to maintain disease control, together with potential ageing and any unknown risk of skin cancer, mean that further courses of UVB may not be appropriate and other treatments be considered.[3,4]

NICE indicate that alternative therapy should be used when patients have had a rapid relapse defined as greater than 50% of baseline disease severity within 3 months.

Given that PUVA treatment twice weekly is at least as effective as NB-UVB three times weekly and induces longer remissions[5], both treatments are only recommended for short-term, intermittent use and UVB has been associated with rapid loss of response, where alternative options such as systemic therapies become the mainstay of treatment, it is unclear that any clinical data regarding UVB would impact on the outcomes of the economic model given that PUVA evidence was searched for in the literature review.

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Clinical effectiveness results

A11. **PRIORITY REQUEST: CS, section 4.7** The NICE scope defines the population as adults with moderate to severe plaque psoriasis, which is further defined in the comparators section as a) people for whom non-biologic systemic treatment or phototherapy is suitable, and b) people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. By comparing to biologic systemic treatment the company seems to have chosen only to analyse population b) in the clinical effectiveness section. However, this is not explicitly stated.

- Please explain why these two populations were not analysed separately in the clinical effectiveness section.

The two populations above were in effect eligible for all three UNCOVER studies- i.e. the populations in the studies consisted of patients who had not had any prior systemic non-biologic therapy, had had prior systemic non-biologic therapy and had had prior biologic therapy. The analyses in clinical effectiveness section are provided for the ITT population and the studies were not pre-specified to recruit patients stratified by the populations stated in the question. Full inclusion/exclusion criteria for the studies have been provided in the submission with the only other point of note being that patients in UNCOVER 2/3 were not allowed to have had prior exposure to etanercept.

We believe these criteria to be consistent with all recent studies for psoriasis treatment that have been assessed by NICE and It is anticipated that ixekizumab will have a similar place in the clinical pathway to NICE approved biologics, i.e. after standard therapies have failed/ are contraindicated or are not tolerated. Further details on the positioning of ixekizumab can be seen in Section 3.3.2 of the CS.

- Please either justify which of these populations the UNCOVER trials apply to if only one or provide data from each of the UNCOVER trials to show the number of patients in each of these populations as well as summaries of the patient characteristics for each population.

- Please conduct all analyses (clinical effectiveness and cost effectiveness), also for the other population, i.e. population a) those for whom non-biologic systemic or phototherapy is suitable (including the following comparators: acitretin, ciclosporin, fumaric acid esters, methotrexate and phototherapy with ultraviolet (UVB) radiation).

The baseline characteristics of the relevant population and the clinical effectiveness results have been sent to NICE via encrypted USB. As responses are consistent with between the populations in question and the ITT population, the results of the NMA

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which populate the economic model can be considered as valid for the analyses presented in the submission.

A12. **CS, section 4.7.2** Please provide a version of Tables 35 and 36 of the CS with results of patients receiving etanercept (induction dosing period) + placebo (maintenance dosing period) and etanercept + ixekizumab 80 mg Q4W, respectively.

Table 3: UNCOVER-2: Maintenance of Response, Results of sPGA (0,1) response at week 60 - NRI (Maintenance Dosing Period Primary Population)

	ETNResp/PBO (N=132)	ETNNonR/IXEQ4W (N=200)
sPGA (0,1), n (%)	**xxxxxxxxxxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxxxxxxxxxx**

ETN = Etanercept; IXE80Q4W = Ixekizumab 80 mg Q4W; Resp = responder; NonR = Non-responder; NRI = non-responder imputation; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; sPGA = static Physician's Global Assessment.

Patients treated with etanercept during the induction period, received two injections of placebo at week 12, then ixekizumab 80 mg Q4W starting at week 16 (i.e. after a four week wash-out) through to week 60

Source: CSR RHBA, Table RHBA 14.65; Page 2,368

Table 4: UNCOVER-2: Maintenance of Response, results of PASI 75, 90 and 100 response at week 60 - NRI (Maintenance Dosing Period Primary Population)

	ETNResp/PBO (N=132)	ETNNonR/IXEQ4W (N=200)
PASI 75, n (%)	**xxxxxxxxxxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxxxxxxxxxx**
PASI 90, n (%)	**xxxxxxxxxxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxxxxxxxxxx**
PASI 100, n (%)	**xxxxxxxxxxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxxxxxxxxxx**

ETN = Etanercept; IXE80Q4W = Ixekizumab 80 mg Q4W; Resp = responder; NonR = Non-responder; NRI = non-responder imputation; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = Psoriasis Area and Severity Index; PBO = placebo.

Patients treated with etanercept during the induction period, received two injections of placebo at week 12, then ixekizumab 80 mg Q4W starting at week 16 (i.e. after a four week wash-out) through to week 60.

Source: CSR RHBA, Table RHBA.14.75, Page 2,664 (PASI75); Page 2,674 (PASI90); Page 2,684 (PASI100)

Odds ratios have not been provided as the UNCOVER -2 and-3 studies were only designed to compare inferential statistics between re-randomized treatment groups in the blinded maintenance period.

- ***The patients in the ETNNonR/IXE80Q4W arm were not randomised (as only responder patients were re-randomised) and should not be compared to responders re-randomised to receive IXE80Q4W, IXE80Q12W or placebo.***
- ***The ETNNonR/IXE 80 Q4W arm should NOT be compared to ETNResp/PBO arm as it is inappropriate to compare a responder population with a non-responder population.***

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Subgroup analysis

A13. **CS, section 4.8** For the subgroup analyses presented, please provide measures of heterogeneity.

Heterogeneity can be assessed by examining the study designs, inclusion and exclusion criteria and the baseline demographic characteristics of participants in the trials. In addition, for subgroup analysis, if absolute treatment effects are consistent within subgroups and between studies relative to the overall pooled treatment effects then studies can be considered comparable. Finally, in order to perform a test for heterogeneity, for a meta-analysis using individual patient data (IPD), for the treatment effect across the three studies (UNCOVER-1, -2 and -3) used in this submission it is necessary to include a by study (or protocol) treatment interaction term in any fitted model for the pooled analysis. If the interaction is non-significant at the 0.05 level, it can be concluded that there are no differences in the reported effects across studies, in other words there is no heterogeneity.

Three pivotal phase III randomised controlled trials (UNCOVER-1, -2 and -3) investigated the efficacy and safety of ixekizumab in patients with moderate-to-severe psoriasis (mean baseline PASI score of approximately 20). The trials were identical in design until the end of the controlled induction period (Week 12) as well as patient inclusion and exclusion criteria (with the exception of the exclusion of patients who had previously received etanercept in UNCOVER-2 and -3)(Table 5). In addition, patients from similar countries were recruited into the trials (Table 6). There were no significant differences in patient demographics or disease severity however trials including etanercept as an active comparator (UNCOVER-2 and -3) had lower rates of prior experience with a biological agent (Table 7 and Table 8), which reflects the additional exclusion criteria related to prior etanercept use. There is no evidence that prior biological exposure modifies PASI 75 treatment response to ixekizumab (treatment*previous biologics therapy p-value: UNCOVER-1: p=0.838, UNCOVER -2: p=0.230 and UNCOVER -3: p=0.835).

Analyses of selected subgroups for each of the individual studies suggests that there was low heterogeneity across the UNCOVER studies (Table 9).

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Table 5: Comparative summary of ixekizumab randomised trials

	Trial design	N	Interventions*	Treatment duration	Summary of main population characteristics	Measures		
						Primary	Key efficacy	Key safety
UNCOVER-1	MC, P3, R, DB, PC, PG	1296	Ixekizumab 80mg Q2W or Q4W induction Q4W or Q12W maintenance Placebo	Induction: 12w Maintenance: 48w LT Extension: 216w	Adults ≥18 years Psoriasis ≥6m Moderate to severe: PASI score ≥12 AND, sPGA ≥3 AND BSA ≥10%	PASI 75 Week 12 sPGA (0,1) Week 12	PASI sPGA	AE AESI Labs
UNCOVER-2	MC,P3, R, DB, PC, AC, PG	1224	Ixekizumab 80mg Q2W or Q4W induction Q4W or Q12W maintenance Placebo Etanercept 50mg BIW	Induction: 12w Maintenance: 48w LT Extension: 216w	Adults ≥18 years Psoriasis ≥6m Moderate to severe: PASI score ≥12 AND, sPGA ≥3 AND BSA ≥10%	PASI 75 Week 12 sPGA (0,1) Week 12	PASI sPGA	AE AESI Labs
UNCOVER-3	MC, P3, R, DB, PC, AC, PG	1346	Ixekizumab 80mg Q2W or Q4W induction Q4W or Q12W maintenance Placebo Etanercept 50mg BIW	Induction: 12w LT Extension: 252w	Adults ≥18 years Psoriasis ≥6m Moderate to severe: PASI score ≥12 AND, sPGA ≥3 AND BSA ≥10%	PASI 75 Week 12 sPGA (0,1) Week 12	PASI sPGA	AE AESI Labs

AC = active comparator; AE = adverse events; AESI = adverse events of special interest; BIW = twice-weekly; BSA = body surface area; DB= double blind; DLQI = dermatology life quality index; Labs = laboratory evaluations; MC=multicentred; P3 = phase 3; PASI = psoriasis area and severity index; PASI 75 = 75% improvement in PASI score; PC=placebo controlled; PG parallel group; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; R=randomised; sPGA = static physician global assessment.

*All trials permitted cross-over at some point; however, efficacy data is available for all trials prior to patient cross-over

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Table 6: Logistical information of trials used to conduct the indirect comparison

Trial	N	Date	Countries
UNCOVER-1	1,296	Dec 2011 to Jun 2014 (W60) LTE ongoing	108 sites in Australia, Canada, Denmark, Germany, Hungary, Italy, Japan, Poland, Romania, United Kingdom, and USA
UNCOVER-2	1,224	May 2012 to Feb 2015 (W60) LTE ongoing	126 sites in Australia, Austria, Canada, Czech Republic, Germany, France, Netherlands, Poland, Romania, Spain, United Kingdom, and USA
UNCOVER-3	1,346	July 2012 to Apr 2015 (W60) LTE ongoing	126 sites in Argentina, Bulgaria, Canada, Chile, Germany, Hungary, Mexico, Poland, Russia, and USA

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Table 7: Baseline demographics of participants in the UNCOVER studies

	Age, y mean (SD)	Male %	Race, %			Weight, kg mean (SD)	BMI mean (SD)	PsO duratn, y mean (SD)	PsA %
			White	Asian	Other				
UNCOVER-1									
Ixekizumab Q2W	45.1 (12.4)	67.2	92.6	4.2	3.2	92.4 (22.7)	30.8 (7.1)	19.9 (11.9)	27.5
Placebo	46.4 (13.4)	70.3	93.0	4.9	2.1	91.8 (25.0)	30.4 (7.6)	19.5 (11.7)	26.7
UNCOVER-2									
Ixekizumab Q2W	44.5 (13.3)	63.0	94.3	3.4	2.3	89.2 (21.6)	30.1 (7.0)	18.3 (12.1)	24.8
Placebo	45.3 (12.1)	71.4	88.7	3.6	7.7	91.8 (21.9)	30.9 (7.1)	19.1 (12.7)	28.0
Etanercept	45.3 (12.8)	65.9	93.5	2.3	4.2	92.9 (22.4)	31.3 (7.3)	18.9 (12.5)	22.1
UNCOVER-3									
Ixekizumab Q2W	45.6 (13.1)	66.0	93.8	3.1	3.1	90.4 (23.4)	30.2 (7.1)	17.8 (12.2)	20.0
Placebo	46.4 (12.1)	71.0	91.2	3.6	5.2	91.0 (21.5)	30.2 (6.3)	18.2 (12.5)	21.8
Etanercept	45.8 (13.8)	70.4	91.9	2.9	5.2	92.2 (24.3)	30.7 (7.6)	18.1 (11.8)	18.8

BMI = body mass index; PsA = psoriatic arthritis; PsO = psoriasis; SD = standard deviation

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Table 8: Baseline demographics of participants in the UNCOVER studies

	PASI score mean (SD)	%BSA involved mean (SD)	sPGA ≥4 %	DLQI score mean (SD)	Previous psoriasis therapy, %			
					Topical	Phototherapy	Conventional systemic	Biological
UNCOVER-1								
Ixekizumab Q2W	20.1 (8.0)	28.2 (17.8)	46.7	13.4 (7.0)	NR	46.4	63.7	40.0
Placebo	20.3 (8.6)	27.4 (17.8)	52.7	12.8 (7.1)	NR	42.9	56.1	42.0
UNCOVER-2								
Ixekizumab Q2W	19.4 (7.3)	25.1 (15.8)	49.3	12.4 (6.9)	NR	46.4	55.8	23.9
Placebo	20.6 (8.4)	27.2 (18.1)	48.8	12.8 (7.2)	NR	44.0	50.6	25.6
Etanercept	19.1 (6.7)	25.3 (15.5)	48.0	12.7 (7.0)	NR	48.3	53.6	21.2
UNCOVER-3								
Ixekizumab Q2W	20.7 (8.2)	28.0 (17.3)	46.2	12.4 (6.9)	NR	39.2	49.4	15.1
Placebo	21.1 (8.4)	28.6 (17.5)	52.3	12.7 (7.0)	NR	31.1	46.1	17.1
Etanercept	20.7 (8.2)	28.3 (17.4)	50.3	11.5 (6.8)	NR	41.1	51.3	15.7

BSA = body surface area; DLQI = Dermatology Life Quality Index; NR = not reported; PASI = Psoriasis Area and Severity Index; SD = standard deviation

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Table 9: Proportion of patients achieving PASI 75 at week 12 (NRI). Primary Psoriasis Placebo-controlled Integrated Analysis Set. ITT population – UNCOVER-1, UNCOVER-2 and UNCOVER-3, by study.

Subgroup	p-value (interaction)[a]	PBO N=792 n/N_x (%)	IXE80 Q4W N=1,165 n/N_x (%)	IXE80 Q2W N=1,169 n/N_x (%)	All IXE N=2,334 n/N_x (%)
Pooled Studies					
Gender					
Male	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
Female		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-1					
Gender		N=431	N=432	N=433	N=865
Male	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
Female		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-2					
Gender		N=168	N=347	N=351	N=698
Male	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
Female		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-3					
Gender		N=193	N=386	N=385	N=771
Male	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
Female		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
Pooled Studies					

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Subgroup	p-value (interaction)[a]	PBO N=792 n/N_x (%)	IXE80 Q4W N=1,165 n/N_x (%)	IXE80 Q2W N=1,169 n/N_x (%)	All IXE N=2,334 n/N_x (%)
Age					
<40 years	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
≥40 years		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-1					
Age		N=431	N=432	N=433	N=865
<40 years	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
≥40 years		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-2					
Age		N=168	N=347	N=351	N=698
<40 years	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
≥40 years		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-3					
Age		N=193	N=386	N=385	N=771
<40 years	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
≥40 years		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
Pooled Studies					
Disease severity					
PASI <20	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx

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Subgroup	p-value (interaction)[a]	PBO N=792 n/Nx (%)	IXE80 Q4W N=1,165 n/Nx (%)	IXE80 Q2W N=1,169 n/Nx (%)	All IXE N=2,334 n/Nx (%)
PASI ≥ 20		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-1					
Disease severity		N=431	N=432	N=433	N=865
PASI <20	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
PASI ≥ 20		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-2					
Disease severity		N=168	N=347	N=351	N=698
PASI <20	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
PASI ≥ 20		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-3					
Disease severity		N=193	N=386	N=385	N=771
PASI <20	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
PASI ≥ 20		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
Pooled Studies					
Previous non-biologic systemic therapy (NBST): inadequate response, intolerance or contraindication					
<3	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
≥3		xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx
UNCOVER-1					

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Subgroup	p-value (interaction)[a]	PBO N=792 n/Nx (%)	IXE80 Q4W N=1,165 n/Nx (%)	IXE80 Q2W N=1,169 n/Nx (%)	All IXE N=2,334 n/Nx (%)
Previous NBST: inadequate response, intolerance or contraindication		N=431	N=432	N=433	N=865
<3	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**
≥3		**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**
UNCOVER-2					
Previous NBST: inadequate response, intolerance or contraindication		N=168	N=347	N=351	N=698
<3	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**
≥3		**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**
UNCOVER-3					
Previous NBST: inadequate response, intolerance or contraindication		N=193	N=386	N=385	N=771
<3	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**
≥3		**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**	**xxxxxxxxxxxxxxxx**

[a] A logistic regression analysis with treatment, subgroup and the interaction of treatment by subgroup included as factors, and the treatment by subgroup interaction is tested at the 10% significance level

[b] p<0.001 versus PBO, c p<0.001 versus 80 mg Q4W, d p≤0.05 versus 80 mg Q4W, e p≤0.05 versus PBO

ITT = intent-to-treat, PASI = psoriasis area and severity index, PBO = placebo, IXE = ixekizumab, IXE80 = ixekizumab 80 mg; N/A = not available; NBST = Non-biologic systemic therapies; NRI = non-responder imputation; Nx = number of patients within subgroup; Q2W = every 2 weeks; Q4W = every 4 weeks

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Network meta-analysis

A14. **CS, section 4.10** Please provide all datasets used in the NMA analyses (in WinBUGs format) which correspond to the results presented.

The datasets used in the NMA analyses (in WinBUGs format) have been sent via encrypted USB to NICE.

Section B: Clarification on cost-effectiveness data

Population and comparators

B1. **PRIORITY REQUEST: CS, section 5** Moderate to severe psoriasis was defined as PASI ≥ 10 and DLQI > 10 (Figure 4). However, the minimum baseline PASI score for enrolment in the UNCOVER trials was 12. NICE CG153 states that severe disease has been defined in NICE technology appraisals as a PASI of ≥ 10 and DLQI > 10. Other authors have defined severe disease as PASI > 12. To estimate utility input for the model, the subgroup of patients with DLQI >10 from the UNCOVER trials was used. For treatment response, the intention-to-treat population was used.

- Please justify how the UNCOVER trials are applicable to the population of moderate to severe psoriasis as opposed to only severe psoriasis.
- Please justify the difference in choice of data (subset) for each of these analyses.

The patient populations in the UNCOVER trial programme are described as having moderate to severe psoriasis with inclusion criteria of BSA>10% and PASI>12 although no restriction was specified for DLQI.

As noted in the manufacturer submission for apremilast[6], moderate disease severity in psoriasis is poorly defined. European Consensus Guidelines defines moderate to severe disease as BSA>10 or PASI≥10 in conjunction with DLQI>10 [7] and DLQI≤10 as mild disease irrespective of whether BSA>10 or PASI>10. The ERG for TA103 (etanercept and efalizumab) defined moderate psoriasis as BSA≥10% and PASI score of 10-20 and severe psoriasis as BSA≥20% and PASI≥20 and states that this is an arbitrary assessment that takes no account of the effect of psoriasis on HRQoL [8]. The manufacturer submissions in previous NICE TAs [9,10] defined moderate to severe psoriasis in the same way; however, the Final Appraisal Determination documents recommended ustekinumab and secukinumab for use in severe psoriasis.

- Please provide an analysis of treatment response and utility gain based on the subgroup of patients with DLQI >10 from the UNCOVER trials.

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PASI response data from the UNCOVER trials are presented in Table 10, dichotomised by baseline DLQI≤10 or >10. PASI 75, 90 and 100 response rates are not significantly different between baseline DLQI subgroups in the UNCOVER trials. As PASI response data by baseline DLQI score was not consistently reported for other comparators, the ITT population was used to inform treatment response estimates. It is therefore deemed unlikely that a network restricted to patients with DLQI>10 is feasible. As such, it is not possible to undertake an economic analysis using both treatment estimates and HRQoL data from the DLQI>10 subgroup.

Table 10: PASI 75, PASI 90, PASI 100 response rates at week 12 (NRI), primary psoriasis placebo-controlled integrated analysis set by subgroups, ITT population - UNCOVER-1, -2 and -3

Subgroup	p-value (interaction)	PBO N=792 n/Ns (%)	IXE80Q4W N=1,165 n/Ns (%)	IXE80Q2W N=1,169 n/Ns (%)
PASI 75				
DLQI ≤10	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
DLQI >10		xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
PASI 90				
DLQI ≤10	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
DLQI >10		xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
PASI 100				
DLQI ≤10	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx
DLQI >10		xxxxxxxxxxxx	xxxxxxxxxxxx	xxxxxxxxxxxx

DLQI = Dermatology Life Quality Index; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; Ns = number of patients in each subgroup; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo

[a] p<0.001 vs placebo (Risk Difference)

B2. **PRIORITY REQUEST: CS, section 5.7.1** The heading of Table 91 states: 'base-case results (Biologic-naïve patients with prior systemic failure, PASI >10 and DLQI≥10)'. The treatment response rates used in the economic model are based on the NMA reported in section 4.10. The studies in this NMA included patients who are not biologic naïve, who may not have failed on systemic treatment, and who may not have a DLQI≥10.

- Please clarify which population is addressed in the base-case analysis, by describing which population the treatment response is based on, and how this relates to the population defined in the scope (moderate to severe plaque psoriasis in adults who are candidates for systemic therapy).
- Please clarify that this is consistent with the population of the UNCOVER trial.

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Inclusion criteria for the UNCOVER trials stated that patients must have moderate to severe disease defined as PASI≥12 and BSA≥10%, and be candidates for phototherapy and/or systemic therapy. In addition, patients across the trials were found to have a mean DLQI score of 12.5. While this is broadly in line with the scope of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy, the population of interest for positioning ixekizumab is in line with NICE recommendations for adalimumab, etanercept, secukinumab and ustekinumab, i.e. patients with prior systemic failure, PASI>10 and DLQI>10. Therefore, the basecase analysis considers ixekizumab cost-effectiveness in the context of NICE approved biologics which applies the stated eligibility criteria. As previously noted, the clinical evidence for the other approved biologics have followed similar population criteria. Additionally, even though other biologics have similar label wording (e.g. secukinumab and now adalimumab), NICE guidance has been consistent with the PASI and DLQI criteria.

Data for comparator treatments was not available for the proportion of patients who were biologic-naive, failed on systemic treatment or had DLQI>10. As it was not possible to judge the feasibility of a network for patients with these characteristics, the ITT population was used instead. The base case analysis uses treatment response data from the ITT population and HRQoL from the DLQI>10 subgroup. As highlighted in the clarification question responses and the submission itself, clinical response to ixekizumab is consistent amongst sub-groups and to the ITT population. In the base case, patients are biologic-naïve in the sense that they are modelled as initiating the first of three biologic treatment sequences.

B3. **PRIORITY REQUEST: CS, section 5.7** The NICE scope defines the population as adults with moderate to severe plaque psoriasis, which is further defined in the comparators section as a) people for whom non-biologic systemic treatment or phototherapy is suitable, and b) people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. By comparing to biologic systemic treatment, the company seems to have chosen only to analyse population b) in the cost-effectiveness section. However, this is not explicitly stated. In addition, the population is described as 'biologic naïve', which is only a sub-set of this population.

- Please explain why only one population appears to have been considered (that is, those with prior failure of systemic therapy), and confirm that the inputs for the model (response, utility gain, costs) are based on this specific population.

The base case analysis considers a population who initiate a treatment sequence of three biologic therapies who are assumed to have prior failure on systemic therapy in accordance with the recommendations by NICE for adalimumab, etanercept, infliximab, secukinumab and ustekinumab. The network for the indirect comparison in the base case analysis is restricted to biologic therapies approved by NICE and does

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not include systemic therapies for which there is connected evidence. However, response data informing the NMA are not differentiated by prior systemic therapy failure due to the lack of data available for comparator therapies. It should be re-iterated again, that evidence has been provided that ixekizumab appears consistently effective across sub-groups versus the ITT population.

Utility gain is modelled in terms of change from baseline EQ-5D-5L associated with each PASI response rate. This data was collected from all patients in the DLQI>10 subgroup of the ITT population and not only those who had prior systemic therapy failure and DLQI>10. Acquisition, administration and monitoring costs are treatment-specific and non-responder costs are incurred in the induction period following failure on a biologic therapy. These costs and resource use rates would not change for a population with versus without prior systemic failure therapy.

- If appropriate, please conduct an analysis using only clinical effectiveness data that are from the appropriate subgroup, i.e. for the biologic naïve then only use data from those who are biologic naïve.

This is not appropriate as an indirect comparison for clinical effectiveness data specific to the biologic-naïve or experienced subgroups was not feasible as the proportion of patients with no prior biologic experience and their associated PASI rates are not available for other comparators. It is therefore not possible to conduct an analysis using only clinical effectiveness data from the biologic-naïve population. Furthermore, it could be argued that the clinical effectiveness data is more appropriate to inform data for a biologic-naïve population rather than biologic-experienced population as only 26.4% of patients enrolled in UNCOVER-1, -2 and -3 had received either only prior biologic or prior biologic and non-biologic systemic therapy (Table 3.4, Pooled studies clinical HTA toolkit). [11]

- Please conduct all analyses (clinical effectiveness and cost effectiveness), also for the other population, i.e. population a) those for whom non-biologic systemic or phototherapy is suitable (including the following comparators: acitretin, ciclosporin, fumaric acid esters, methotrexate and phototherapy with ultraviolet (UVB) radiation).

In a sensitivity analysis, the population of interest is those patients for whom non-biologic systemic treatment or phototherapy is suitable was conducted (Section 5.8.3, p291). The indirect comparison network informing this analysis includes systemic therapies for which there is evidence to inform a connected network, i.e. methotrexate and ciclosporin. There was insufficient evidence to include other non-biologic systemic therapies and phototherapy (i.e. acitretin, fumaric acid esters, and phototherapy) that were listed in the scope.

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- If the company defines the population in terms of biologic experience then please justify how the clinical effectiveness data are most appropriate for the biologic naïve as opposed to the biologic experienced.

Please refer to the above response regarding the proportion of patients across the UNCOVER trials that were biologic-naïve.

B4. **CS, section 5** For the modelling of BSC:

- Please provide a definition of BSC as used in the economic model.
- In the model BSC includes an induction period. Please justify and describe the impact of (removing) this induction period on the model outcomes.

BSC in the economic model is informed by costs from Fonia et al (2010) [12] as per ERG recommendations for TA350 for secukinumab and TA368 for apremilast. The costs sourced from the Fonia et al (2010) study and used in the model are the mean cost per patient of systemic and supportive drugs, and inpatient and outpatient admissions in the 12 months before biologic therapy initiation. Systemic and supportive therapies in the study encompass acitretin, ciclosporin, fumaric acid esters, hydroxycarbamide, methotrexate, mycophenolate mofetil, amoxicillin, erythromycin, flucloxacillin and prednisolone. Inpatient and outpatient admissions include inpatient admissions, intensive care unit admissions, high dependency unit admissions, accident and emergency visits, outpatient visits, day ward admissions and phototherapy.

An induction period for BSC was incorporated for consistency in the way in which health utility gains are assigned to active treatments. In the base case analysis, patients receiving active treatment are assumed to accrue health utility gains from the end of the induction period onwards while on treatment. If the induction period associated with BSC were removed from the analysis, patients would accrue health utility gains each model cycle as soon as they initiate BSC, which is unlikely to be reflective of a clinical response to BSC. Treatment continuation at the end of the induction period is dependent on attaining a minimum response of PASI75. Patients initiating a sequence with a treatment with a lower initial PASI75 response would proceed to BSC sooner than those initiating on a treatment with a higher initial PASI75 response rate. Ixekizumab is associated with the highest PASI75 response rate; therefore patients initiating a sequence with ixekizumab would receive additional health utility gains in the BSC induction period of the treatment sequence later than patients initiating a sequence on any other biologic. This would result in a lower incremental QALY gain for the ixekizumab sequence relative to other comparator sequences due to the effect of discounting of utility gains incurred further in the future.

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B5. **CS, section 5.2.3, table 69** Please provide further justification of the treatment sequences used in the economic model:

- Please justify why market share would be an appropriate source to determine the order of biologic treatments in the sequence, and provide sensitivity analyses with alternative order of biologics in the treatment sequences.
- Please justify why treatments are only used once in a treatment sequence.
- Please justify why all treatment sequences consist of three biologics followed by BSC.
- Please confirm that the treatment sequences listed in Table 69 include all sequences used in UK current practice.

In the absence of any official guidance on the ordering of biologics within a treatment sequence, market share data was used to determine the sequences as this is thought to likely reflect clinical practice in England. All treatment sequences consist of three biologic treatments followed by BSC. The NICE pathway for biologic treatment in psoriasis states that a second biologic should be considered following the failure of the initial biologic treatment (and a second biologic was deemed cost-effective in CG153), and specialist referral is suggested on failure of the second biologic. The NICE pathway suggests that it is reasonable to model a three treatment sequence as there is likely to significant local variation in biologic use beyond the third biologics with the potential that individual funding requests (IFR) having to be submitted in order to prescribe more than three biologic treatments

The decision to use each treatment only once in a sequence was pragmatic and likely reflective of clinical practice. With several biologic treatment options available, there would need to be a clear clinical rationale to re-treat a patient with a treatment that they have failed on. Using treatments more than once in a sequence would also multiply the number of feasible treatment sequences by several factors and likely not be helpful for decision-making.

The treatment sequences listed in Table 69 do not include all sequences used in UK current practice. The option of seven therapies including two doses of ustekinumab in three possible positions within a sequence would result in 210 sequence permutations, therefore an exhaustive list was not provided.

Drug survival rates from the BADBIR study[13] is presented in Table 11 and an alternative ordering of sequences based on these drug survival rates is presented in Table 12 and Table 13.

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Table 11: BADBIR drug survival rates

	Etanercept	Infliximab	Adalimumab	Ustekinumab
Year 1	0.70	0.65	0.79	0.89
Year 2	0.51	0.50	0.67	0.82
Year 3	0.40	0.35	0.59	0.75

Table 12: Alternative ordering of sequences based on BADBIR drug survival rates

1st line	2nd line	3rd line	4th line
Ixekizumab	Ustekinumab 90mg	Adalimumab	BSC
Adalimumab	Ustekinumab 90mg	Etanercept	BSC
Etanercept	Ustekinumab 90mg	Adalimumab	BSC
Infliximab	Ustekinumab 90mg	Adalimumab	BSC
Secukinumab	Ustekinumab 90mg	Adalimumab	BSC
Ustekinumab 45mg	Adalimumab	Etanercept	BSC
Ustekinumab 90mg	Adalimumab	Etanercept	BSC

Table 13: Alternative ordering of sequences based on BADBIR drug survival rates

Sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER Ixe vs comparator
UST 45 mg	£133,799	1.16	Referent	Referent	Referent	£35,332
ETN	£134,025	1.17	£226	0.01	£15,227	£36,885
ADA	£134,032	1.17	£234	0.01	Extendedly dominated	£36,866
UST 90 mg	£134,401	1.17	£602	0.02	Extendedly dominated	£35,454
IXEQ2W	£141,116	1.36	£7,317	0.21	£36,885	NA
INF	£150,350	1.33	£16,551	0.17	Dominated	Dominated
SEC 300 mg	£167,195	1.33	£33,396	0.17	Dominated	Dominated

Model structure

B6. **PRIORITY REQUEST: CS, section 5.2.2** The model structure is based on health states defined by the response to treatment that is a function of a change in disease state and not absolute disease severity. The transition to the treatment maintenance health state is based on a percentage reduction in PASI score. As a result, patients in the treatment maintenance health state with a response may be heterogeneous in terms of quality of life and costs.

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- Please justify the use of relative PASI reduction as opposed to absolute PASI reduction as measure of response. Please also justify the different PASI reduction threshold used (50, 75, 90, 100).
- Please justify the chosen structure by showing that patients with a response are homogeneous in terms of utility gain due to a response and to costs (medical resource use).

Relative PASI reduction is used as the measure of response in the model rather than absolute PASI in accordance with treatment response assessment in CG153, previous NICE guidance, BAD guidelines and the European Consensus guidelines [3,7,14] which uses attainment of PASI75 or PASI50 in conjunction with a five-point decrease in DLQI as the basis of continuing treatment. PASI75 is also the recommended response assessment threshold for systemic treatment in European consensus guidelines [7]. PASI50, 75 and 90 are commonly reported thresholds of relative PASI reduction from baseline PASI score in all recent RCTs for psoriasis treatments and have been used to calculate health utility gains in the manufacturer's models for previous NICE TAs in psoriasis [6,8-10,15,16]. PASI100 denotes complete clearance of symptoms and as such is a clinically meaningful response threshold to model.

The HRQoL impact of modelling PASI reduction in absolute terms may not be linear depending on baseline PASI score; for example, a ten point absolute reduction in PASI score at one extreme of 72 to 62 may not affect HRQoL to the same extent as a ten point reduction from a score of 12 to 2.

Utility gains associated with a specific PASI response range (0-49, 50-74, 75-89, 90-99. 100) represent the mean utility gain experienced by patients within that range, therefore a patient with a PASI75 response is modelled as experiencing the same gain as a patient with a PASI89 response. This is a necessary assumption and simplification in a Markov model framework has been used in previous economic evaluations in psoriasis. Medical resource use, with the exception of non-responder costs, is independent of PASI response. Non-responder costs are independent of the actual level of response beyond a binary response criterion of PASI 75 in the base case.

Treatment effectiveness

B7. **PRIORITY REQUEST: CS, section 5.2.4** Please justify why the discontinuation rate is equal for all comparators and constant over time.

- Please provide a sensitivity analysis using trial data to inform treatment specific discontinuation rates for the comparators, and the UNCOVER trial data to determine ixekizumab discontinuation rate.
- Please provide scenario analyses using changing treatment discontinuation rates over time.

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A discontinuation rate of 20% has been assumed in previous NICE TAs in psoriasis and is a widely used modelling assumption that has been supported by clinicians and observational data [13]. Scenario analyses using changing treatment discontinuation rates over time have not been undertaken as there is no long term data available to inform this for all comparators; while BADBIR data is available for adalimumab, etanercept, infliximab and ustekinumab for three years[13], this is not available for IL-17 agents. There is evidence to suggest that treatment discontinuation rates may plateau in the long term [17]. This could be a conservative assumption with respect to ixekizumab since older biologic agents may have higher discontinuation rates than newer ones.

Year 1 discontinuation rates for biologics reported in Warren 2015 and trial discontinuation rates for ixekizumab and secukinumab are presented in Table 14 and results are presented in Table 15.

Table 14: Biologic therapy-specific discontinuation rates

Biologic	Year 1 discontinuation rate	Source
Ixekizumab	5.3%	UNCOVER-3 long term extension period
Adalimumab	21%	Warren 2015
Etanercept	30%	Warren 2015
Infliximab	35%	Warren 2015
Ustekinumab 45mg, 90mg	11%	Warren 2015
Secukinumab	11.7%	TA350

Table 15: Biologic therapy-specific discontinuation rates

Treatment sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER Ixe vs comparator
ETN sequence 1C	£142,972	1.29	Referent	Referent	Referent	£24,145
UST 45 mg sequence 1F	£146,900	1.35	£3,928	0.06	Extendedly dominated	£20,467
ADA sequence 1B	£147,569	1.37	£4,597	0.09	Extendedly dominated	£20,135
UST 90 mg sequence 1G	£147,819	1.38	£4,847	0.09	Extendedly dominated	£19,958
INF sequence 1D	£149,587	1.37	£6,615	0.09	Dominated	£17,052
IXE Q2W sequence 1A	£160,327	2.00	£17,355	0.72	£24,145	N/A
SEC 300 mg 1E	£193,944	1.63	£50,972	0.35	Dominated	Dominated

ADA = adalimumab; ETN = etanercept; ICER = incremental cost-effective ratio; INF = infliximab; Ixe = ixekizumab; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

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B8. **CS, section 5.8.3, table 105** The scenario analysis on decreased efficacy in patients previously treated with biologics shows an increase in the ICER of ixekizumab versus etanercept. This seems a plausible scenario as failure of a biologic treatment is indicated to be a significant negative predictor of time to treatment discontinuation.[17]

- Please justify why this effect is not used to estimate the treatment effect of biologics during the second and subsequent lines in the treatment sequence in the base-case analysis.

An indirect comparison network for patients with prior TNF-inhibitor use was not feasible; therefore an effect modifier from a Danish study was used in a scenario analysis.[17] As this was a post-hoc calculation from a non-UK study, it was not considered sufficiently robust to apply in the base case. While this study does show previous failure on a biologic treatment to be a significant negative predictor of time to treatment discontinuation, analysis of the UNCOVER trials indicates that this may not be the case for ixekizumab. PASI responses observed in UNCOVER-2 in ixekizumab patients who had a previous inadequate response to etanercept therapy were consistent with those who had received ixekizumab in the induction period. No significant difference was found for PASI 75 response between patients who had never had previous biologic exposure and those who had 1, 2 and ≥3 previous exposures (Table 45, Section 4.8.2).

Health related quality of life

B9. **PRIORITY REQUEST: CS, section 5.4** Utility gain estimates were determined using linear regression.

- Please justify why PASI response is used to predict utility gain given it is difficult to describe the clinical severity for any specific PASI number (dramatic improvements in patients' appearances can be obtained without reaching the 75% in PASI).

Although PASI and PASI response may have some drawbacks, the measure is consistently reported in all recent clinical studies and used in all relevant NICE technology appraisals. As they key clinical measure, associating utility gain to PASI response was considered to be the reasonable and consistent approach. Whilst PASI75 may not be reached and still result in acceptable patient benefit, PASI75 is the threshold recommended in NICE guidance, as highlighted in the response to question B6.

- Please use alternative methods, such as a gamma model (using a log-link) using transformed utility (1-utility) and provide tables with summary statistics for these different methods.

Table 16 shows the summary statistics for the gamma model.

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Table 16: Summary statistics for the gamma model

Analysis Of Maximum Likelihood Parameter Estimates								
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**
resp_w12	No Response	1	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**
resp_w12	PASI 50	1	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**
resp_w12	PASI 75	1	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**
resp_w12	PASI 90	1	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**
resp_w12	PASI 100	0	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**
eq5d5l_base		1	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**
Scale		1	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**	**xxxxxxx**

- Please provide in addition to the covariates used in equation 2, analyses with baseline PASI as a covariate, repeat these analyses without adjusting for baseline EQ-5D-5L, and provide summary statistics for these different analyses.

Table 17: Baseline PASI adjusted HRQoL regression model

Parameter	***Estimate***		***Standard Error***	***t Value***	***Pr > |t|***	***95% Confidence Limits***	
Intercept	**xxxxxxxxxxx**	**x**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**
resp_w12 No Response	**xxxxxxxxxxx**	**x**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**
resp_w12 PASI 50	**xxxxxxxxxxx**	**x**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**
resp_w12 PASI 75	**xxxxxxxxxxx**	**x**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**
resp_w12 PASI 90	**xxxxxxxxxxx**	**x**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**
resp_w12 PASI 100	**xxxxxxxxxxx**	**x**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**
pasi_base	**xxxxxxxxxxx**		**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**	**xxxxxxxxxxx**

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Table 18: Baseline PASI adjusted utility gain estimate

Change in EQ5D = PASI response (Week 12) + BL PASI	Best PASI Response at Week 12	LS mean	Std error
eq5d5lchg_w12	No Response	**xxxxxxxxxxxxxx**	**xxxxxxxxxxxxxx**
eq5d5lchg_w12	PASI 50	**xxxxxxxxxxxxxx**	**xxxxxxxxxxxxxx**
eq5d5lchg_w12	PASI 75	**xxxxxxxxxxxxxx**	**xxxxxxxxxxxxxx**
eq5d5lchg_w12	PASI 90	**xxxxxxxxxxxxxx**	**xxxxxxxxxxxxxx**
eq5d5lchg_w12	PASI 100	**xxxxxxxxxxxxxx**	**xxxxxxxxxxxxxx**

- Please check for interaction between PASI response and baseline EQ-5D-5L to assess whether the assumption of constant utility gain over time is justified.

The requested analysis is provided below, however we do not feel there is sufficient data to test this assumption based on available study data. The assumption that the utility gain based on initial PASI response at the end of the trial period (week 12) is consistent with previous modelling approaches and is the only feasible assumption given the available data. It should also be noted that ixekizumab long-term data shows that some patients may improve from an initial PASI 75 response to a PASI 90 response or higher therefore it could be argued that this assumption underestimates the utility benefit of ixekizumab.

Table 19: HRQoL regression model adjusted for interaction between baseline PASI and baseline EQ-5D-5L

Parameter	*Estimate*		*Standard Error*	*t Value*	*Pr > |t|*	*95% Confidence Limits*	
Intercept	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
resp_w12 No Response	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
resp_w12 PASI 50	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
resp_w12 PASI 75	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
resp_w12 PASI 90	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
resp_w12 PASI 100	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
eq5d5l_base	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
*eq5d5l_base*resp_w12 No Response*	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
*eq5d5l_base*resp_w12 PASI 50*	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
*eq5d5l_base*resp_w12 PASI 75*	**xxxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**

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Parameter	*Estimate*		*Standard Error*	*t Value*	*Pr > |t|*	*95% Confidence Limits*	
*eq5d5l_base*resp_w12 PASI 90*	**xxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**
*eq5d5l_base*resp_w12 PASI 100*	**xxxxxxxxxx**	**x**	**xxxxxxxxxx**	**xxxxx**	**xxxxx**	**xxxxxxxxxx**	**xxxxxxxxxx**

B10. **CS, section 5.4** Please clarify how the utility gain estimates in Table 80 are determined using the ANOVA results presented in CS Table 70.

Both table 70 and table 80 shows results from the regression model described in section 5.4.1. Table 70 shows the parameter estimates for α, β_1 (vector with one β_1 value for each PASI category) and β_2 in Equation 1.

Equation 1: HRQoL regression model

$$\text{Change from baseline EQ} - \text{5D} - \text{5L} = \alpha + \beta_1 \times (\text{PASI} - \text{response at week 12}) + \beta_2 \times (\text{baseline EQ} - \text{5D} - \text{5L}) + \varepsilon$$

Table 80 shows the LS mean results for "$Change\ from\ baseline\ EQ - 5D - 5L$" for each PASI category.

The values in table 80 can be calculated using the parameter estimates from table 70 included in Equation 2 and the mean baseline EQ5D-5L.
With a mean baseline EQ5D-5L of 0.7608 (see table 1) we get the following equation for PASI <50 (non-response):

Equation 2: change from baseline EQ-5D-5L for non-responders

$$\text{Change from baseline EQ} - \text{5D} - \text{5L} = 0.6465 + (-0.1409) * 1 + \beta_2 \times (-0.6491) * 0.7608 = 0.012$$

This result is the same result as the LS mean in table 80.

B11. **CS, section 5.4.4** Please perform a sensitivity analysis to show the impact of adverse events on both costs and utility on the results of the model.

Adverse event costs are incorporated in a sensitivity analysis. As explained in the CS, HRQoL impact is not modelled due to the lack of utility data associated with non-melanoma skin cancer, malignancies other than NMSC and infections in the context of psoriasis. Furthermore, as malignancies may manifest long after treatment

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discontinuation, in the context of a treatment sequencing approach, it would be difficult to trace back malignancies to specific treatments.

B12. **CS, section 5.4** 100% PASI reduction is considered as a separate subgroup in the model.

- Please provide PASI response input for the model using 90-100% reduction subgroup (instead of 90-99% and 100% reduction separately), including utility gain.
- Please provide the results of a cost-effectiveness analysis using these model inputs.

The regression model used to model utility gain in the base case as a function of PASI response and baseline EQ-5D-5L was re-run using four categorical variables of PASI response: PASI 0-49, PASI 50-74, PASI 75-89, PASI 90-100. PASI 90-100 was used as the reference category. Parameter estimates and change from baseline EQ-5D-5L associated with PASI response are presented in Table 20 and Table 21.

Table 20: HRQoL analysis with four PASI response categories

PASI response	Coefficient	LSmean Change from baseline EQ-5D-5L
Intercept	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
PASI 0-49	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
PASI 50-74	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
PASI 75-89	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
PASI 90-100	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Baseline EQ-5D-5L	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Table 21: Four PASI category HRQoL analysis - deterministic results

Sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER Ixe versus comparator
ETN sequence 1C	£144,635	1.27	Referent	Referent	Referent	£34,547
UST 45 mg sequence 1F	£148,218	1.31	£3,583	0.04	Extendedly dominated	£18,811
ADA sequence 1B	£148,350	1.32	£3,715	0.05	Extendedly dominated	£19,784
UST 90 mg	£148,719	1.32	£4,083	0.06	Extendedly dominated	£17,267

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sequence 1G						
INF sequence 1D	£150,350	1.33	£5,714	0.06	Extendedly dominated	£4,422
IXE Q2W sequence 1A	£150,889	1.45	£6,254	0.18	£34,547	N/A
SEC 300 mg 1E	£177,101	1.42	£32,466	0.15	Dominated	Dominated

ADA = adalimumab; ETN = etanercept; ICER = incremental cost-effective ratio; INF = infliximab; Ixe = ixekizumab; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

B13. **CS, section 5.4.1** For all patients who dropped out before the end of the induction period (week 12), the last EQ-5D-5L value, if collected at the visit prior to drop-out, was used as an estimate for the week 12 value using the last-observation carried forward approach.

- Please provide information on how many patients the last-observation carried forward approach was used for and at which time points EQ-5D-5L values were taken from.
- Please justify why the last-observation carried forward is a suitable method to handle these missing values.

In the UNCOVER 1, 2 and 3 studies EQ-5D-5L data was collected at baseline and at week 12. EQ-5D was not scheduled to be collected at the visits between baseline and week 12. As an exception EQ-5D was collected (if possible) at the last visit before a patient discontinued the study. Only these patients will have an EQ-5D-5L value on a visit before week 12 that can be used for last observation carried forward imputation. Values missing for any other reason were not imputed as no previous post baseline observations were available. Results from ongoing analyses can be added to show how many patients had an EQ-5D value collected before week 12 (which was used for LOCF).

Last observation carried forward imputation of missing values allows the use of all collected data. Other approaches like observed cases may bias the results as this approach would exclude the patients that discontinued. Patients discontinuing could be expected to have a lower quality of life, therefore excluding them could inflate the EQ-5D change from baseline. Using last observation carried forward for both PASI and EQ-5D gives us observations collected from the same visit within patient as both of them would be collected at the last visit before discontinuation.

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B14. **CS, section 5.4.5** HRQoL is assumed to be constant over time in the analysis although EQ-5D-3L population norms for the UK general population are shown to decrease with age.

- Please justify why HRQoL is assumed to be constant and show how the HRQoL in the model compares to HRQoL of age-matched general UK population.

Please note EQ-5D-3L was not collected in the UNCOVER studies, only EQ-5D-5L was collected. We are not aware of any available age-adjusted population norms for EQ-5D-5L. The tables below present the utility gain estimates adjusting for age and are similar to the base case analysis. Prior models submitted to NICE for psoriasis followed a similar process and did not take into account age-adjusted changes in utility.

Table 22: Age-adjusted HRQoL regression model

Parameter	Estimate		Standard Error	t Value	Pr > |t|	95% Confidence Limits	
Intercept	xxxxxxxxxxxxx	x	xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx
resp_w12 No Response	xxxxxxxxxxxxx	x	xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx
resp_w12 PASI 50	xxxxxxxxxxxxx	x	xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx
resp_w12 PASI 75	xxxxxxxxxxxxx	x	xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx
resp_w12 PASI 90	xxxxxxxxxxxxx	x	xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx
resp_w12 PASI 100	xxxxxxxxxxxxx	x	xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx
eq5d5l_base	xxxxxxxxxxxxx		xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx
age	xxxxxxxxxxxxx		xxxxxxxxx	xxxxx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx

Table 23: Age-adjusted estimate of utility gain by PASI response

Change in EQ5D = PASI response (Week 12) + BL EQ5D + AGE	Best PASI Response at Week 12	LS mean	Standard error
eq5d5lchg_w12	No Response	xxxxxxxxxxxxx	xxxxxxxxxxxxx
eq5d5lchg_w12	PASI 50	xxxxxxxxxxxxx	xxxxxxxxxxxxx
eq5d5lchg_w12	PASI 75	xxxxxxxxxxxxx	xxxxxxxxxxxxx
eq5d5lchg_w12	PASI 90	xxxxxxxxxxxxx	xxxxxxxxxxxxx
eq5d5lchg_w12	PASI 100	xxxxxxxxxxxxx	xxxxxxxxxxxxx

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Costs

B15. **CS, section 5.5.2** The costs of BSC include inpatient costs, while this does not seem to be the case for the other treatments.

- Please justify why inpatient costs are included for BSC but not for other treatments.
- Please provide a sensitivity analysis using alternative estimates for BSC costs, for example, using BSC costs equal to the estimates provided by Fiona et al. (12 months after initiation of biological therapy instead of 12 months before biological initiation, CS Table 83).

Hospitalisation costs, referred to in the manufacturer submission as non-responder costs, are applied for other treatments in the induction period following previous failure on biologic therapy. These capture the cost of inpatient stays as reported in Fonia et al (2010).[12]

Costs from the 12 months following biological therapy initiation are not considered appropriate to use as BSC following failure on three prior biologic therapies as this would not adequately capture the increase in healthcare resource use due to biologic treatment failure - i.e. the costs from Fonia following biologic therapy initiation would be confounded by the fact that patients were being treated with biologics when the definition of BSC in the economic model precludes the use of biologic treatment.

B16. **CS, section 5.5.2** Please clarify how the costs for becoming a non-responder were determined and provide further justification as to why these costs are not already covered by the costs incurred during the induction and maintenance periods.

Costs incurred during the induction and maintenance periods of biologic treatment are drug acquisition and administration, and monitoring costs. BSC costs are incurred only after discontinuing from the third biologic in the sequence. The cost for becoming a non-responder was sourced from Fonia et al 2010 [12] as the cost of inpatient admissions, ICU admissions, HDU admissions, A&E visits, day ward admissions and phototherapy incurred 12 months before biologic therapy initiation. Patients who have experienced PASI <50 accrue this cost in the induction period of the subsequent biologic therapy to reflect that patients typically have higher disease activity and therefore worse health after treatment failure This was inflated to 2015, divided by 12 and applied on a monthly basis.

These costs are not covered by the maintenance period of biologic treatment, as these patients have responded to treatment and incur drug treatment costs and monitoring costs. In the induction period for a patient moving on to the next biologic treatment in the sequence a proportion of the best supportive care cost is applied as per the preferred assumption in TA368 for apremilast in psoriasis.

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B17. **CS, section 5.5.2** Please explain how the mean weight from UNCOVER, used to calculate the costs of infliximab, is representative for the population of patients with moderate to severe psoriasis in the UK.

Body mass index data collected in BADBIR suggest that 81.6% of the patient cohort is overweight or obese.[13] The mean weights in the UNCOVER trial arms range from 89.0 kg to 93.0 kg. These are broadly similar to the mean weights from trials in other manufacturer submissions. Weights in the trials informing ustekinumab TA 180 ranged from 90.4 kg to 93.8 kg; for secukinumab in TA 350, 82.0 kg to 92.6 kg; for adalimumab in TA146, 88.6 kg to 100.2 kg; and for infliximab in TA134, 85.0 kg to 92.2 kg.

Table 24: Mean weight of patients in previous technology appraisals

Manufacturer submission	Trial	Weight (kg)
Ixekizumab	UNCOVER-1: IXE 80mg Q2W; IXE 80mg Q4W; PBO	92.4; 92.5; 91.8
	UNCOVER-2: IXE 80mg Q2W; IXE 80mg Q4W; PBO	89.0; 93.0; 92.0
	UNCOVER-3: IXE 80mg Q2W; IXE 80mg Q4W; PBO	90.0; 91.0; 91.0
TA180; ustekinumab [9]	PHOENIX-1: UST 45mg; UST 90mg; PBO	93.7; 93.8; 94.2
	PHOENIX-2: UST 45mg; UST 90mg; PBO	90.3; 91.5; 91.1
	ACCEPT: ETN 50mg; UST 45mg; UST 90mg	90.8; 90.4; 91.0
TA 350; secukinumab [10]	FIXTURE: SEC 300mg; PBO	83.0; 82.0
	ERASURE: SEC 300mg; PBO	88.8; 89.7
	JUNCTURE: SEC 300mg; PBO	91.0; 90.2
	FEATURE: SEC 300mg; PBO	92.6; 88.4
TA146; adalimumab [15]	CHAMPION: ADA, PBO	81.7; 82.6
	REVEAL: ADA, PBO	92.3; 94.1
	M02-528: ADA, PBO	93.0; 94.0
	M02-529: ADA, PBO	92.4; 96.2
	M03-596: ADA, PBO	88.6 ; 100.2
TA134; infliximab [16]	Chaudhari et al 2001: INF, PBO	87.0; 85.0
	EXPRESS II: INF, PBO	92.2; 91.1

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ADA = adalimumab; ETN = etanercept; ICER = incremental cost-effective ratio; INF = infliximab; Ixe = ixekizumab; PBO = placebo; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

B18. **CS, section 5.5.2** Please use the higher and lower quartiles of the NHS reference costs as inputs for the probabilistic sensitivity analysis and provide the results for this analysis.

The upper and lower quartiles of NHS reference costs presented in Table 25 were entered as inputs into the probabilistic sensitivity analysis.[18] The probabilistic CE plane and results tables are presented in Figure 1 and Table 26.

Table 25: NHS reference costs - national average unit costs, lower quartile and upper quartile unit costs

Currency code	Currency description	Cost in model	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Derived SE
WF01A	Non-Admitted Face to Face Attendance, Follow-up (Dermatology)	Intravenous administration (infliximab)	£97.08	£71.87	£106.94	£128.80
-	Dermatology	Physician visit	£101.58	NR*	NR*	£128.80
DAPS05	Haematology	Full blood count	£3.01	£1.87	£3.67	£4.10
DAPS04	Clinical Biochemistry	Urea & electrolytes; liver function test, GFR	£1.19	£0.75	£1.38	£1.60

GFR = glomerular filtration rate; NR = not reported; SE = standard error

*Interquartile range assumed to be equivalent to that of WF01A Non-Admitted Face to Face Attendance, Follow-up (Dermatology)

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Figure 1: Probabilistic CE plane

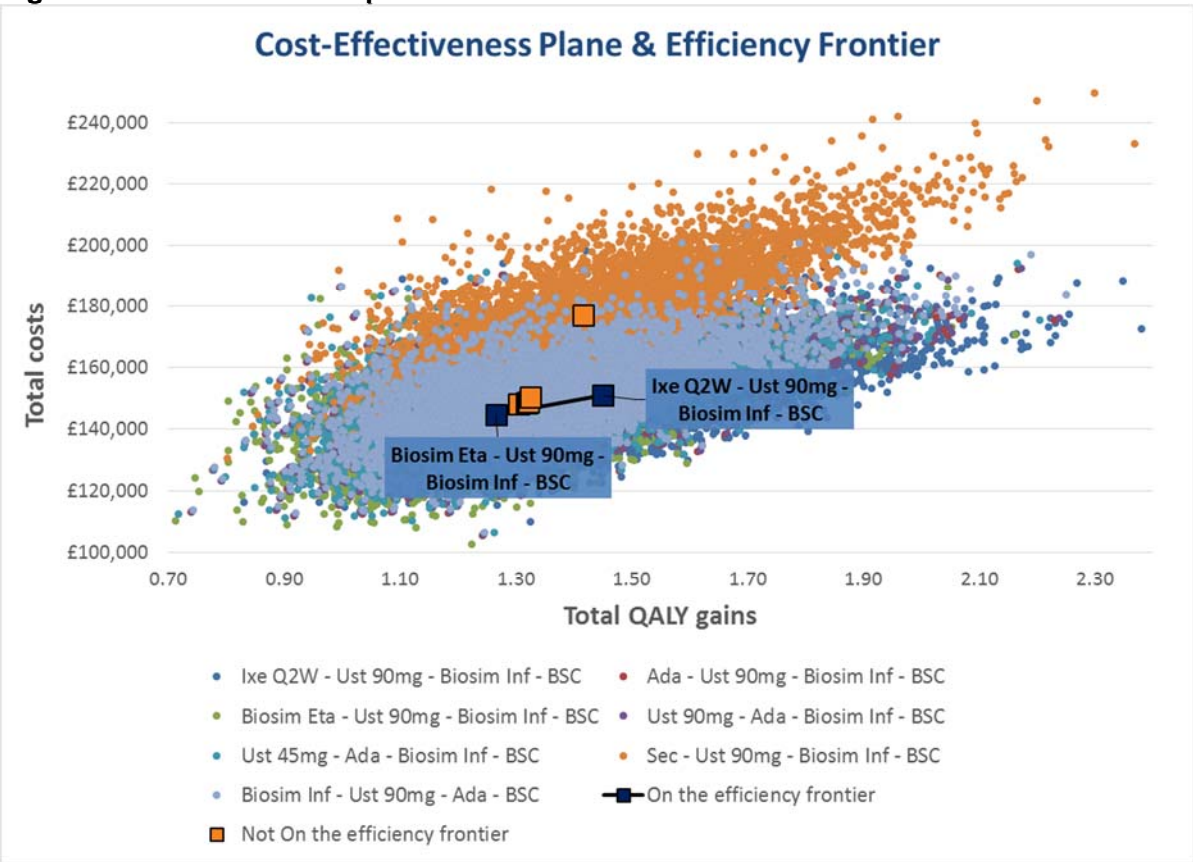

Table 26: Probabilistic CE results

Treatment sequence	Total costs	Total QALYs	ICER (incremental)
ETN sequence 1C	£145,653	1.30	Referent
UST 45 mg sequence 1F	£149,285	1.34	Extendedly dominated
ADA sequence 1B	£149,412	1.35	Extendedly dominated
UST 90 mg sequence 1G	£149,791	1.35	Extendedly dominated
INF sequence 1D	£151,681	1.36	Extendedly dominated
IXE Q2W sequence 1A	£151,766	1.48	£32,566
SEC 300 mg 1E	£179,209	1.45	Dominated

ADA = adalimumab; CE = cost-effectivenes; ETN = etanercept; ICER = incremental cost-effective ratio; INF = infliximab; Ixe = ixekizumab; SEC = secukinumab; UST = ustekinumab

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B19. **CS, section 5.5.2** Please justify which assumptions the resource use for the induction and maintenance periods are based on (CS Table 87). Please provide the primary source.

Resource use for therapies in the induction and maintenance periods are based on Table 7 and Table 10 of Appendix O of the cost-effectiveness analysis accompanying NICE Clinical Guideline 153.[3] A value of zero was entered for the number of physician visits associated with infliximab in the maintenance period as it was assumed that patients receiving infliximab would receive these visits during their outpatient visit for IV administration.

Results

B20. **CS, section 5.7** Please provide a summary of life years gained by health state using the format of Table 93 of the CS.

Mortality as modelled in the analysis is not differentiated by treatment; the driver of the QALY calculations is the health state utility gain associated with each PASI response. Whether single treatment comparators, treatment sequence comparators or treatments with different PASI response rates are chosen, life years gained are the same for all interventions, therefore incremental, absolute incremental and % absolute incremental life years gained are zero.

Excel model

B21. **PRIORITY REQUEST:** The model is programmed in VBA with an Excel user interface. The variables used in the VBA code are not defined, nor linked to the CS report. This severely hampers the transparency of the model.

- Please provide a full list of all parameter names used in the model.
- In addition, for each parameter in this list, provide the name used in the VBA code, the name used in the Excel sheet, cell reference in Excel sheet, a description, the value if applicable, se (standard error) and if applicable the corresponding name/description used in the CS report, as listed in the CS report (summary of variables applied in the economic model). As an example we completed the Table for “inputStartAge” (see Table below).

These have been sent in an excel file via encrypted USB to NICE.

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B22. The model can only calculate the results of ixekizumab versus one comparator at a time. As a consequence, a fully incremental probabilistic analysis with all comparators cannot be performed easily.

- Please adapt the model to make this possible, i.e. by incorporating the possibility to include all comparators simultaneously.

The model currently has the functionality to calculate results in a fully incremental analysis for both deterministic and probabilistic analyses.

The deterministic analysis is located on the worksheet "FullyIncrementalAnalysis". This can also be navigated to via the "Main" worksheet by clicking on "Fully incremental analysis" in the navigation bar. Select comparators using the dropdown lists in Table 1 for the fully incremental analysis of single treatments and Table 2 for the fully incremental analysis of treatment sequences, and click the "Run Tables" button to run the analysis. Deterministic results are displayed in the blue shaded area in rows 29:51; these are total costs, total QALYs, incremental costs, incremental QALYs, fully incremental analysis ICER results and pairwise ICER results for the ixekizumab intervention versus each other comparator.

The probabilistic fully incremental analysis is on the worksheet "PSA_CEAC_multi" and can be accessed via the "Sensitivity analysis" tab of the navigation bar, clicking on "PSA" and then clicking "PSA CEAC multi". Comparators can be selected in the dropdown lists in J12:M19 and the probabilistic analysis is run by clicking the "Run Multiple CEAC" button.

B23. In order to reproduce the results and to increase the transparency of the VBA code and the Excel interface, please explain whether/how the state trace PASI response (columns AI-BD) of the Patient distribution tabs can be calculated by using the 'Transition matrix'-tab.

A manual calculation of the state trace and outputs generated from the model are provided in the Excel workbook sent via encrypted USB to NICE. As the transition matrix does not include mortality, this has been excluded from the attached example for simplicity. The transition matrix is used to calculate the patient distribution in all health states (i.e. trial, maintenance, BSC and dead), and the patient distribution in the health states is used to calculate the PASI-response state trace.

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References

1. NICE pathways. Phototherapy for psoriasis 2015. Available from: https://pathways.nice.org.uk/pathways/psoriasis/phototherapy-for-psoriasis.pdf.
2. Paul C, Gallini A, Archier E, Castela E, Devaux S, Aractingi S, et al. Evidence-based recommendations on topical treatment and phototherapy of psoriasis: systematic review and expert opinion of a panel of dermatologists. J Eur Acad Dermatol Venereol. 2012;26 Suppl 3:1-10.
3. National Institute for Health and Care Excellence. The assessment and management of psoriasis. NICE guidelines [CG153]. 2012.
4. Bhutani T, Liao W. A Practical Approach to Home UVB Phototherapy for the Treatment of Generalized Psoriasis. Pract Dermatol. 2010;7(2):31-5.
5. Koo J, Lebwohl M. Duration of remission of psoriasis therapies. J Am Acad Dermatol. 1999;41(1):51-9.
6. National Institute for Health and Care Excellence. Apremilast for treating moderate to severe plaque psoriasis [TA368]. 2015.
7. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1-10.
8. Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technol Assess. 2006;10(46):1-233, i-iv.
9. National Institute for Health and Care Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis [TA180]. 2009.
10. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis [TA350]. 2015.
11. Eli Lilly and Company Limited. Clinical Section of HTA Toolkit for Pooled Studies. Data on file. 2015.
12. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. Br J Dermatol. 2010;163(4):807-16.
13. Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, Burden AD, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-40.
14. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987-1019.
15. National Institute for Health and Care Excellence. Adalimumab for the treatment of adults with psoriasis [TA146]. 2008.
16. National Institute for Health and Care Excellence. Infliximab for the treatment of adults with psoriasis [TA134]. 2008.
17. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol. 2015;172(1):244-52.
18. NHS reference costs 2014 to 2015. National schedule of reference costs: the main schedule [Internet]. 2015. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Pamela McHenry and Prof Catherine Smith, on behalf of the British Association of Dermatologists' Therapy & Guidelines and Biologic Interventions Register sub-committees

Name of your organisation: British Association of Dermatologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

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

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Moderate-to-severe psoriasis is currently treated with either phototherapy, progressing if necessary to conventional systemic therapies such as methotrexate and ciclosporin. As recognised and indicated in NICE guidance, ciclosporin and phototherapy cannot be used 'long-term' and so for those patients whose disease relapses rapidly following induction of clearance, methotrexate is the only approved intervention for long-term use. In those individuals unable to be controlled adequately by these means, biological therapies are prescribed if stipulated disease severity criteria are met (PASI 10, DLQI 10). Currently, the choice for these is TNF antagonists (infliximab, adalimumab or etanercept), ustekinumab or secukinumab. For those who do not respond to a first biologic, a second may be offered and after that referral to for further biologics or other approaches to those with interest/expertise in biologic therapy. The published NICE guidelines for the assessment and treatment of psoriasis CG53 and the British Association of Dermatologists' guidelines for the use of biological therapies inform this process (the latter is currently being updated). Whilst the approach nationally may not be uniform, quality standards exist against which to audit current practice.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Subgroups that differ from the 'typical' patient where IL-17 blockade may be of benefit include:

(i) primary treatment failures to existing biologic therapies
(ii) patients who lose response to biologics (around 15% of people, year on year)
(iii) patients who are intolerant of or in whom existing biologic therapies are contra-indicated, lose response to existing biologic therapies
(iv) patients with psoriasis and psoriatic arthritis who cannot use or have failed TNFi (Il-17 inhibitors are considered equivalent in efficacy to TNFi for psoriatic arthritis whereas ustekinumab is generally less effective)
(v) patients with severe disease where achievement of PASI 90 over-rides other aspects given the superior efficacy of IL-17 blockade

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

There will be very limited surveillance data on the safety and efficacy of this drug. As such, ixekizumab initially would not be a usual first-line agent; instead it would be used following sequential failure or contraindication of other biological therapies unless there was a clinical need for achievement of PASI 90 in the short term (for example those with very severe disease). The use of this agent is therefore restricted to departments used to handling severe psoriasis and biological therapies, who are participating in our long term pharmacovigilance registry (BADBIR); this effectively means the treatment is hospital-based secondary/ tertiary care units. It would not be suitable for use in primary care.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

The use of this drug is likely to be influenced by the NICE guidance and accumulated safety data going forward.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

An evidence review for NICE guidelines for the assessment and management of psoriasis CG153 was recently published. They consider all the available evidence for the diagnosis and management of psoriasis. There is no evidence available for the efficacy and safety of ixekizumab at UK national level yet. The British Association of Dermatologists' guidelines are currently being updated and may include recommendations on ixekizumab.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

This therapy will potentially provide an alternative for those patients who do not respond or have failed therapy to a first biologic (likely adalimumab or ustekinumab)

It has a different mode of action, and has slightly extended activity compared to secukinumab given it binds both 17 A and F. Ixekizumab is a subcutaneous injection appearing as a comparator with other biological therapies. Currently though, there is limited safety data which will mean in the first instance, that it is unlikely to be used as a first-line biological therapy but rather reserved for sequential use after primary or secondary failure. Accrual of long-term safety data will be essential to properly establish the place in therapy (for example, via the British Association of Dermatologists Biologics Interventions Register, BADBIR).

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There is no 'real world data' available. Data from trials indicate a safety record comparable to biologic therapies currently available for psoriasis. IL-17 blockade confers additional risk of candida infection but to date these infections have been superficial and minor.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must

include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

There are none beyond that supplied by the manufacturers.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The resources required to deliver this drug from secondary/tertiary care settings are already in place. Staff would not need any extra training once they were familiar with its licensing indications. A recommendation that all patients being treated with ixekizumab should be entered onto a long-term safety register (i.e. BADBIR) would ensure comprehensive, high quality data including opportunity to compare efficacy and safety with existing biologic therapies is available.

Equality

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We do not see any issues with respect to equality in general. For those individuals with severe psoriasis who have failed to be controlled with the biological therapies currently licensed though, excluding ixekizumab means denying these individuals a possible therapy, since IL-17A blockade is not an otherwise available pharmacological intervention.

The intervention is not currently licensed in children and young people.

When considering use of ixekizumab for psoriasis the committee may wish to review the criteria for biologic therapy in general.
The current disease severity criteria were established at the beginning of the biologic era. The profession, public and patients now recognise the limitations of the PASI and DLQI in failing to identify all patients who would benefit very greatly from biologic therapy. The PASI score tends to underestimate disease severity in people with brown or black skin and thus the current disease severity criteria for biologics and therefore the current disease severity criteria may be potentially discriminatory. In addition, it is recognised that the DLQI has limited validity in those not working, who are older and may also miss anxiety and depression. Finally, patients with limited body surface area involvement, but nevertheless severe disease at high need sites (for example, hands and feet, genital sites, face and scalp) do not currently 'qualify' for biologics as the PASI is relatively low. The numbers of patients overall affected in this way is likely to be small, but nevertheless in the absence of access to biologics, high consumers of health care and suffering major impact.

A further difficulty with the current approach to treatment response is the requirement to demonstrate a change i.e. PASI 50. In those who are switching because of side effects or in whom their current treatment is losing response but not complete loss of response to their 'baseline' activity, patients may be forced to come off all therapy to achieve the baseline and to ensure an adequate 'delta' is demonstrated. Ultimately, response to therapy should be based on the absolute level of disease activity. Revised draft recommendations from our BAD Biologics guideline (due for public

consultation imminently) as well as the NICE GL attempts to address this issue with the following recommendations:
Offer biologic therapy to people with psoriasis if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated( ) and
the psoriasis has a large impact on physical, psychological or social wellbeing (for example a DLQI of 10 or more) and one or more of the following apply:
• the psoriasis is extensive (for example, BSA>10%, or a PASI≥10, or at least moderate on physician's global assessment( )
• the psoriasis is severe at localised sites and associated with significant functional impairment and /or high levels of distress (for example nail disease or involvement at high-impact sites).
Consider biologic therapy earlier in the treatment pathway (for example if methotrexate has failed, is not tolerated or is contra-indicated) in people with psoriasis and active psoriatic arthritis ( ) or in people with extensive and persistent chronic stable plaque psoriasis.

Review response to biologic therapy by taking into account:

- psoriasis disease severity compared with baseline (for example, Psoriasis Area and Severity Index [PASI] baseline to endpoint score) and how it relates to the agreed treatment goal (for example PASI 5 or less)
- control of psoriatic arthritis disease activity and / or inflammatory bowel disease (in consultation with a rheumatologist and / or gastroenterologist))
- the impact of psoriasis on the person's physical, psychological and social wellbeing
- the benefits versus the risks of continued treatment
- the views of the person undergoing treatment (and their family or carers where appropriate)

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Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Society for Rheumatology

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? Yes, Policy and Public Affairs Officer
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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Psoriasis is treated by GPs and dermatologists in the UK. Most moderate/severe psoriasis is referred to secondary care for further treatment. In general patients receive topical therapies, systemic non biologic drugs and systemic biologic therapies (often in that order). There are well established treatment recommendations for the management of psoriasis and for the use of biologic therapies in moderate to severe disease. Ixekizumab is the second interleukin (IL) 17 inhibitor to become available for psoriasis (after Secukinumab which is already NICE approved). As a class of drugs, ixekizumab and Secukinumab appear to have similar clinical responses and safety signals.

For patients with moderate to severe psoriasis who have failed standard systemic therapies such as methotrexate/cyclosporine, the options for treatment are TNF inhibitors (etanercept, adalimumab, infliximab), IL12/23 inhibitor (ustekinumab) or an IL17 inhibitor. All of these therapies are highly efficacious for the treatment of psoriasis and the related condition psoriatic arthritis which occurs in up to 30% of people with psoriasis.

The IL17 drugs have been shown to be superior to anti-TNF therapies (both head to head with etanercept) and Secukinumab has demonstrated superior efficacy to ustekinumab. I am currently acting as the British Society of Rheumatology rep for the British Association of Dermatology Guidelines for the management of PsA and they have performed a large network meta-analysis to compare the therapies. They felt that ustekinumab and Secukinumab were the best treatments for psoriasis from the data available and I believe that ixekizumab has similar response rates to Secukinumab. Importantly for patients with psoriatic arthritis (around 30% of patients with psoriasis) the results in psoriatic arthritis appear to be (no head to head trials) superior with IL17 inhibitors compared to ustekinumab so either Secukinumab or ixekizumab would be a better option for those with arthritis.

Variation in practice may arise with different rheumatology/ dermatology collaborations / combined clinics where there may be greater emphasis on considering total disease burden (skin/ joints/ spine/ etc etc) and as such potentially greater systemic drug use (DMARD and Biologic).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Not that I am aware. Obviously there are safety issues with comorbidities that should be addressed prior to biologic prescription. Neither of the IL17 inhibitors have shown any signal with depressive or suicidal ideation as was identified in the brodalumab programme. Both Secukinumab and ixekizumab are IL17A monoclonal antibodies rather than IL17 receptor antagonists which may explain a biological difference.

A specific caution for both IL17 inhibitors is the possible emergence or exacerbation of disease amongst patients with inflammatory bowel disease. There is no indication this is any different between Secukinumab and Ixekizumab.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Secondary care dermatology clinics alongside other biologics already approved for treatment of psoriasis. No new professional input would be required.

Ixekizumab is administered subcutaneously at baseline then at weeks 2, 4, 6, 8, 10 and 12, and then every 4 weeks thereafter. As with other self-administered subcutaneous biologic and DMARD drugs community provision is required for drug delivery and sharps collection but this is no different from existing technologies (methotrexate/ anti-TNF / IL12/23 inhibition or seculinumab).

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Ixekizumab is not currently available but Secukinumab (already approved) is a very similar compound with the same mode of action

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

As stated above, I am involved with the ongoing BAD guidelines in development led by Professor Catherine Smith at Kings College London. The network meta-analysis did not consider ixekizumab as it is not currently available. However it did suggest that Secukinumab and ustekinumab should both be considered as first line therapies with Secukinumab preferred for patients with psoriatic arthritis. I believe that ixekizumab has similar mode of action, efficacy and safety profile to Secukinumab.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical

implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

I believe that ixekizumab is similar in use for both health professionals and patients to the other approved biologic therapies including Secukinumab. There are no additional requirements for this particular drug.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

I would recommend a similar position to that of Secukinumab for patients with moderate to severe psoriasis who have failed standard systemic therapies and/or phototherapy.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

I think the trials were relatively reflective of UK practice although some patients may not have previously failed systemic therapies. Certainly many of the patients in the trials had previously failed systemic therapies and the drug was effective in this population group.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

I am not aware of any additional safety signals related to ixekizumab beyond that found in the trials although obviously the IL17 agents are newer and have less cumulative experience than earlier biologic therapies such as the TNF inhibitors. There is a specific safety signal related to fungal infections because of the IL17 blockade but both in trials and in my previous clinical practice (observing practice in the USA) this is commonly mild and easy to treat in the majority of cases.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from

registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No – although access to the network meta-analysis performed for the BAD guidelines may already have been shared or could be requested via Professor Catherine Smith at KCL

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

This technology can be implemented alongside existing biologics in dermatology secondary care. I do not envisage any requirement for additional resources required for this specific drug.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

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- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities. **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** No issues.

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Patient/carer organisation submission (STA)

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Psoriasis and Psoriatic Arthritis Alliance

Your position in the organisation: [redacted]

Brief description of the organisation:

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

PAPAA is a principal source of advice, support and information on psoriasis and psoriatic arthritis in the United Kingdom. PAPAA provides support to people with psoriasis and psoriatic arthritis, their families and carers. PAPAA also supports healthcare professionals and assists the wider community to understand the needs of people affected by both conditions.

The organisation maintains a register of people with/or interested in both conditions. The register currently has >13,000 people, and is free to join.

Funding of the organisation is mainly via donations, legacies, and subscriptions.

Primary activity is to provide information, education and support, via a website, information line (both electronic and voice), along with the provision of printed information, produced under The Information Standard scheme. Other activities include a biannual journal called Skin 'n' Bones Connection. Disease management and training programmes are also an important role the charity wishes to take forward.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: *None*

The organisation has a strict funding and external involvement policy and does not accept funding from commercial companies either directly, in kind or via third party agencies. This includes but not limited to, pharmaceutical companies, the tobacco industry, public relations agencies, lobbying firms and other organisations including charities whose activities could cause conflict, due to their own funding sources and policies.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

In order to inform this submission we carried an online survey (17 June 2016), via the PAPAA website as free text form submissions, and promoted via social media. At the point of producing this submission, the mean age of responders was 49 years old (range 37 - 51) with a split of male 54% female 46%. 80% respondents live in England.

We asked the following questions:

1. *What is it like to live with psoriasis?*
2. *What do you want a treatment to provide and what is most important?*
3. *What do you think of the current treatments available on the NHS?*
4. *How acceptable are these different treatments and which do you prefer and why?*

All replies were anonymous, with only basic personal data collected of age, gender and location. The responses have been slightly edited to remove patient and professional identifiers. The following are a selection, and reflect the general views of those who responded.

It needs to be taken into consideration that the responders to this survey may be more proactive, in seeking information, have access to the internet and social media, therefore not be 100% representative of the total psoriatic population, where many live with disease, which is well-controlled and adequately managed by the current medications and treatments available.

What is it like to live with psoriasis?

“Worried for the future. At the moment the side effects from methotrexate are worse than the condition!”

“Awful.It's a combination of pain, weakness, deformity, dreadful fatigue and the uncertainty of knowing what each day will bring.”

“There are also huge psychological issues around "what might have been" as well as appearance in terms of skin problems, deformity and "disabledness" - even from a young age.”

“Frustrating and embarrassing. I often live in cyclical stress of knowing I could break out and knowing I need to control my stress levels.”

“When at its worst and uncontrolled it was unbearable. I used to get it on the back of my head so as it shed it always looked like dandruff. I had it on my back and worst of all around my backside, which used to get so raw I literally could not walk at all. And I am only in my 30s.”

“Intrusive. I have found my life has become a lot more insular due to the constant fatigue and attitude towards skin issues.”

“It's embarrassing & demoralising for me. I have very bad psoriasis on both knees and elbows. I do wear T shirts & short sleeved tops but I ALWAYS have to wear long dresses, trousers or leggings to hide my unsightly knees, otherwise I notice other people staring at my knees. That's not a good feeling.”

“As a teenager horrendous, suicide attempt, eating disorder, still have issues with body image 30 yrs later. Worst comment received: being told by a passing stranger I should kill myself so people didn't have to look at me, but received unpleasant / embarrassing comments most days from total strangers.”

“The shame of smelling of coal tar and leaving piles of scales wherever I was sat. Not forgetting the itching, pain, sleepless nights.”

"Unable to get jobs in anything relating to food/ drink, public facing because of it. First medical to get into nurse training was failed as having psoriasis proves you're mentally incapable of holding a job down (2nd Dr not so antiquated in attitude)."

" Has been less severe over last decade, controlled with tight diet that is slightly restricting socially but prefer this to the psoriasis, even ventured back to dermatology (gave up on them as no topical treatments worked and not offered anything else)"

"I've had it since I was 13, that horrible self conscious age, when you really want to fit in, I've hated it all the years I've had it, I've had it get that bad that I've considered suicide, as an end to the horrible painful, itchy scales and the looks off people that think you have a contagious disease."

"Only had symptoms in the last four years, as an adult. Is a struggle to live with. More so when coupled with arthritic symptoms too."

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

What do you want a treatment to provide and what is most important?

"Ideally a cure but failing that a calming of the symptoms. The visual of psoriasis is awful but I can live with that if the cracking skin and pain can be reduced. I wish to continue an active lifestyle."

"Maintenance without extreme health risks"

"A treatment would ideally provide relief from psoriatic based skin complaints with the added bonus of not taking any medication that has been proven to cause quite severe side affects"

"I would like treatment that works! Coal tar cream keeps the crusty skin to pink BUT it never clears it up AND it stains. It's not a very good treatment when you work as a receptionist for general public. Nothing I have tried ever clears

it up. I would like a liquid or clear cream to apply at night maybe wash off in morning?"

"Ease of use, accessible when needed. No disabling side effects."

"Relief and a "normalish" life"

"Simply...a cure. Joint pain relief is more important to me, rather than skin-side"

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

What do you think of the current treatments available on the NHS?

"Thankful that there are some treatments but having difficulty dealing with the side effects. Have psychosomatic symptoms."

"There appears to be a reasonable range available, but prescribing guidelines do not seem to be uniform nationwide."

"They're scary. You trade one disease for many others, including cancer. Who wants that?"

"Poor availability. 30+ years of heavy topical steroid use has impacted. Only recently had access to acitretin and methotrexate which did nothing for me. Had to push very hard to get access to these and only once I was at the point of not being able to carry out day to day activities any more. Currently on ciclosporin which is having a positive impact but clear concern from the specialist over safety."

"Scary"

"I am lucky. My initial treatments were useless, I used tonnes of creams and useless sulfasalasine, which didn't help."

"That depends to whom you speak. I have found the advice/knowledge of the disease varies massively between supposed professionals. I always try to go

with as much research as possible so I cannot be 'palmed' off with whatever they assume I need."

"Nothing works. I have had psoriasis for 27 years and no treatment I have tried has ever worked"

"More treatments available, less emphasis for severe disease on the unpleasant topical treatments of 80s/ 90s"

"I love humira, I've been on it 6 months and I wish to god I'd of known about it when it first came out!"

"I've been on a lot of topical treatments with no success. And also newer biologics like stelara and otezla, with limited success. I am about to start cosentyx".

How acceptable are these different treatments and which do you prefer and why?

"Only ever been offered methotrexate so far"

"The acceptable ones are those that work and different patients appear to have different rates of success as well as a range of different side-effects; some tolerable, some not."

"I think NICE should maintain a wide range of different options."

"I am taking methotrexate and apremilast, but I don't feel they are helping with my chronic pain. Apremilast cleared my skin lesions, but not helping with pain."

"Lotions and creams are difficult and time consuming with limited effect. Ciclosproin is the only systemic treatment with any success but already aware I cannot take this for long. Enquired about other treatments (cosentyx) many time but this is not available to me."

"Because I don't have debilitating symptoms the risks don't outweigh the benefits."

"Humira is the best, no psoriasis or arthritis. All the other treatments were ineffective."

"Coal tar is very good for me but it stains and is messy. It never fully works just keeps it at bay.".

"It has cleared my skin and as a woman that loves fashion and clothes, I can finally dress in short sleeves and show my legs. Not be all covered up and worrying about how awful my skin is."

"I have a phobia of needles, so prefer tablets. Though tablets have side effects too."

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

A reduction in visible symptoms of psoriasis, with 100% clearance being a goal, but with minimal side-effects or at least the ability to manage any adverse events.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

We have no information to answer this question.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

We have no comments to add.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

The high cost of new therapies appears to limit or delay access. People complain that they often have to wait to qualify, whilst remaining on a failing treatment with their symptoms worsening. The side effects also worry people, methotrexate appears to be most disliked and feared.

Please list any concerns patients or carers have about the treatment being appraised.

The cost of these treatments and how that cost will limit patient access, is of concern. There are also concerns about the safety and long-term risk benefits, particularly the chance of developing lymphomas or malignancies.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Not that we are aware, but as the target is IL17, and if responders could be identified before treatment starts, that could prove to be a useful group to target.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

✓☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The trial UNCOVER-2 & UNCOVER-3 compared ixekizumab with placebo, and anti-TNF etanercept, which is in use within the NHS, it would appear plausible that this would match what is currently the patient experience of these types of therapy.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes, we think issues that patients find important have been studied. The study looked at PASI75 (75% improvement from base case) PASI90 and PASI100 (clearance) with a figure of 40% achieving the latter. Patients want clearance, so that gets some way towards meeting that, in a significant group in the trial. The trial also suggested, *"...achieving PASI90 or a PASI100 has become a*

new therapeutic goal". As an organisation, we would agree with this and believe that this should become the standard minimum target for any new treatment of psoriasis being appraised.

Improvements of itch were reported at week 1 with more than 80% showing improvements at week 12. Itch is a significant issue to patients. Improvement in quality of life is also important and 40% reported improvement by week 12. Whether these sustain over time is another matter.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Cannot comment.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ✓☐ No

If yes, please provide references to the relevant studies.

n/a

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

No.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

There is always a suggestion around self-injecting and those with phobias, or poor hand mobility, which this group may have if psoriatic arthritis is present, but looking at the feedback we receive, people appear to cope with the therapies and methods of administration, or find ways to cope, as long as there is a treatment benefit.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ✓☐ No

Not particularly, given similar targeted treatment exist within the NHS.

If yes, please explain what makes it significantly different from other treatments for the condition.

n/a

Are there any other issues that you would like the Appraisal Committee to consider?

Adding long-term monitoring as a condition of use, via registries such as BADBIR.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Recognition that psoriasis for some can be a debilitating disease that impacts all aspects of life, physically and psychologically.
- Clearance of all symptoms is important to people with psoriasis, with no visible signs of disease.
- Low or manageable side-effects.

- Access to treatments and a wide choice available in pathway if treatments fail.
- Ability to live a full life unhidden by disease or treatment

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Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by the **British Society for Rheumatology** and consequently I will not be submitting a personal statement.

Name: Neil McHugh

Signed: 

Date: 16/09/2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **British Association of Dermatologists (BAD)** and consequently I will not be submitting a personal statement.

Name: Prof Catherine Smith

Signed: [redacted]

Date: 28/09/16

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Psoriasis and Psoriatic Arthritis Alliance and consequently I will not be submitting a personal statement.

Name: .....David Chandler.....

Signed: .  .....

Date: .....6/9/16.....

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Ixekizumab for treating moderate to severe chronic plaque psoriasis

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views 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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Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Manuela Joore acted as health economist project lead on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Xavier Pouwels, Marije Oosterhoff, Bram Ramaekers, Anoukh van Giessen and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Ching-Yun Wei acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ADA	Adalimumab
AE	Adverse event
AESI	Adverse event of special interest
AiC	Academic in confidence
BAD	British Association of Dermatologists
BID	Twice daily
BIW	Twice weekly
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CEM	Cost-effectiveness model
CG	Clinical guideline
CI	Confidence interval
CiC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
DEF	Data extraction form
DLQI	Dermatology Life Quality Index
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EED	Economic Evaluations Database
EMA	European Medicines Agency
EOW	Every other week
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life-5 Dimensions, five-level scale
ERG	Evidence Review Group
ETN	Etanercept
ETV	Early termination visit
EUCTR	European Clinical Trials Register
EUR	Erasmus University Rotterdam
GFR	Glomerular filtration rate
GP	General Practitioner
HADS	Hospital anxiety and depression scale
HAM-D	Hamilton Rating Scale for Depression
HEED	Health Economics Evaluations Database
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICHUSHI	Igaku-Chuo-Zasshi (Japanese Medical Research Database)
ICTRP	International Clinical Trials Registry Platform
IGA	Investigator's Global Assessment
IL-17A	Interleukin-17A+
INF	Infliximab
ISE	Injection site reaction
ITT	Intention to Treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
IXE	Ixekizumab
KSR	Kleijnen Systematic Reviews

LOCF	Last-observation-carried-forward
LSM	Least squares mean
mAb	Monoclonal antibody
MCID	Minimal clinically important difference
MeSH	Medical Subject Headings
MIMS	Monthly Index of Medical Specialities
mg	Milligram
MTC	Mixed Treatment Comparison
MTX	Methotrexate
N/A	Not applicable
NAPSI	Nail Psoriasis Severity Index
NBST	Non-biologic systemic therapies
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
NR	Not reported
NRS	Numerical rating scale
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PCP	Pneumocystis pneumonia
PDI	Psoriasis Disability Index
PGA	Physician Global Assessment
PPASI	Palmoplantar Psoriasis Severity Index
PRESS	Peer Review of Electronic Search Strategies
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analyses
PSI	Psoriasis symptom inventory
PSS	Personal Social Services
PSSI	Psoriasis Scalp Severity Index
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen plus ultraviolet A light
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
Q12W	Once every 12 weeks
QALY	Quality-adjusted Life Year
QID	Four times a day
QIDS	Quick inventory of depressive symptomatology
QIW	Four times a week
RCT	Randomised controlled trial
RRfC	Response to request for clarification
SAE	Serious adverse event
SC	Subcutaneous
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF-36	Short form 36
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
sPGA	Static Physician Global Assessment

STA	Single Technology Appraisal
UMC	University Medical Centre
UST	Ustekinumab
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TNF-α	Tumour necrosis factor alpha
Trt	Treatment
TSD	Technical Support Document
TTO	Time trade off
UK	United Kingdom
UVA	Ultraviolet A
UVB	Ultraviolet B
UST	Ustekinumab
VAS	Visual analogue scale
VBA	Visual Basic for Applications
WHO	World Health Organisation
WPAI	Work and activity impairment questionnaire
WTP	Willingness to pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The company described the disease as "*a common chronic inflammatory skin disease that is characterised by the appearance of prototypic red, thick and scaly plaques*" which causes physical disability, pain, discomfort and psychological stress, including impairment in personal and professional relationships, and poor health-related quality of life.

The population, according to the final scope issues by the National Institute for Health and Care Excellence (NICE), is defined as *"adults with moderate to severe plaque psoriasis"*. In the decision problem presented in the company submission (CS), the population definition is narrower (*"moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"*) but appears to be in line with the final scope. However, there is no agreed consensus on the terminology used to clarify the severity of psoriasis with various Psoriasis Area and Severity Index (PASI) thresholds suggested to define moderate to severe or severe psoriasis, respectively.

The definition of the intervention is in line with the definition in the final scope and identical to the definition used in the summary of product characteristics (SmPC) by the European Medicines Agency (EMA) which reads: *"The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks"*.

Four comparators *"for people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated"* are listed in line with the final scope issued by NICE, namely *"TNF-α inhibitors (etanercept, infliximab, adalimumab), ustekinumab, secukinumab, best supportive care"*. Two additional comparators, *"systemic non-biological therapies (including acitretin, ciclosporin, fumaric acid esters, methotrexate)"* and *"phototherapy with UVB [ultraviolet B] radiation"* are listed *"if non-biologic treatment or phototherapy is suitable"*. Some of these comparators were excluded in the CS as *"there was insufficient evidence to include other non-biologic systemic therapies and phototherapy (i.e. acitretin, fumaric acid esters, and phototherapy) that were listed in the scope"*. However, it is unclear how many studies have been excluded and whether this could have had an impact on the network meta-analysis (NMA).

The outcomes reported in the CS are broadly in line with the final scope. However, as the CS states *"psoriasis symptoms of the face have not been included in the submission as there is no reference to this outcome measure in the SmPC, which focuses on psoriasis of the nails, scalp and palmoplantar areas"*.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS and response to clarification provided sufficient details for the ERG to appraise the searches. A good range of databases were searched, and additional searches of conference proceedings and other relevant resources including trials databases, specialist and organisational websites and HTA agencies were reported.

The evidence base for the clinical efficacy of ixekizumab in the treatment of moderate to severe plaque psoriasis in adults consists of three randomised controlled trials, as identified by a systematic literature review: UNCOVER-1, UNCOVER-2 and UNCOVER-3. The UNCOVER studies were phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient trials comparing the efficacy and safety of ixekizumab to placebo in patients with moderate to severe

plaque psoriasis. In addition, the UNCOVER-2 and UNCOVER-3 studies included an active comparator (etanercept) arm.

The primary outcomes were sPGA (0,1) and PASI 75 at week 12. In all three UNCOVER trials, there were statistically significant increases in sPGA (0,1) and PASI 75 response rates for patients treated with ixekizumab compared with placebo and etanercept at week 12. Furthermore, the improvements in PASI response rate appeared to be maintained for up to 60 weeks during of the long-term extension period. Health-related quality of life improved compared to baseline in significantly more patients with ixekizumab than with placebo and etanercept. The relative performance of ixekizumab in difficult-to-treat areas, including nails, scalp and palmoplantar areas was broadly better than placebo and etanercept. However, the improvement in psoriasis symptoms of the face which is included in the final scope was not reported in any of the UNCOVER studies. Table I presents outcomes reported in the UNCOVER trials after 12 weeks.

Ixekizumab was generally well tolerated in the UNCOVER trials, with similar discontinuation rates due to adverse events as placebo or etanercept. The most frequent adverse events of special interest observed in the UNCOVER studies were infections and injection site reactions. Two deaths were recorded in the UNCOVER-1 trial (one by myocardial infarction and the other of unknown causes).

Three NMAs were conducted to compare the relative efficacy of ixekizumab against a network of relevant comparators, including adalimumab, ciclosporin, etanercept, infliximab, methotrexate, secukinumab, and ustekinumab. [redacted]

The result of two scenario analyses comparing ixekizumab with etanercept 50 mg twice weekly (BIW) and standard systemic treatments, respectively, were also consistent with the base-case.

Table I: Summary of results for clinical endpoints (ITT population, 12 weeks)

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
Severity of psoriasis (sPGA)											
sPGA (0,1), n (%)	14 (3.2)	330 (76.4)†	354 (81.8)†	4 (2.4)	129 (36.0)†	253 (72.9)†‡	292 (83.2)†‡	13 (6.7)	159 (41.6)†‡	291 (75.4)†‡	310 (80.5)†‡
OR vs. PBO (95%CI) p-value	-	102.89 (57.52, 184.04) <0.001	146.51 (81.02, 264.92) <0.001	-	27.58 (9.40, 80.98) <0.001	120.29 (39.95, 362.22) <0.001	282.24 (76.03, 1047.7) <0.001	-	11.30 (6.01, 21.25) <0.001	40.84 (21.10, 79.03) <0.001	50.47 (26.54, 95.98) <0.001
OR vs. ETN (95% CI) p-value	-	-	-	-	-	5.37 (3.82, 7.56) <0.001	10.70 (7.23, 15.85) <0.001	-	-	4.80 (3.46, 6.67) <0.001	6.47 (4.55, 9.20) <0.001
Response rate (PASI 75)											
PASI 75, n (%)	17 (3.9)	357 (82.6)†	386 (89.1)†	4 (2.4)	149 (41.6)†	269 (77.5)†‡	315 (89.7)†‡	14 (7.3)	204 (53.4)†‡	325 (84.2)†‡	336 (87.3)†‡
OR vs. PBO (95%CI) p-value	-	125.54 (72.26, 218.10) <0.001	223.94 (125.05, 401.03) <0.001	-	30.73 (10.83, 87.16) <0.001	160.50 (51.33, 501.87) <0.001	997.29 (173.11, 5,745.5) <0.001	-	13.71 (7.61, 24.72) <0.001	68.95 (34.53, 137.68) <0.001	72.29 (36.11, 144.73) <0.001
OR vs. ETN (95% CI) p-value	-	-	-	-	-	5.05 (3.60, 7.09) <0.001	13.28 (8.66, 20.34) <0.001	-	-	4.91 (3.46, 6.98) <0.001	6.46 (4.42, 9.45) <0.001
Health-related quality of life (DLQI)											
Change from baseline, LSM (SE)	-0.7 (0.29)	-10.3 (0.29)†	-10.7 (0.28)†	[redacted]	[redacted]	[redacted]	[redacted]	-1.5 (0.32)	-8.1 (0.23)†	-9.6 (0.23)†‡	-10.0 (0.23)†‡
Patients with DLQI (0,1) (NRI), n (%)	20 (4.6)	258 (59.7)†	287 (66.3)†	[redacted]	[redacted]	[redacted]	[redacted]	15 (7.8)	167 (43.7)†	246 (63.7)†‡	249 (64.7)†‡

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
OR vs. PBO (95%CI)	-	31.16 (19.09, 50.85) <0.001	41.54 (25.37, 68.02) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	10.51 (5.75, 19.20) <0.001	21.05 (11.58, 38.27) <0.001	21.00 (14.1, 27.9) <0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	2.32 (1.72, 3.12) <0.001	2.38 (1.77, 3.20) <0.001
Psoriasis symptoms on the face, scalp and nail											
Face[#]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NAPSI score mean change from baseline, LSM (SE)	2.30 (0.736)	-7.14 (0.733)[†]	-7.12 (0.696)[†]	[redacted]	[redacted]	[redacted]	[redacted]	1.12 (0.98)	-6.64 (0.68)[†]	-9.84 (0.70)[†‡]	-10.41 (0.70)[†‡]
Patients with NAPSI (0) (NRI), n (%)	10 (3.5)	36 (12.7)[†]	48 (16.9)[†]	[redacted]	[redacted]	[redacted]	[redacted]	5 (4.3)	24 (10.2)	45 (19.7)[†]	40 (17.5)[†]
OR vs. PBO (95%CI)	-	3.99 (1.94, 8.21) <0.001	5.74 (2.84, 11.63) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	p=0.099	p<0.001	p<0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	p=0.004	p=0.009
PSSI score mean change from baseline, LSM (SE)	-1.5 (0.55)	-18.3 (0.54)[†]	-19.0 (0.54)[†]	[redacted]	[redacted]	[redacted]	[redacted]	-5.0 (0.51)	-15.6 (0.37)[†]	-18.1 (0.37)[†‡]	-18.6 (0.36)[†‡]
Patients with PSSI (0) (NRI), n (%)	21 (5.3)	287 (69.5)	290 (73.8)	[redacted]	[redacted]	[redacted]	[redacted]	16 (9.1)	178 (51.1)[†]	253 (72.5)[†‡]	264 (75.6)[†‡]
OR vs. PBO (95%CI)	-	42.24 (25.86, 69.02) <0.001	53.11 (32.25, 87.49) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	<0.001	<0.001	<0.001

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	<0.001	<0.001
PPASI score mean change from baseline, LSM (SE)	0.57 (0.64)	-5.34 (0.63)†	-5.39 (0.59)†	[redacted]	[redacted]	[redacted]	[redacted]	-2.55 (1.02)	-6.13 (0.78)	-7.65 (0.84)†	-7.64 (0.80)†
Patients with PPASI 100 (NRI), n (%)	27 (20.3)	86 (65.6)†	98 (70.0)†	[redacted]	[redacted]	[redacted]	[redacted]	15 (27.8)	57 (60.0)	54 (62.1)†	61 (63.5)†
OR vs. PBO (95%CI)	-	7.68 (4.39, 13.43) <0.001	9.72 (5.52, 17.11) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	<0.001	<0.001	<0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	p=0.466	p=0.236

Source: Based on Tables 21-25, 29, 31, 33, 34, 37-45 of the CS[1], Griffiths et al. 2015[2] and CSRs for UNCOVER-1 and -2[3, 4]

Data are least squares mean (SE), n (%), or % (CI). Data were analysed with the Cochran-Mantel-Haenszel test with non-responder imputation for response rates and mixed-models repeated-measure analysis for least squares mean change from baseline Itch NRS, DLQI, NAPSI, PSSI and PPASI

† p<0·001 compared with placebo. ‡ p<0·001 compared with etanercept; # Included in the final scope but not reported in any of the studies

ETN = etanercept; ITT = intention to treat; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; n = number of patients in the specified category; N = number of patients in the analysis population; NAPSI = Nail Psoriasis Severity Index; NR = not reported; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; Q2W = once every 2 weeks; Q4W = once every 4 weeks; sPGA = static Physician Global Assessment

Table II: Summary of results for clinical endpoints (ITT population) at week 60

	UNCOVER-1						UNCOVER-2					
Endpoint	IXE80 Q4W /PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W	IXE80 Q4W/ PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W
Relapse rate – Clinical responses at 60 weeks												
sPGA (0,1), n (%)	8 (7.3%)	78 (70.9%)	9 (7.7%)	89 (74.8%)	17 (7.5%)	167 (72.9%)	4 (4.9)	56 (65.9)	7 (7.4)	84 (82.4)	11 (6.3)	140 (74.9)
OR vs. PBO (95%CI)	-	33.10 (14.33, 76.45) <0.001		38.82 (17.35, 86.87) <0.001	-	35.84 (20.01, 64.20) <0.001	-	37.66 (12.53, 113.16) <0.001	-	58.00 (23.04, 145.99) <0.001	-	44.67 (22.32, 89.41) <0.001
PASI 75, n (%)	9 (8.3)	85 (77.3)	11 (9.4)	93 (78.2)	20 (8.8)	178 (77.7)	6 (7.3)	60 (70.6)	8 (8.5)	91 (89.2)	14 (8.0)	151 (80.7)
OR vs. PBO (95%CI)	-	41.33 (18.12, 94.31) <0.001	-	38.09 (17.64, 82.23) <0.001	-	39.53 (22.45, 68.63) <0.001	-	30.40 (11.72, 78.84) <0.001	-	88.93 (34.14, 231.61) <0.001	-	48.53 (25.19, 93.52) <0.001
Psoriasis symptoms on the scalp and nail												
Face	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NAPSI score *mean change from baseline, LSM (SE)*	-9.32 (1.26)	-18.34 (1.32)†	-8.77 (1.28)	-19.49 (1.28)†	-9.06 (0.90)	-18.93 (0.92)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with NAPSI (0), n (%)	3 (3.8)	33 (44.6)†	0 (0)	38 (50.0)†	3 (1.9)	71 (47.3)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UNCOVER-1						UNCOVER-2					
Endpoint	IXE80 Q4W /PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W	IXE80 Q4W/ PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W
OR vs. PBO (95%CI)	-	20.12 (5.80, 69.75) <0.001	-	N/A N/A <0.001	-	46.72 (14.24, 153.30) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSSI score *mean change from baseline,* LSM (SE)	-12.2 (0.80)	-19.0 (0.81)†	-8.9 (0.81)	-19.5 (0.78)†	-10.6 (0.58)	-19.2 (0.57)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with PSSI (0), n (%)	5 (4.7)	73 (70.2)†	7 (6.9)	75 (68.2)†	12 (5.7)	148 (69.2)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. PBO (95%CI)	-	48.97 (18.14, 132.17) <0.001	-	29.60 (12.42, 70.51) <0.001	-	37.49 (19.52, 72.01) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPASI score mean change from baseline, LSM (SE)	-5.81 (1.07)	-5.88 (1.15)	-2.58 (1.05)	-6.20 (1.09)	-4.17 (0.77)	-6.07 (0.81)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with PPASI 100, n (%)	5 (14.3)	22 (71.0)†	2 (5.4)	21 (63.6)†	7 (9.7)	43 (67.2)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UNCOVER-1						UNCOVER-2					
Endpoint	IXE80 Q4W /PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W	IXE80 Q4W/ PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W
OR vs. PBO (95%CI)	-	15.09 (4.30, 52.94) <0.001	-	42.96 (8.36, 220.77) <0.001	-	23.06 (8.70, 61.12) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Tables 26-28, 30, 32, 35, 36 of the CS[1] and CSRs for UNCOVER-1 and -2[3, 4]

Data are least squares mean (SE), n (%), or % (CI). Data were analysed with the Cochran-Mantel-Haenszel test with non-responder imputation for response rates and mixed-models repeated-measure analysis for least squares mean change from baseline NAPSI, PSSI and PPASI

† p<0·001 compared with placebo. ‡ p<0·001 compared with etanercept; # Included in the final scope but not reported in any of the studies-

IXE = ixekizumab; IXE80 = ixekizumab 80 mg; n = number of patients in the specified category; N = number of patients in the analysis population; NAPSI = Nail Psoriasis Severity Index; NNT = number needed to treat; NR = not reported; NRI = non-responder imputation; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PBO = placebo; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS and response to clarification provided sufficient details for the ERG to appraise the searches. A good range of databases were searched, and additional searches of conference proceedings and other relevant resources including trials databases, specialist and organisational websites and health technology assessment (HTA) agencies were reported.

As the inclusion and exclusion criteria of the systematic literature review (SLR) were in line with the decision problem defined in the CS, not all comparators defined in the final scope were included, as discussed before. Furthermore, it is unclear whether any language restrictions were used in the SLR.

The company did not specify which data were extracted or how many reviewers were involved in the data extraction process. The CS did not report sufficient information to determine whether the extracted data were assessed for accuracy.

Patients included in the UNCOVER trials might not be reflective of the population in the final scope. In the CS, *moderate to severe* psoriasis was defined as a total PASI score of 10 or more and a DLQI score of more than 10. However, the patients recruited in the UNCOVER trails were those with PASI score greater than or equal to 12 and no restriction related to DLQI. The ERG notes that there is no agreed consensus on diagnostic criteria or tests available to set a threshold between moderate and severe in current clinical guideline. According to the clinical expert the ERG consulted, PASI score of more than 10 (or 12) is used as the cut-off for moderate/severe psoriasis combined when using systematic therapy rather than topical therapy. Therefore, it seems that the UNCOVER trials failed to include patients with moderate psoriasis according to a widely used definition and there is an issue with generalisability.

Furthermore, evidence of improvement of facial psoriasis which was required in the final scope is not available in any UNCOVER trials. The ERG considers that this is a potential limitation of the PASI and subsequently the trials, which ideally should have included some relevant measures to detect clinical improvement of facial psoriasis.

Thirty-one studies were included in the NMA base-case analysis. The ERG thinks that an additional study, Gordon 2006, should also have been included and analysis was rerun to include these data. This resulted in small changes in PASI 75 and PASI 90 responses at week 12 of [redacted], respectively, comparing with [redacted] in the CS. Overall, the ERG believes that it was appropriate to undertake the NMA and the results obtained by the company were robust when compared with the results of the ERG analysis. However, it should be noted again that the populations in the UNCOVER trials and the other studies used to inform the NMA were not fully in line with the final scope. The patients recruited in the trails were not always those with PASI score of 10 or more and their baseline DLQI scores were not clear. Therefore, it was not possible to conduct a NMA in the population with both, PASI >10 and DLQI <10.

1.4 Summary of cost effectiveness submitted evidence by the company

A de novo Markov state-transition model was developed in Visual Basic for Applications (VBA) with a Microsoft Excel interface. The model consists of four treatment-related health states: induction (trial) period, maintenance, best supportive care (BSC) and death. At the end of the induction period, PASI response categories are used to determine the utility gain experienced in the maintenance state. Patients who meet the minimum base-case response criterion of PASI 75 continue treatment in the maintenance state. If patients do not have an adequate level of response, they enter

another induction period upon initiating the next treatment line, either active treatment or BSC. Only the treatment specific impact of adverse events (AEs; malignancies and severe infections) on costs (and not utilities) is incorporated in the model, and is solely applied in a scenario analysis. Treatment discontinuation is assumed to be equal across all treatments.

Each treatment sequence considered consists of three biologic treatments followed by BSC. The biologic treatments included are: adalimumab, etanercept, ustekinumab, secukinumab and infliximab. The ordering of the biologic treatments was based on market share, with the assumption that treatments are not repeated, and alternate in terms of mechanism of action. Ixekizumab was only modelled as a first line treatment.

The base-case economic evaluation considers biological-naïve patients who have failed to respond to prior conventional systemic therapies, and are eligible for biologic therapies approved in the UK, i.e. as a first line biologic therapy.

The difference between the treatment sequences is driven by a difference in PASI response (which determines the proportion of patients eligible for maintenance treatment, and hence utility gain and costs of treatment) and a difference in costs of single treatments. PASI response for each single treatment was based on the absolute probabilities of achieving ≥75% (≥50% and ≥90% used in sensitivity analyses) reduction in PASI estimated in the NMA. PASI response of BSC was based on the placebo groups in the trials included in the NMA. It is assumed that PASI response of a treatment is not influenced by the position of the treatment in the treatment sequence.

Utility gains associated with a PASI response were estimated using regression analysis on the European Quality of Life-5 Dimensions, five-level scale (EQ-5D-5L) data obtained in the subgroup of patients with DLQI > 10 at baseline in the UNCOVER trials. For all patients who discontinued the study before the end of the induction period (week 12), the last EQ-5D-5L value, if collected at the visit prior to discontinuation, was used as a proxy for the week 12 value using the last-observation-carried-forward (LOCF) method. In the case that no previous post-baseline observations were available, no value was imputed.

The following health care costs were considered: drug costs, drug administration costs, monitoring costs (during the induction and maintenance periods), non-responder costs and BSC costs. AE costs were not considered in the base-case analysis but included in a scenario analysis. Drug costs were mostly based on list prices, except for ustekinumab 90 mg. The biosimilar prices of etanercept and infliximab were used in the company base-case analysis. BSC costs (applied after failing three biologic treatments) were assumed to equal the health care costs incurred by a biologic-naïve patient population.

As labelled by the company, base-case results were provided for biologic naïve patients with prior systemic failure and moderate to severe psoriasis (PASI≥10 and DLQI>10). The incremental cost effectiveness ratio (ICER) for the ixekizumab sequence versus the etanercept sequence was £33,858. Other treatment sequences were dominated (secukinumab sequence) or extendedly dominated by the ixekizumab sequence. The results of the probabilistic sensitivity analysis show that the etanercept sequence and the ixekizumab sequence have the highest probabilities of being cost effective. The etanercept sequence is the most cost effective treatment sequence up to a willingness to pay (WTP) threshold of £34,000. For a WTP threshold above £34,000 the ixekizumab sequence had the highest probability of cost effectiveness.

The most influential parameters in the deterministic sensitivity analyses of the ixekizumab versus the etanercept sequence were drug costs, discount rates (both costs and QALYs), and the annual discontinuation rate. In the deterministic sensitivity analyses of the ixekizumab versus the secukinumab sequence, PASI 75 response rates for both ixekizumab and secukinumab were the most influential parameters.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG agrees that the treatment sequencing approach is superior to comparing single treatments. Apart from the treatment sequencing approach and modelling 100% PASI response as a separate category, the model structure is similar to models used in previous technology appraisals. Although common in this field, the ERG questioned the use of relative PASI response to model the cost effectiveness as it may not reflect true differences in costs and health-related quality of life between treatments and treatment sequences. Regarding the model structure, the ERG also questioned the exclusion of the consequences of AEs, the assumption of no utility gain in the induction phase, and equal discontinuation rates for all treatments. Perspective, time horizon and discounting are in accordance with the NICE reference case.

The population in the base-case analysis was labelled by the company as biologic naïve patients with prior systemic failure and moderate to severe psoriasis (PASI≥10 and DLQI>10). This is not fully in line with the scope, nor is it fully in line with the populations used to estimate values for input parameters. According to the ERG, the base-case analysis reflects a population for whom biologic treatment is considered. Part of this population will be biologic naïve and the majority of these patients will have failed prior systemic treatment, but in the UNCOVER trials combined 74% were biologic naïve and only 36% of the patients had never used previous systemic therapies.

Although the ERG acknowledges that the submission could not possibly include all possible treatment sequences, the ERG thinks it is especially important to also consider a treatment sequence in which ixekizumab is a second line treatment instead of a first line treatment. According to the clinical expert consulted by the ERG, currently, clinicians would likely be inclined to use ixekizumab as a second line of therapy because more experience and safety data for TNF α inhibitors and ustekinumab are available than for ixekizumab.

PASI response was based on the NMA, and all usual caveats apply to the validity of comparative effectiveness estimates derived with this methodology. In addition, the ERG concludes that the populations included in the trials in the NMA may not fully reflect the population in the scope, as it was impossible to perform the NMA on patients with PASI≥10 *and* DLQI>10. The assumption that BSC after three lines of biologic treatment equals placebo alongside a (mostly first line) biologic is questionable. It seems however plausible to assume that the treatment response to BSC in that setting (i.e. after failure to three biologic therapies) will be very modest. It is debatable to assume that discontinuation is equal across all treatments, but reliable data to inform treatment specific discontinuation rates were lacking.

The ERG considered the utility estimates used by the company as uncertain for the following two reasons. First, one regression model was fitted, and alternative models were presented upon request. However, because performance and diagnostic statistics were not provided, the ERG was unable to determine whether the model that was used to determine utility gain per PASI response category is the optimal one. Second, the ERG questions the use of the last-observation-carried-forward method to impute values for patients who discontinued. Because the number of patients this concerned and the reasons for discontinuation are unknown, the ERG was unable to assess the impact.

Although the ERG agrees with the use of the subset of patients with DLQI>10 at baseline from UNCOVER to estimate utility gain, as it describes the population in the scope better, the ERG is concerned about the inconsistency with using the total ITT population to calculate PASI response.

In general, the ERG considers the costs as consistent with previous TAs and adequate for the current decision problem. An area of concern is the costs of BSC. There is a lack of evidence on the costs of BSC in patients who have failed three biologic therapies, which renders the estimate uncertain. In addition, the ERG could not reproduce the estimates of AE costs. The recalculated estimates by the ERG, which formed part of the ERG base-case, are higher for 'Malignancy other than NMSC' and 'Severe Infection' than the ones provided in the CS. The ERG also corrected a minor calculation error in the annual number of administrations for secukinumab during the maintenance period and used the lower and upper quartiles of NHS reference costs to implement costs distributions in the PSA. Based on the new ERG base-case, the PSA was executed and a large number of sensitivity analyses were conducted.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Overall, the CS report was well presented.

Searches were carried out on a broad range of databases including those recommended in the NICE 2013 guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. Supplementary searches of conference proceedings and other relevant resources including trials databases, specialist and organisational websites and HTA agencies, and the checking of references lists were undertaken by the company in order to identify additional studies not retrieved by the main searches.

The evidence for clinical effectiveness was based on three randomised controlled trials and the methodological quality is likely to be reliable. The company's NMA was robust, with little variation in estimates from the ERG analysis. Methods used to conduct the NMA are in line with current NICE guidance.

The treatment sequencing approach adopted by the company is superior to comparing single treatments. An NMA was used to inform treatment response instead of naïve comparison of study arms.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned by the restrictive nature of the Ovid search strategy reported in section 4.1. The broad range of additional resources searched may have mitigated against some loss of recall. However, the ERG conducted a small independent clinical effectiveness search. Screening a sample of titles and abstracts of identified references, the ERG did not identify any further relevant papers.

Insufficient details were reported on how the inclusion screening, data extraction and quality assessment was done. This could be a limitation of the review, e.g. if relevant studies were missed or incorrect study details were extracted by a single reviewer only, i.e. not by at least two independent reviewers as is best practice.

The ERG notes that there is no agreed consensus on diagnostic criteria or tests available to set a threshold between moderate and severe in the current clinical guideline. However, it should be noted again that the populations in the UNCOVER trials and the other studies used to inform the NMA were

not fully in line with the final scope. In addition, results for one outcome defined in the final scope, psoriasis symptoms of the face, have not been reported.

Not all relevant treatment sequences were included, especially omitting a sequence with ixekizumab as second line treatment was not realistic. The population in the base-case analysis did not reflect the scope and was not always consistent with the sources used to inform input parameters. The Excel model was overly complicated and not transparent.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG defined a new base-case that included multiple adjustments to the original base-case presented in the CS. The ERG fixed errors in the calculation of AE rates and costs, used lower and upper quartiles of NHS reference costs to calculate standard errors (SEs) for use in the PSA, corrected the number of administration of secukinumab during the maintenance period and used linear utility gains during the induction period instead of no gain during the induction period. In addition, the ERG added a treatment sequence, with ixekizumab as second line therapy (ADA-IXE: Adalimumab>Ixekizumab>Biosimilar infliximab>BSC). Adalimumab has been chosen as first line therapy in this sequence as it had the largest market share for first line therapy of psoriatic patients in 2014 according to the company.

Fixing the errors increased the costs of all comparators, and applying linear utility gain in the induction period increased QALYs for all treatment sequences. In the ERG base-case incremental analysis, the ADA-IXE sequence has an ICER of £25,532 versus the etanercept sequence, and the ixekizumab in the first line sequence has an ICER of £39,129 compared to ADA-IXE (i.e. ixekizumab in the second line sequence). The ADA-IXE sequence has a probability of being cost effective of 22.8% at a threshold of £20,000, and 52.9% at a threshold of £30,000. This is 2.8% and 13.2% respectively for ixekizumab in the first line sequence.

Additional exploratory sensitivity analyses were performed to examine the potential impact of various alternative assumptions. These analyses were performed on the ERG base-case, and on the company base-case if the company had not reported the analysis in the CS.

1. Use of the ITT population from the UNCOVER trials to calculate utility gains for PASI responses instead of restricting to patients with DLQI>10,
2. Use of effectiveness data of ixekizumab from the DLQI>10 population of the UNCOVER trials instead of the ITT population (based on the NMA),
3. Use of effect modification (i.e. reduced treatment effectiveness for subsequent treatments),
4. Variation of BSC costs (plus/minus 20%),
5. Replacing the ustekinumab 90 mg sequence with a sequence with secukinumab as second line therapy: Adalimumab>Secukinumab>Infliximab>BSC

The choice of utility increment values and BSC costs were the two most influential adjustments on the ERG base-case analysis. All exploratory analyses increased the (fully) incremental ICER of the ixekizumab treatment sequence, except when the BSC costs were increased. In each fully incremental analysis, ADA-IXE was compared to the etanercept sequence, followed by ixekizumab as first line compared to ADA-IXE. All other comparators were (extendedly) dominated. Adding the sequence with secukinumab as second line therapy did not influence this finding. The largest impact on the ICER was observed when using the ITT population from the UNCOVER trials to calculate utility gain per PASI response category. This increased the ICER of the ADA-IXE sequence versus the etanercept sequence to £36,314, and the ICER of ixekizumab in the first line sequence versus ADA-IXE to £55,243. Use of effectiveness data of ixekizumab from the DLQI>10 population of the UNCOVER

trials led to higher ICERs for the aforementioned comparisons, £26,499 and £40,308 respectively. Including effect modification increased the ICER of the ADA-IXE sequence versus the etanercept sequence to £35,191, but decreased the ICER of ixekizumab in the first line sequence versus ADA-IXE to £35,514. Increasing BSC costs decreased both ICERs (£17,532 and £32,673 respectively) and decreasing BSC increased both ICERS (£33,352 and £45,709, respectively). When replacing the ustekinumab 90 mg sequence by the sequence with secukinumab as a second line treatment, the ICERs amount to £25,423 and £38,914, respectively. One should note that secukinumab is available in the NHS under a confidential PAS price arrangement. Consequently, the analyses presented in the current report do not represent the true value for money of secukinumab.

2. BACKGROUND

This chapter provides a review of the evidence submitted by Eli Lilly in support of ixekizumab (trade name Taltz®) for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systematic therapy.[1] The background section of the report by the Evidence Review Group (ERG) outlines and critiques the company's description of the underlying health problem and the overview of current service provision. The information is taken from Chapter 3 of the company submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying health problem of this appraisal is plaque psoriasis described in the CS Section 3.1 as "*a common chronic inflammatory skin disease that is characterised by the appearance of prototypic red, thick and scaly plaques*".[1] Psoriasis is considered to be a T-cell mediated autoimmune disorder that leads to accumulation of inflammatory cells, angiogenesis and epidermal hyperproliferation.[5, 6] Plaque psoriasis is by far the most common form of the condition (90% of people with psoriasis) and is characterised by well delineated red, scaly plaques.[7] The most commonly affected areas of the body are the scalp, trunk, buttocks and limbs, with a predilection for extensor surfaces such as the elbows and knees.[8] People with psoriatic disease are also at greater risk of developing co-morbidities including cardiovascular disease, obesity, depression and other health conditions.[9-11]

Due to the chronic nature of the condition, psoriasis is associated with considerable burden to economics. The company cites that *"the cost of psoriasis to healthcare systems is comparable to diseases such as pancreatic cancer, melanoma, prostate cancer and asthma, and includes both direct costs (e.g. medication, physician visits, laboratory tests and hospitalisations) and indirect costs (e.g. loss of productivity)"*.[1] Psoriasis causes physical disability, pain, discomfort and psychological stress, including impairment in personal and professional relationships, and poor health-related quality of life.[12-20]

Psoriasis occurs worldwide but prevalence varies among different populations.[12] According to the CS, *"the prevalence of psoriasis in England has been estimated at 1.75%, with approximately 2.55% of these patients being eligible for treatment with biologic therapy"*.[21] Higher mortality rates have been reported for severe psoriasis (patients with history of systemic therapy) in the UK.[22] It is noted that *"sixteen deaths from psoriasis were registered in England and Wales during 2014 (ICD-10 L40.0)"*.[23]

ERG comment: The description of the disease is in line with the relevant clinical guidance by the National Institute for Health and Care Excellence; (NICE CG153[7]) therefore, the ERG considers the company's description of the disease to be appropriate. The references for this section supplied by the company were also checked and found to be correctly cited.

2.2 Critique of company's overview of current service provision

The company refer to the NICE clinical guideline CG153[7] for the assessment and management of psoriasis.

In general, NICE CG153 describes traditional topical therapies (such as corticosteroids, vitamin D and vitamin D analogues, dithranol and tar preparations) as first line treatment. Second line therapies include phototherapies (broad- or narrow-band ultraviolet B (UVB) light and psoralen plus UVA light [PUVA]) and systemic non-biological agents such as ciclosporin, methotrexate and acitretin. Systemic biological therapies are introduced as third line treatment options, aimed at patients who failed to respond to systemic non-biological therapies and/or PUVA, have contraindications or who are intolerant to these treatments.[7] This is subject to certain disease severity criteria which for etanercept,

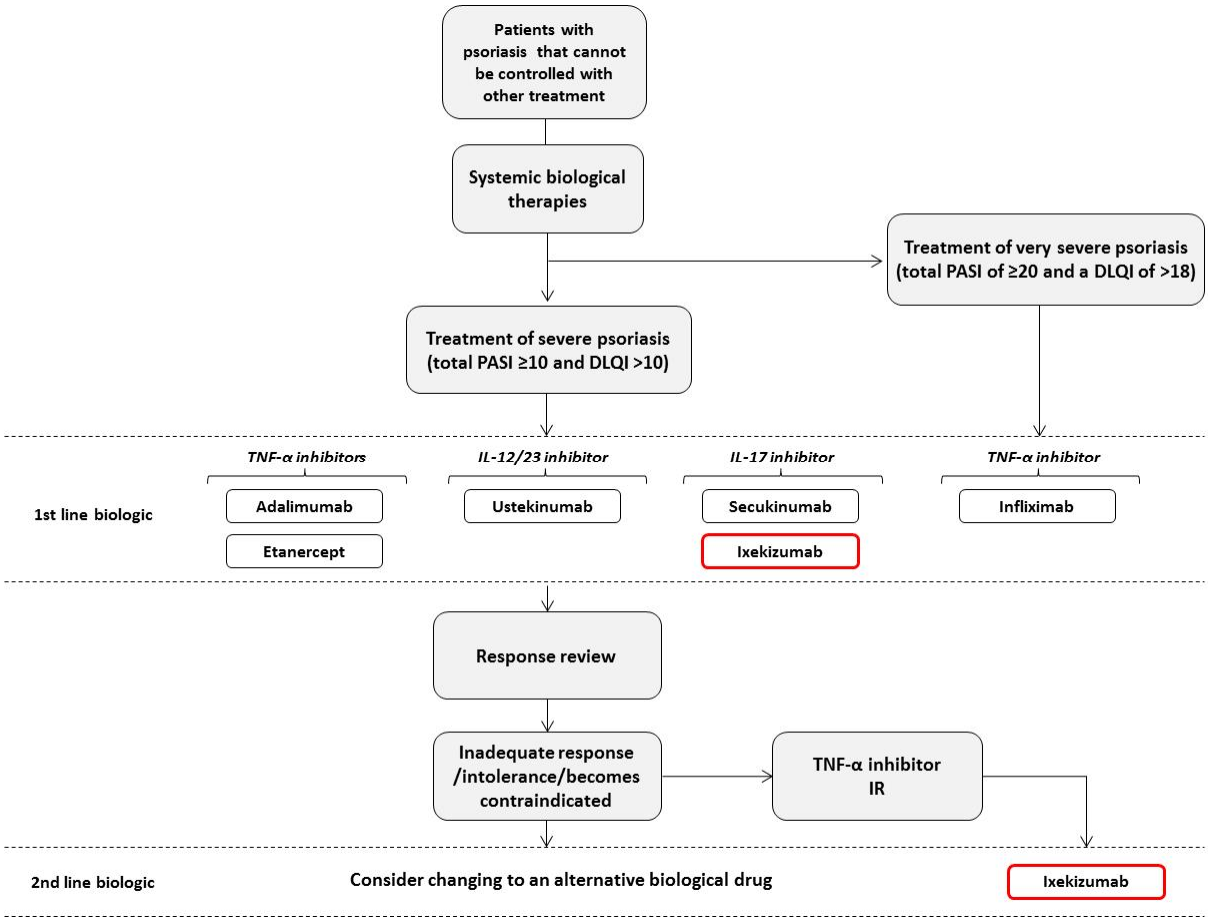
adalimumab and ustekinumab are a Psoriasis Area and Severity Index (PASI) score ≥ 10 and a Dermatology Life Quality Index (DLQI) > 10 (severe disease) and for infliximab, a PASI ≥ 20 and a DLQI > 18 (very severe disease).[7]

Secukinumab, a biologic option which became available recently, is recommended when the disease is severe, also defined by a PASI ≥ 10 and a DLQI > 10 (NICE Technology Appraisal TA350).[21] These recommendations can be viewed in the context of other treatment guidelines including the British Association of Dermatologists (BAD) in 2009.[24]

The CS states that despite a variety of treatment options currently available, systemic therapy for the treatment of moderate to severe psoriasis are associated with a number of limitations, including poor adherence and patient satisfaction.[25] Furthermore, the CS highlights that there is an unmet need for achieving optimal levels of skin clearance in difficult-to-treat area, such as the face and scalp and improving drug survival rates of current biologic therapies.[26-29]

Ixekizumab is a recombinant humanised IgG4 monoclonal antibody (mAb) designed and engineered to selectively inhibit interleukin-17A (IL-17A), a pro-inflammatory cytokine. Ixekizumab gained marketing authorisation *"for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"* on 26 April 2016 from the European Commission. The licensed dose of ixekizumab is 160 mg by subcutaneous injection (SC) injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every four weeks.[1] Figure 2.1 presents the proposed position of ixekizumab in the current treatment pathway.[7]

Figure 2.1 Proposed position of ixekizumab within the treatment pathway for patients with moderate to severe psoriasis (total PASI ≥ 10 and DLQI > 10) in accordance with NICE recommendations



Source: Section 3.3 of the CS[1]
DLQI = Dermatology Life Quality Index; IL = interleukin; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; TNF-α = tumour necrosis factor alpha

ERG comment: In general, the company does appear to illustrate the current state of service provision for psoriasis in the United Kingdom (UK), relevant to the decision problem under consideration adequately. However, one concern is that switching from TNF-α inhibitors has not been considered as part of current service provision. The company could have discussed whether the same behaviour reflects current service provision for adults whom have not tolerated TNF-α inhibitors.

The ERG also notice that there is no agreed consensus on the terminology used to define the severity of psoriasis.[7] In the CS, *moderate to severe* psoriasis was defined as a total PASI score of 10 or more and a DLQI score of more than 10 (Figure 4 of the CS).[1] However, NICE CG153 states that *severe* disease has been defined in NICE technology appraisals as a PASI ≥ 10 and DLQI > 10.[7] Other authors have defined *severe* disease as PASI > 12.[30]

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company presents its response to the decision problem in Section 1.1 of the CS. This is reproduced below.

Table 3.1: Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe plaque psoriasis	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy	As per summary of product characteristics (SmPC)
Intervention	Ixekizumab (Taltz®)	Ixekizumab 160 mg SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks	As per reference case and final label
Comparator(s)	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies (including acitretin, ciclosporin, fumaric acid esters, methotrexate) • Phototherapy with UVB radiation For people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-α inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Best supportive care	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies (including ciclosporin and methotrexate) • Phototherapy with UVB radiation For people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-α inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Best supportive care	Fumaric acid esters, acitretin or phototherapy with UVB radiation have not been included in this submission as insufficient data for these comparators was identified from the systematic literature review (SLR) to allow indirect comparisons to be conducted in the network meta-analysis (NMA). However, it is anticipated that ixekizumab will have a similar place in the clinical pathway to NICE approved biologics, i.e. after standard therapies have failed/ are contraindicated or are not tolerated.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • severity of psoriasis • psoriasis symptoms on the face, scalp and nails • mortality • response rate • relapse rate • adverse effects of treatment • health-related quality of life	This submission includes a range of outcome measures to assess the clinical ixekizumab, including: • Psoriasis Area and Severity Index (PASI) – including PASI 75/90/100. The primary focus of the submission is PASI 75 as this was the co-primary endpoint of the included studies and is the measure of response used by NICE. • static Physician Global Assessment (sPGA) – a validated, standardised global score used in conjunction with PASI to assess efficacy • PASI 90 – high-levels of skin clearance used as an indicator of clear or almost clear skin • PASI 100 – complete clearance of skin symptoms used as an indicator of disease remission • Relapse rate assessed based on the maintenance of response at week 60. • Psoriasis of the nails, scalp and palmoplantar areas is assessed using area-specific measures including NAPSI, PSSI and PPASI • Adverse events (including background mortality) will be reported for ixekizumab and comparators based on the results	Psoriasis symptoms of the face have not been included in the submission as there is no reference to this outcome measure in the SmPC, which focuses on psoriasis of the nails, scalp and palmoplantar areas. These outcomes measures have not been explicitly taken into account in the cost-effectiveness model which is based on standard overall PASI response. Mortality was included in the reporting of adverse events. Treatment effect on mortality has not been included due to data limitations.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		from the clinical studies • Health-related quality of life (HRQoL) measured using DLQI	
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 (QALY). 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 patient access schemes (PAS) for the intervention or comparator technologies should be taken into account. For the comparators, the availability and cost of biosimilars should be taken into consideration.	Cost-effectiveness expressed as incremental cost per quality-adjusted life year, with a lifetime model horizon, considering costs from an NHS and PSS perspective.	As per the reference case

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe) Where the evidence allows, sequencing of different drugs and the place of ixekizumab in such a sequence will be considered.	Subgroup analyses have been reported according to the severity of psoriasis as measured by DLQI scores and previous use of systemic non-biological and biological therapies.	As per the reference case
Special considerations including issues related to equity or equality	No equity or equality issues identified.	No equity or equality issues identified.	As per the reference case

Source: Table 1 of the CS[1]

DLQI = Dermatology Life Quality Index; HRQoL = Health-related quality of life; NAPSI = Nail Psoriasis Severity Index; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PAS = patient access scheme; PASI = Psoriasis Area and Severity Index; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Personal Social Services; PSSI = Psoriasis Scalp Severity Index; QALY = quality adjusted life year; SLR = systematic literature review; SmPC = summary of product characteristics; sPGA = static Physician Global Assessment; TNF-α = tumour necrosis factor alpha

3.1 Population

In the final scope issued by the National Institute for Health and Care Excellence (NICE), the patient population is described as *"adults with moderate to severe plaque psoriasis"*.[31]

The definition of the patient population addressed in the company submission (CS) is *"moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"*.[1]

ERG comment: The population in the CS appears in line with the population defined in the final scope. However, as highlighted in Section 2.2, there is no agreed consensus on the terminology used to clarify the severity of psoriasis with various Psoriasis Area and Severity Index (PASI) thresholds suggested to define moderate to severe or severe psoriasis, respectively. In addition, certain locations of psoriasis are likely to have a greater impact on how the disease is perceived by individuals affected by psoriasis. For example, a relatively small affected area in the face might have a big psychological impact on patients. A detailed discussion of the included trials can be found in Section 4.2.

3.2 Intervention

The final scope defined *"ixekizumab (Taltz®)"* as the intervention of interest.[31] In the CS, the definition of the intervention reads: *"ixekizumab 160 mg by subcutaneous injection (SC) injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks"*.[1]

ERG comment: The definition in the CS is in line with the definition in the final scope and identical to the definition used in the summary of product characteristics (SmPC) by the European Medicines Agency (EMA) which reads: *"The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks"*.[32]

3.3 Comparators

As detailed in Table 3.1, the final scope included six treatments. Two of them, *"systemic non-biological therapies (including acitretin, ciclosporin, fumaric acid esters, methotrexate)"* and *"phototherapy with UVB [ultraviolet B] radiation"* are listed *"if non-biologic treatment or phototherapy is suitable"*. Four additional treatments are listed *"for people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated"*, namely *"TNF-α inhibitors (etanercept, infliximab, adalimumab), ustekinumab, secukinumab, best supportive care"*.[31]

The CS highlights that *"fumaric acid esters, acitretin or phototherapy with UVB radiation have not been included in this submission as insufficient data for these comparators was identified from the systematic literature review (SLR) to allow indirect comparisons to be conducted in the network meta-analysis (NMA). However, it is anticipated that ixekizumab will have a similar place in the clinical pathway to NICE approved biologics, i.e. after standard therapies have failed/ are contraindicated or are not tolerated"*.[1]

ERG comment: The ERG feels that it is inappropriate to exclude treatments that were specified in the final scope from the decision problem addressed in the company submission.[1] In the response to the request for clarification, the company confirmed that *"there was insufficient evidence to include*

other non-biologic systemic therapies and phototherapy (i.e. acitretin, fumaric acid esters, and phototherapy) that were listed in the scope" and that *"the SLR did not include UVB in the inclusion criteria. The original search strategies were designed before the NICE scope was confirmed and also before the final licensed label was confirmed"*.[33]

It is unclear how many studies assessing UVB were missed by not including this comparator in the PICO (see Table 4.2). While the company *"expect ixekizumab to occupy a similar position in the treatment pathway to current biologics, so it could be argued that the inclusion of UVB is of limited relevance"*,[33] it should be noted that studies including this comparator could potentially have contributed to the NMA, i.e. might have resulted in more robust effect estimates.

3.4 Outcomes

The outcomes reported in the CS[1] are broadly in line with the outcomes listed in the final scope specified by NICE.[31]

However, as the CS states *"psoriasis symptoms of the face have not been included in the submission as there is no reference to this outcome measure in the SmPC, which focuses on psoriasis of the nails, scalp and palmoplantar areas"*.[1]

ERG comment: As detailed before (Section 3.1), certain locations of psoriasis, such as the face, are likely to have a greater impact on how the disease is perceived by individuals affected by psoriasis. Due to the lack of evidence on this outcome, it is more difficult to draw any firm conclusions for patients with psoriasis symptoms of the face.

3.5 Other relevant factors

Ixekizumab is provided under a patient access scheme (PAS) price agreement (simple discount on the list price) in the NHS. The ERG is not aware of the percentage of discount. All analysis presented in the current report include this PAS price for ixekizumab.

Secukinumab is also provided under a PAS price agreement (simple discount on the list price) in the NHS. Consequently, the analyses presented in the current report do not represent the true value for money of secukinumab. The ERG prepared a confidential appendix in which the PAS price of secukinumab is used.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[34] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[35] The ERG has presented only the major limitations of each search strategy in the report.

Systematic literature review (CS Section 4.1.1)

The company submission stated that searches were originally undertaken in December 2014 and updated in November 2015. Searches were reported for a broad range of databases, including Embase, Medline, Medline in process, PsycINFO, EconLit, ACP Journal Club, Cochrane's CENTRAL, DARE, CDSR and Methodology register, the HTA database and NHS EED. Searches were also reported for four trials registries (Clinical trials.gov, PharmNet.bund, EUCTR, WHO ICTRP) and the EMA, SMC and NICE websites. For this last set of resources, only a strategy for Clinical trials.gov appeared in the appendices, the ERG requested search dates and full strategies for the remaining six resources, the company responded that the searches were conducted in November 2015 and were searched using the Keyword "Psoriasis".[33] Supplementary searches were carried out on Google and duckduckgo.com. Table 4.1 gives details of additional grey literature searches from the original literature review.

Table 4.1: Psoriasis grey literature search for the original SLR

Grey literature	
Key dermatological society conferences	Value in Health Journal/ISPOR (International) Pso: Gene to Clinic
Country-specific databases	Health Quality Ontario (HQO) Ottawa Hospital Research Institute (OHRI) McMaster University Health Forum British Association of Dermatologists (BAD) Australia and New Zealand Clinical Trials Registry (ANZCTR)
Key dermatology conferences	American Academy of Dermatology European Academy of Dermatology and Venereology International Investigative Dermatology Society for Investigative Dermatology World Congress of Dermatology
Country-specific databases	Japanese Medical Research Database (Igaku-Chuo-Zasshi (ICHUSHI))

Source: Table 4 of the CS appendix[36]
BAD = British Association of Dermatologists; CS = company submission; HQO = Health Quality Ontario; ICHUSHI = Igaku-Chuo-Zasshi (Japanese Medical Research Database); OHRI = Ottawa Hospital Research Institute; SLR = systematic literature review

Conferences were initially searched for the years 2013-2014 during the original review, in addition to this, three key conferences (American Academy of Dermatology, European Academy of Dermatology and Venereology and World Congress of Dermatology) were further reviewed for the period of 2014 to 2015.

In the points of clarification the ERG queried the rationale behind the Ovid search reported in Table 1 of the Appendices.[37] The company responded that this search was designed to retrieve information on health-related quality of life (HRQoL), adverse events (AEs) and studies reporting data on key clinical efficacy measures: Psoriasis Area and Severity Index (PASI), PGA (Physician Global Assessment), sPGA (static Physician Global Assessment), IGA (Investigator's Global Assessment), itch, itch numerical rating scale (NRS). The company also reported "*that the shortlisted studies populating the network meta-analysis (NMA) are consistent with those included in recent NICE STAs which infers that all relevant evidence has been identified and appropriately incorporated"*.[33]

Despite this response the ERG still has concerns regarding this restrictive approach. Further limitations of the combined Ovid search included the lack of Emtree/MeSH for the condition and limited use of truncation and synonyms for both the condition and drug terms listed. Whilst the broad range of databases searched and supplementary searches may have mitigated against some loss of recall, relevant papers may still have been missed. Given the company's later clarification that non-RCT evidence was not actively sought, the ERG suggests that a more appropriate approach may have been to combine the condition and drugs facets with a validated RCT filter. The ERG conducted a small independent clinical effectiveness search accordingly (Appendix 1). Screening a sample of 600 titles and abstracts of identified references, the ERG did not identify any further relevant papers.

Indirect and mixed treatment comparisons (CS Section 4.10.1)

Section 4.10.1 states that *"the SLR described in Section 4.1 was used to identify all potential studies that may have been relevant for indirect comparison with ixekizumab"*.[1] In utilising the same strategies reported in 4.1 the same limitations as described above will have applied.

Non-randomised and non-controlled evidence (CS Section 4.11)

The company submission states that *"no relevant non-randomised or non-controlled evidence was identified from the evidence search"*.[1] The company later clarified in their response to the request for clarification that non-randomised/non-controlled evidence was not actively searched for due to the availability of data from the three RCTs for ixekizumab and numerous RCTs for the other relevant comparators.[33] For clarity the following exclusion criteria were also provided:

- Studies pooling moderate to severe psoriasis results with other comorbidities (e.g. PsA), and not presenting results separately
- Cohort studies
- Cross-sectional studies
- Epidemiological/ecological studies
- Observational studies
- Case-control studies
- Editorials
- Single case reports
- Letters
- Animal studies

For completeness, the company also provided the following inclusion criteria from the updated search protocol:

- Clinical trials, including randomised clinical trials and open-label trials, phase II–IV
- Publications presenting un-pooled data relating to moderate to severe psoriasis
- NMAs/mixed treatment comparisons (MTCs) of comparators listed above
- Human studies.[33]

Adverse Events (Section 4.12)

The ERG queried the lack of information regarding the search methods utilised for the gathering of data on adverse events. In reply, the company stated that *"the data presented on adverse events in Section 4.12 was collected from the UNCOVER-1, -2 and -3 studies and not from the SLR. Information was taken from journal publications and the CSRs which have been shared with NICE".*[33]

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 4.2.

Table 4.2: Inclusion and exclusion PICOS criteria for both the original and update SLR

	Inclusion	Exclusion
Population	Patients with moderate, severe, or very severe psoriasis	Patients with mild psoriasis
Interventions and comparators	Placebo Non-biologic approved treatments: Acitretin Apremilast Cyclosporine/ Ciclosporin Fumaric acid esters† Methotrexate PUVA Approved Biologic treatments: Adalimumab Etanercept Infliximab Ustekinumab Secukinumab Biosimilars of the above (where appropriate) Experimental treatments: Ixekizumab Brodalumab Guselkumab Namilumab Ponesimod Tildrakizumab Tofacitinib Biosimilars of the above (where appropriate)	Interventions not listed within the inclusion criteria, including those specifically for mild to moderate psoriasis: corticosteroids, vitamin A & analogues, vitamin D & analogues, tar preparations
Outcomes	Key clinical outcomes: PASI, relative and absolute: PASI 50* PASI 75	Any outcomes not listed in the following subsets of inclusion criteria: Key clinical outcomes

	Inclusion	Exclusion
	PASI 90 PASI 100 Global assessments, relative and absolute: PGA 0, 1 sPGA 0, 1 IGA 0, 1 <u>Key quality of life outcomes:</u> SF-36 DLQI <u>Safety outcomes:</u> Infections Adverse events Death Malignancy Immunogenicity Injection site reactions Infusion reactions Withdrawals Serious and severe adverse events Treatment-emergent adverse events Cardiovascular adverse events <u>Additional outcomes:</u> Patient's global assessment Skin pain VAS Healthcare resource utilisation[**] Health status[*] (e.g. EQ-5D) Depression[**] (e.g. HADS, QIDS) (Work) productivity** (e.g. WPAI) Itch[**] (E.g. itch VAS, itch NRS)	Key quality of life outcomes Safety outcomes
Trial design	Clinical trials, including RCTs and open-label trials, phase II-IV Publications presenting un-pooled data relating to moderate to severe psoriasis NMAs/MTCs of comparators listed above Human trials	Trials pooling moderate to severe psoriasis results with other comorbidities (e.g. PsA), and not presenting results separately Cohort trials Cross-sectional trials Epidemiological/ecological trials Observational trials Case-control trials Editorials Single case reports Letters Animal trials

Source: Based on table 7 of the CS[1]

Footnote: [†] Not licensed in the UK; [*] PASI 50 added after the initial approval of the protocol as an additional inclusion criterion. PASI 50 was only considered for the data extraction stage of this SLR. PASI 50 was not considered an inclusion criterion for the abstract screening phase; [**] Additional outcome measures were reported within the DEF where data were available. As there are a broad range of instruments that can be used to capture data on healthcare resource utilisation, health status, depression, work productivity and itch, the reported measures used to capture these data were recorded within the DEF and data ranges captured where data were available.

DEF = data extraction form; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol five dimensions;

	Inclusion	Exclusion
HADS = hospital anxiety and depression scale; MTC = mixed treatment comparison; NMA = network meta-analysis; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; PUVA = psoralen plus ultraviolet A light; QIDS = quick inventory of depressive symptomatology; RCT = randomised controlled trial; SF-36 = short form 36; SLR = systematic literature review; UK = United Kingdom; VAS = visual analogue scale; WPAI = work and activity impairment questionnaire		

ERG comment: One outcome defined in the final scope, namely UVB, was not included. As discussed in Section 3.3, studies including this comparator could potentially have contributed to the NMA, i.e. might have resulted in more robust effect estimates.

No language restrictions were reported, i.e. it is unclear whether any restrictions were imposed based on publication language. It is unclear how many people were involved in screening for relevant publications.

4.1.3 Critique of data extraction

The CS did not report any details on how the data extraction was performed.

ERG comment: The company did not specify which data were extracted or how many reviewers were involved in the data extraction process. The CS did not report sufficient information to determine whether the extracted data were assessed for accuracy.

4.1.4 Quality assessment

In the CS, the company does not explicitly state which risk of bias tool was used. However, the risk of bias of included trials is reported in Table 7 of the CS[1] as well as in Appendices 7 and 9 of the CS.[36] The Appendix contains a list of questions that were used in the quality assessment.

ERG comment: While not explicitly stated, it seems that the quality assessment was based on the Cochrane risk of bias tool. However, the company did not report the number of reviewers involved in the assessment of risk of bias.[38] The use of only one reviewer to conduct the quality assessment would not be considered best practice and increases the risk of inappropriate assessment.

4.1.5 Evidence synthesis

According to the CS, *"head-to-head RCTs between all comparators specified in the NICE scope have not been conducted"*.[1] However, a network meta-analysis (NMA) *"was conducted to estimate the comparative efficacy between these treatments"*. The methods of analysis were detailed in the Section 4.10.12 of the CS[1]:

"The analyses followed the principles given in the NICE DSU technical support document 3 by Dias and colleagues for ordered categorical data, the key details of which are reproduced below. The approach utilised uses a multinomial likelihood model with a probit link:

$$p_{ikj} = \Phi\ (\mu_i + z_{ij} + \delta_{i,bk} I_{\{k \neq 1\}}$$

where j represents the different PASI response thresholds, k is an arm of a trial i oand therefore p_{ijk} is the probability that a patient in arm k of trial i belongs to category j. The pooled effect of the experimental treatment versus the control (in this case, the placebo arm of the included studies) is to change the probit (Z) score of the control by $\delta_{i,bk}$ standard deviations. The term z_{ij} specifies the cut-offs at which the individual moves from one category to the next in trial i. This model allows inclusion of trials using different thresholds or trials reporting different numbers of thresholds- which is the case here as not all included studies reported PASI 100 outcomes.

The analysis also follows the guidance from TSD2 by Dias and colleagues to re-write the multinomial likelihood as a series of conditional binomials. Analyses were carried out with 30,000 iterations and with a burn-in period of 10,000."

ERG comment: The reported methods for conducting the NMA are in line with the methods described in the relevant NICE Decision Unit (DSU) guidance.[39]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The evidence base for the clinical efficacy of ixekizumab in the treatment of psoriasis consists of three randomised controlled trials (RCTs), as identified by a systematic literature review (SLR): UNCOVER-1, UNCOVER-2 and UNCOVER-3. The UNCOVER studies are phase III RCTs which comprise the main evidence base for the clinical efficacy and safety of ixekizumab presented in the CS. An additional phase II RCT (NCT01107457) was also identified through the SLR; however, the data were not discussed in the CS *"due to the availability of data from the three phase III UNCOVER trials. In addition, the ixekizumab dosing regimen investigated in the phase II study was different to the licensed dose of ixekizumab (ixekizumab 10 mg, 25 mg, 75 mg or 150 mg of at week 0, 2, 4, 8, 12, and 16)".*[1]

The UNCOVER studies were phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient trials comparing the efficacy and safety of ixekizumab to placebo in patients with moderate to severe plaque psoriasis. In addition, the UNCOVER-2 and UNCOVER-3 studies included an active comparator (etanercept) arm. The main methodological features of the UNCOVER trials have been summarised in Table 14 of the CS, replicated in Table 4.3 below. The company noted that not all pre-specified secondary and exploratory objectives were discussed in detail in the CS. Table 4.4 summarises the definitions of primary and secondary efficacy outcomes, provided in Section 4.3.6 and Appendix 6 of the CS.[36] The demographics and baseline characteristics of patients in the UNCOVER trials are summarised in Table 4.5.

Table 4.3: Summary of methodology of the UNCOVER studies

Trial number (acronym)	**UNCOVER- 1**[3, 40]	**UNCOVER-2**[2, 4]	**UNCOVER-3**[2, 41]
Settings and locations where the data were collected (Further details can be seen in CS Appendix 5)	108 sites in 11 countries: Japan, Australia, Germany, Denmark, United Kingdom, Hungary, Italy, Poland, Romania, Canada, United States	127 sites in 12 countries: Australia, Austria, Czech Republic, Germany, Spain, France, United Kingdom, Netherlands, Poland, Romania, Canada, United States	125 sites in 10 countries: Argentina, Chile, Mexico, Bulgaria, Germany, Hungary, Poland, Russia, Canada, United States
Duration of trial and time trial was conducted			Screening Period (prior to week 0)
	Blinded Induction Dosing Period (week 0-12 – primary endpoint assessment)		
	Blinded Maintenance Dosing Period (week 12-60) Long-term Extension Period (week 60-264)		Open-label long-term extension period (week 12-264)
	Post-Treatment Follow-Up Period (from the last treatment period visit or ETV up to a minimum of 12 weeks after that visit) Duration of trial (including long-term safety and efficacy follow up): 5 years		
Trial design	Randomised, double-blind, placebo-controlled, parallel-group	Randomised, double-blind, placebo-controlled, active-comparator, parallel-group. Non-inferiority/superiority to active comparator study	
Main eligibility criteria for participants	Adult patients (≥18 years of age) with moderate to severe plaque psoriasis who were candidates for phototherapy and/or systemic therapy		
		Patients with prior use of etanercept were excluded	
Number of patients randomised	1,296	1,224	1,346
Trial arms (n=number randomised/not randomised; treatment period) including how and when they were administered	**Induction dosing period** Ixekizumab Q2W (n = 433) Ixekizumab Q4W (n = 432) Placebo (n =431) **Maintenance dosing period** Ixekizumab Q4W (n = 229) Ixekizumab Q12W (n= 227)	**Induction dosing period** Ixekizumab Q2W (n = 351) Ixekizumab Q4W (n= 347) Etanercept (n = 358) Placebo (n =168) **Maintenance dosing period** Ixekizumab Q4W (n = 187)	**Induction dosing period** Ixekizumab Q2W (n = 385) Ixekizumab Q4W (n = 386) Etanercept (n = 382) Placebo (n = 193)

Trial number (acronym)	**UNCOVER- 1**[3, 40]	**UNCOVER-2**[2, 4]	**UNCOVER-3**[2, 41]
	Placebo (n = 226)	Ixekizumab Q12W (n = 181) Placebo (n = 176)	
Randomisation and masking	Computer-generated random sequence using an IVRS. Study site personnel, including outcomes assessor(s) and patients were blinded to study treatment until after all patients discontinued from treatment or completed week 60.		Computer-generated random sequence using an IVRS. Study site personnel, including outcomes assessor(s) and patients were blinded to study treatment until after all patients discontinued from treatment or completed week 12.
	Clinical trial material (syringes [and contents] containing either ixekizumab or placebo were visibly indistinguishable from each other).	Clinical trial material (syringes [and contents] containing either [ixekizumab or placebo for ixekizumab] and [etanercept or placebo for etanercept] were visibly indistinguishable from each other).	
Primary objectives (including scoring methods and timings of assessments)	Co-primary (gated) outcomes were to assess whether ixekizumab 80 mg (Q2W and Q4W) was superior to placebo at week 12 as measured by the proportions of patients achieving: • sPGA (0,1) with at least a 2-point improvement from baseline • PASI 75	Co-primary (gated) outcomes were to assess whether ixekizumab 80 mg (Q2W and Q4W) was superior to placebo and non-inferior and superior to etanercept at week 12 as measured by the proportions of patients achieving: • sPGA (0,1) with at least a 2-point improvement from baseline • PASI 75	
Major secondary outcomes (including scoring methods and timings of assessments)	Major secondary (gated) outcomes were assessed over 12-week or 48-week treatment periods with final assessments made at week 12 or week 60 and included:		Major secondary (gated) outcomes were assessed over a 12-week treatment period with final assessments made at week 12 and included:
	• Superiority of ixekizumab (Q2W and Q4W) to placebo at week 12 as measured by: • proportion of patients achieving sPGA (0), PASI 90, and PASI 100		

<table>
<tr><th>Trial number (acronym)</th><th>UNCOVER- 1[3, 40]</th><th>UNCOVER-2[2, 4]</th><th>UNCOVER-3[2, 41]</th></tr>
<tr><td rowspan="2"></td><td>• proportion of patients achieving Itch Numerical Rating Scale (NRS) ≥4-point reduction from baseline for patients who had baseline Itch NRS ≥4
• change from baseline in Dermatology life quality index (DLQI) total score and NAPSI score</td><td>• Superiority of ixekizumab (Q2W and Q4W) to placebo as measured by:
  • proportion of patients achieving sPGA (0), PASI 90, and PASI 100 at week 12
• Superiority of ixekizumab (Q4W and Q12W) to etanercept in the proportion of patients maintaining:
  • sPGA (0), PASI 90, and PASI 100 at week 12</td><td>• proportion of patients achieving Itch Numerical Rating Scale (NRS) ≥4-point reduction from baseline for patients who had baseline Itch NRS ≥4
• change from baseline in DLQI total score and NAPSI score</td></tr>
<tr><td colspan="2">• Superiority of ixekizumab (Q4W and Q12W) to placebo in the proportion of patients maintaining:
  • sPGA (0,1) from week 12 to week 60</td><td></td></tr>
<tr><td>Other secondary outcomes presented in this submission</td><td colspan="2">Other secondary outcomes were assessed over 12-week or 48-week treatment periods with final assessments made at week 12 or week 60 and included:
  • proportion of patients maintaining PASI 75, PASI 90 and PASI 100 from week 12 to week 60</td><td>Other secondary outcomes were assessed over 12-week treatment periods and included:
• change from baseline in PSSI score at week 12
• change from baseline in PPASI score at week 12</td></tr>
</table>

Trial number (acronym)	UNCOVER- 1[3, 40]	UNCOVER-2[2, 4]	UNCOVER-3[2, 41]
	• change from baseline in NAPSI score at week 60 • change from baseline in Psoriasis Scalp Severity Index (PSSI) score at week 12 and 60 • change from baseline in Palmoplantar Psoriasis Severity Index (PPASI) score at week 12 and 60		
Selected subgroups	Gender Age Geographic region Disease severity Weight BMI Specific psoriasis locations at baseline Previous non-biologic systemic therapy Previous biologic systemic therapy TNF-α insufficient responders		

Source: Based on Table 14 of the CS[1]
BMI = body mass index; DLQI = Dermatology Life Quality Index; ETV = early termination visit; IVRS = interactive voice response system; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI /75/90/100 = ≥75%/≥90%/100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; Q2W = once every 2 weeks; Q4W = once every 4 weeks; Q12W = once every 12 weeks; sPGA = static Physician Global Assessment; TNF-α = tumour necrosis factor alpha

Table 4.4: Primary and secondary efficacy outcomes and definition

Study outcome	Definition
Primary	
Static Physician Global Assessment (sPGA)	The sPGA is the physician's determination of the severity of the patient's psoriasis lesions overall at a given time point.[42] Overall lesions are categorised by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). A sPGA score of (0, 1) indicates clear or minimal psoriasis which is indicative of treatment success. The EMA considers that PASI alone is not sufficient to evaluate psoriasis severity at baseline and on treatment and recommends using 2 endpoints to assess efficacy: a validated, standardised global score (e.g. PGA) in conjunction with the PASI.[42] The assessment was carried out by site investigators who had been trained in specific assessment techniques.
Psoriasis Area and Severity Index (PASI)	The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease.[43] The PASI has been the most frequently used endpoint and measure of psoriasis severity in clinical trials. An improvement of ≥75% from baseline in PASI score (or PASI 75) is considered clinically meaningful and the main indication of treatment effectiveness in patients with moderate to severe psoriasis.[8, 42] Higher levels of clearance, including 90% to 99% and 100% improvements from baseline in PASI score (PASI 90 and PASI 100, respectively) were also measured in the UNCOVER trials. Clear or almost clear has been defined as an improvement of PASI >90%.[42] The assessment was carried out by site investigators who had been trained in specific assessment techniques.
Secondary	
Itch Numeric Rating Scale (NRS)	The Itch NRS is a single-item, patient-reported outcomes measure designed to capture information on the overall severity of a patient's itching due to their psoriatic skin condition by having the patient circle the integer that best describes the worst level of itching in the past 24 hours on an 11 point NRS, anchored at 0 representing "no itching" and 10 representing "worst itch imaginable." In the UNCOVER trials, a responder definition was defined as achieving an Itch NRS ≥4 point reduction from baseline for patients who had baseline Itch NRS ≥4.
Dermatology Life Quality Index (DLQI)	The DLQI is a validated, dermatology-specific, patient-reported measure that evaluates a patient's health related quality of life (HRQoL). This questionnaire has 10 items that are grouped in 6 domains, namely: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include: "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as "0." Totals range from 0 to 30 (less to more impairment).[44, 45] A DLQI total score of 0 to 1 is considered as a patient's skin disease having no effect on their HRQoL,[46] and a 5-point change from baseline is considered as the minimal clinically important difference (MCID) threshold.[47, 48]
Nail Psoriasis Severity	The NAPSI was used only if the patient had fingernail psoriasis at

Study outcome	Definition
Index (NAPSI)	baseline. This scale was used to evaluate the severity of fingernail bed psoriasis and fingernail matrix psoriasis by area of involvement in the fingernail unit. In the UNCOVER trials, only fingernail involvement was assessed. Each fingernail was divided with imaginary horizontal and longitudinal lines into quadrants. Each fingernail was then given a score for fingernail bed psoriasis (0 to 4) and fingernail matrix psoriasis (0f to 4) depending on the presence (score of 1) or absence (score of 0) of any of the features of fingernail bed and fingernail matrix psoriasis in each quadrant. The NAPSI score for a fingernail was the sum of scores in fingernail bed and fingernail matrix from each quadrant (maximum of 8). Each fingernail was evaluated, and the sum of all the fingernails was the total NAPSI score (range, 0 to 80).
Source: Based on Section 4.3.6 of the CS[1] and Appendix 6[36] DLQI = Dermatology Life Quality Index; EMA = European Medicines Agency; HRQoL = health related quality of life; MCID = minimal clinically important difference; NAPSI = Nail Psoriasis Severity Index; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; sPGA = Static Physician Global Assessment	

Table 4.5: Patient demographics and baseline characteristics in UNCOVER trials

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
	Placebo (N=431)	IXE 80 mg Q4W (N=432)	IXE 80 mg Q2W (N=433)	Placebo (N=168)	IXE 80 mg Q4W (N=347)	IXE 80 mg Q2W (N=351)	Etanercept 80 mg Q4W (N=358)	Placebo (N=193)	IXE 80 mg Q4W (N=386)	IXE 80 mg Q2W (N=385)	Etanercept 80 mg Q4W (N=382)
Patient demographics											
Age (years) *Mean (SD)*	46.4 (13.4)	45.6 (12.95)	45.1 (12.40)	45.3 (12.13)	45.0 (13.53)	44.5 (13.27)	45.3 (12.79)	46.4 (12.11)	45.6 (12.76)	45.6 (13.10)	45.8 (13.84)
Gender, n (%) *Male* *Female*	303 (70.3) 128 (29.7)	289 (66.9) 143 (33.1)	291 (67.2) 142 (32.8)	120 (71.4) 48 (28.6)	244 (70.3) 103 (29.7)	221 (63.0) 130 (37.0)	236 (65.9) 122 (34.1)	137 (71.0) 56 (29.0)	258 (66.8) 128 (33.2)	254 (66.0) 131 (34.0)	269 (70.4) 113 (29.6)
Race, n (%) *White* *Asian* *Black* *Other*	401 (93.0) 21 (4.9) 8 (1.9) 1 (0.2)	397 (91.9) 23 (5.3) 10 (2.3) 2 (0.4)	401 (92.6) 18 (4.2) 8 (1.8) 6 (1.4)	149 (88.7) 6 (3.6) 10 (6.0) 3 (1.8)	315 (91.8) 11 (3.2) 11 (3.2) 6 (1.8)	330 (94.3) 12 (3.4) 5 (1.4) 3 (0.9)	331 (93.5) 8 (2.3) 13 (3.7) 2 (0.6)	176 (91.2) 7 (3.6) 8 (4.1) 2 (1.0)	360 (93.3) 11 (2.8) 9 (2.3) 6 (1.6)	361 (93.8) 12 (3.1) 5 (1.3) 7 (1.8)	351 (91.9) 11 (2.9) 10 (2.6) 10 (2.6)
Geographical region, n (%) *North America* *Europe* *Asia* *Australia*	223 (51.7) 176 (40.8) 13 (3.0) 19 (4.4)	225 (52.1) 180 (41.7) 12 (2.8) 15 (3.5)	225 (52.0) 192 (44.3) 8 (1.8) 8 (1.8)	89 (53.0) 72 (42.9) 7 (4.2)	187 (53.9) 145 (41.8) 15 (4.3)	188 (53.6) 147 (41.9) 16 (4.6)	193 (53.9) 152 (42.5) 13 (3.6)	91 (47.2) 88 (45.6) 14 (7.3)	191 (49.5) 166 (43.0) 29 (7.5)	183 (47.5) 173 (44.9) 29 (7.5)	190 (49.7) 162 (42.4) 30 (7.9)
Weight (kg) *Mean (SD)* *Range*	91.82 (24.950) 45.8- 186.0	92.49 (23.891) 47.0- 200.0	92.43 (22.681) 48.0- 190.5	91.83 (21.897) 50.0- 165.0	92.51 (22.523) 46.8- 216.2	89.17 (21.638) 41.0- 162.3	92.85 (22.365) 48.6-173.2	90.97 (21.450) 55.5- 176.0	91.23 (23.916) 46.4- 200.0	90.35 (23.440) 52.0- 176.5	92.15 (24.305) 43.0-177.0

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
	Placebo (N=431)	IXE 80 mg Q4W (N=432)	IXE 80 mg Q2W (N=433)	Placebo (N=168)	IXE 80 mg Q4W (N=347)	IXE 80 mg Q2W (N=351)	Etanercept 80 mg Q4W (N=358)	Placebo (N=193)	IXE 80 mg Q4W (N=386)	IXE 80 mg Q2W (N=385)	Etanercept 80 mg Q4W (N=382)
Weight Category, n (%) *<80 kg* *≥80 to <100 kg* *≥100 kg*	147 (34.1) 142 (32.9) 142 (32.9)	132 (30.6) 158 (36.6) 142 (32.9)	133 (30.7) 155 (35.8) 145 (33.5)	50 (30.1) 61 (36.7) 55 (33.1)	97 (28.0) 130 (37.6) 119 (34.4)	123 (35.0) 133 (37.9) 95 (27.1)	111 (31.1) 121 (33.9) 125 (35.0)	61 (31.8) 77 (40.1) 54 (28.1)	125 (32.8) 149 (39.1) 107 (28.1)	138 (35.9) 137 (35.7) 109 (28.4)	123 (32.2) 133 (34.8) 126 (33.0)
BMI (kg/m^2), *Mean (SD)* *Range*	30.43 (7.608) 16.07-66.00	30.69 (7.500) 17.40-76.39	30.82 (7.117) 17.63-64.65	30.85 (7.141) 18.3-60.6	30.62 (6.589) 17.2-53.8	30.08 (7.020) 15.2-60.2	31.25 (7.252) 17.0-58.6	30.24 (6.339) 19.8-55.5	30.67 (7.310) 17.5-61.3	30.21 (7.139) 18.5-56.8	30.73 (7.586) 16.9-57.2
Baseline characteristics											
BSA (%), *Mean (SD)* *Range*	27.4 (17.77) 10-95	27.4 (16.20) 10-92	28.2 (17.83) 10-95	27.2 (18.12) 10-92	27.0 (17.23) 10-85	25.1 (15.82) 10-95	25.3 (15.50) 10-90	28.6 (17.45) 10-90	28.4 (16.49) 10-94	28.0 (17.30) 10-90	28.3 (17.43) 10-95
Duration of psoriasis (years), *Mean (SD)* *Range*	19.50 (11.73) 0.5-61.7	19.49 (11.91) 0.6-60.9	19.89 (11.91) 0.6-60.0	19.05 (12.710) 0.5-63.4	18.52 (12.738) 0.5-60.3	18.33 (12.120) 0.5-61.4	18.89 (12.455) 0.6-56.9	18.24 (12.515) 0.5-51.3	18.45 (12.471) 0.4-63.4	17.80 (12.191) 0.5-63.0	18.12 (11.787) 0.7-50.3
sPGA, n (%) *3* *4* *5*	204 (47.3) 193 (44.8) 34 (7.9)	197 (45.6) 205 (47.5) 30 (6.9)	231 (53.3) 179 (41.3) 23 (5.3)	86 (51.2) 70 (41.7) 12 (7.1)	166 (47.8) 164 (47.3)	178 (50.7) 151 (43.0)	186 (52.0) 156 (43.6) 16 (4.5)	92 (47.7) 91 (47.2) 10 (5.2)	206 (53.8) 159 (41.5)	207 (53.8) 157 (40.8) 21 (5.5)	190 (49.7) 174 (45.5) 18 (4.7)

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
	Placebo (N=431)	IXE 80 mg Q4W (N=432)	IXE 80 mg Q2W (N=433)	Placebo (N=168)	IXE 80 mg Q4W (N=347)	IXE 80 mg Q2W (N=351)	Etanercept 80 mg Q4W (N=358)	Placebo (N=193)	IXE 80 mg Q4W (N=386)	IXE 80 mg Q2W (N=385)	Etanercept 80 mg Q4W (N=382)
					17 (4.9)	22 (6.3)			18 (4.7)		
PASI score, *Mean (SD)* *Range*	20.32 (8.64) 12.0-69.2	20.03 (7.30) 12.0-61.2	20.09 (7.99) 12.0-60.0	20.57 (8.366) 12-54	20.04 (6.962) 12-46.8	19.35 (7.339) 12-57.5	19.07 (6.701) 12-61.2	21.11 (8.388) 12.0-49.1	21.15 (8.142) 12.0-60.0	20.73 (8.176) 12.0-63.0	20.68 (8.167) 12.0-57.0
NAPSI, *Mean (SD)* *Range*	26.09 (20.492) 0.0-80.0	24.12 (18.243) 1.0-80.0	24.64 (18.916) 1.0-80.0	27.62 (20.937) 1-80	23.70 (18.696) 1-80	26.27 (20.388) 1-80	30.44 (20.648) 1-80	25.47 (19.625) 1.0-80.0	26.19 (20.155) 1.0-80.0	26.14 (20.095) 1.0-80.0	25.09 (20.021) 1.0-80.0
DLQI, *Mean (SD)* *Range*	12.8 (7.11) 0-30	13.2 (7.02) 0-30	13.4 (7.02) 0-30	12.8 (7.24) 0-30	11.6 (6.65)	12.4 (6.86) 0-30	12.7 (7.03) 0-30	12.7 (7.00) 0-29	11.9 (6.97) 0-30	12.4 (6.93) 0-30	11.5 (6.84) 0-30
Itch NRS, *Mean (SD)* *Range*	7.0 (2.58) 0-10	7.0 (2.50) 0-10	7.2 (2.39) 0-10	6.4 (2.67) 0-10	6.5 (2.50) 0-10	6.7 (2.51) 0-10	6.6 (2.58) 0-10	6.5 (2.63) 0-10	6.3 (2.60) 0-10	6.4 (2.59) 0-10	6.2 (2.63) 0-10
Patients with nail psoriasis, n (%)	283 (65.7)	283 (65.5)	284 (65.5)	113 (67.3)	219 (63.1)	209 (59.5)	229 (64.0)	116 (60.1)	228 (59.1)	229 (59.5)	236 (61.8)
Previous systemic therapies, n (%) *Never used* *Biologics*	132 (30.6) 57 (13.2)	132 (30.6) 62 (14.4)	108 (24.9) 49 (11.3)	64 (38.1) 19 (11.3)	115 (33.1)	126 (35.9)	133 (37.2) 33 (9.2)	88 (45.6) 16 (8.3)	162 (42.0)	170 (44.2) 25 (6.5)	160 (41.9) 26 (6.8)

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
	Placebo (N=431)	IXE 80 mg Q4W (N=432)	IXE 80 mg Q2W (N=433)	Placebo (N=168)	IXE 80 mg Q4W (N=347)	IXE 80 mg Q2W (N=351)	Etanercept 80 mg Q4W (N=358)	Placebo (N=193)	IXE 80 mg Q4W (N=386)	IXE 80 mg Q2W (N=385)	Etanercept 80 mg Q4W (N=382)
Non-biologics	118 (27.4)	132 (30.6)	152 (35.1)	61 (36.3)	28 (8.1)	29 (8.3)	149 (41.6)	72 (37.3)	23 (6.0)	157 (40.8)	162 (42.4)
Biologics and non-biologics	124 (28.8)	106 (24.5)	124 (28.6)	24 (14.3)	147 (42.4)	141 (40.2)	43.(12.0)	17 (8.8)	166 (43.0)	33 (8.6)	34 (8.9)
					57 (16.4)	55 (15.7)			35 (9.1)		
Previous phototherapy, n (%)	185 (42.9)	205 (47.5)	201 (46.4)	74 (44.0)	160 (46.1)	163 (46.4)	173 (48.3)	60 (31.1)	154 (39.9)	151 (39.2)	157 (41.1)

Source: Based on Tables 17, 18 and 19 of the CS[2-4, 13, 40, 41]

Notes: For weight and baseline is defined as the safety baseline for each period. Previous non biologic systemic therapy includes the following: methotrexate, ciclosporin, retinoids, and PUVA.

BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; IXE = ixekizumab; kg = kilogram; m^2 = meters squared; N = number of patients in the analysis population; n = number of patients in the specified category; PASI = Psoriasis Area and Severity Index; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SD = standard deviation; sPGA = static Physician Global Assessment.

ERG comment:

Patient characteristics

The UNCOVER trials included patients with *moderate to severe* psoriasis, defined by a PASI score of greater than or equal to 12 and no restriction related to DLQI. However, *severe* psoriasis was defined as a total PASI score of 10 or more and a DLQI score of more than 10 (Figure 4 of the CS, NICE CG153).[1, 7] Therefore, the company was asked to confirm how the UNCOVER trials are applicable to the population of moderate to severe psoriasis as opposed to severe psoriasis. In response to request for clarification, the company argued that "*inclusion criteria for the UNCOVER trials stated that patients must have moderate to severe disease defined as PASI≥12 and BSA≥10%, and be candidates for phototherapy and/or systemic therapy. In addition, patients across the trials were found to have a mean DLQI score of 12.5. While this is broadly in line with the scope of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy, the population of interest for positioning ixekizumab is in line with NICE recommendations for adalimumab, etanercept, secukinumab and ustekinumab, i.e. patients with prior systemic failure, PASI>10 and DLQI>10"*.[33]

According to expert clinical feedback, a PASI score of more than 10 (or 12) appears to be commonly used as the threshold for moderate/severe psoriasis combined when using systemic therapy rather than topical therapy.

The ERG notes that there seems to be no universally agreed consensus on diagnostic criteria or tests available to set a threshold between moderate and severe in current clinical guideline.[7] However, it is likely that the UNCOVER trials (inclusion of patients with PASI > 12) failed to include some patients with moderate or less severe psoriasis, i.e. patients with PASI score under 12 (assuming threshold for moderate to severe or severe psoriasis: PASI > 10). Furthermore, the UNCOVER trials did not apply restrictions related to DLQI.

Overall, the population in the CS does not fully match the population defined in the scope which limits the generalisability of the results.

Outcomes

The final scope issued by NICE set out severity of psoriasis, psoriasis symptoms on the face, scalp and nails, mortality, response rate, relapse rate, adverse effects of treatment and health-related quality of life as outcomes.[31] The ERG notes that not all efficacy outcomes specified in the scope were assessed and reported in the each UNCOVER study. An overview of efficacy outcomes reported in the company submission is presented in Table 4.6.

As detailed before (Section 3.1), certain locations of psoriasis, such as the face, are likely to have a greater impact on how the disease is perceived by individuals affected by psoriasis. Due to the lack of evidence on this outcome, it is more difficult to draw any firm conclusions for patients with psoriasis symptoms of the face.

Furthermore, the ERG notes that the NICE scope further defines the population as a) people for whom non-biologic systemic treatment or phototherapy is suitable, and b) people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.[31] Although the two populations were in effect eligible for all three UNCOVER studies, these two populations were not analysed separately in the clinical effectiveness section. In response to a query from the ERG, the company responded that inclusion/exclusion criteria for the UNCOVER studies are consistent with all recent studies for psoriasis treatment that have been assessed by NICE and it is anticipated that ixekizumab will have a similar place in the clinical

pathway to NICE approved biologics.[33] In addition, the company provided the baseline characteristics of the relevant population (prior exposure to biological and/or non-biological systemic treatment and/or PUVA/UVB) and the PASI responses at week 12. The company stated that "*as responses are consistent with between the populations in question and the ITT population, the results of the NMA which populate the economic model can be considered as valid for the analyses presented in the submission*". The results of these analyses are provided in the response to clarification question A11 and discussed in Sections 4.3 and 4.4 of this report.

Table 4.6: Overview of efficacy outcomes reported in the company submission

Outcome	Final scope	UNCOVER-1	UNCOVER-2	UNCOVER-3	Table
Severity of psoriasis					
sPGA (0,1) at week 12	"Severity of psoriasis"	reported	reported	reported	Table 4.8
sPGA (0) at week 12		reported	reported	reported	Table 4.8
Response rate					
PASI 75 at week 12	"Response rate"	reported	reported	reported	Table 4.8
PASI 90 at week 12		reported	reported	reported	Table 4.8
PASI 100 at week 12		reported	reported	reported	Table 4.8
Psoriasis symptoms on the face, scalp and nails					
Face	"Psoriasis symptoms on the face, scalp and nails"	not reported	not reported	not reported	N/A
PSSI		reported	not reported in the CS, but data retrieved from the CSR	reported	Table 4.8, Table 4.9
NAPSI		reported	not reported in the CS, but data retrieved from the CSR	reported	Table 4.8, Table 4.9
PPASI		reported	not reported in the CS, but data retrieved from the CSR	reported	Table 4.8, Table 4.9
Mortality					
Mortality	"Mortality", including in the report of "Adverse events"	reported	reported	reported	Table 4.11, Table 4.12
Relapse rate					
PASI 75 at week 60	"Relapse rate"	reported	reported	reported (data up to 108 weeks)	Table 4.9, Figure 4.1
PASI 90 at week 60	"Relapse rate"	reported	reported	reported (data up to 108 weeks)	Table 4.9, Figure 4.2
PASI 100 at week 60	"Relapse rate"	reported	reported	reported (data up to 108 weeks)	Table 4.9, Figure 4.3
sPGA (0,1) at week 60	"Relapse rate"	reported	reported	not reported	Table 4.9

Outcome	Final scope	UNCOVER-1	UNCOVER-2	UNCOVER-3	Table
Adverse effects of treatment					
Patients with ≥1 TEAE	"Adverse effects of treatment"	reported	reported	reported	Table 4.11, Table 4.12
Discontinuations from Study Drug due to AE (including death)	"Adverse effects of treatment"	reported	reported	reported	Table 4.11, Table 4.12
Deaths	"Adverse effects of treatment"	reported	reported	reported	Table 4.11, Table 4.12
SAEs	"Adverse effects of treatment"	reported	reported	reported	Table 4.11, Table 4.12
Health-related quality of life					
Itch NRS at week 12	It was not defined in the final scope	reported	not reported in the CS, but data retrieved from references	reported	Table 4.8
DLQI at week 12	"Health-related quality of life"	reported	not reported in the CS, but data retrieved from references	reported	Table 4.8

Source: Based on Table 1 of the CS[1]

AE= Adverse Event; CS = company submission; DLQI = Dermatology Life Quality Index; NAPSI = Nail Psoriasis Severity Index; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PPASI= Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; SAE= Serious Adverse Event; sPGA = static Physician Global Assessment; TEAE= Treatment Emergent Adverse Events

Quality assessment

Table 4.7 provides an overview of the quality assessment of the UNCOVER RCTs. Appendix 7 of the CS presents a complete quality assessment of the UNCOVER RCTs with supporting evidence on how each of the quality criteria was rated.[1]

Table 4.7: Quality assessment of UNCOVER studies by CS and ERG

	UNCOVER-1		UNCOVER-2		UNCOVER-3	
	CS	ERG	CS	ERG	CS	ERG
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	Yes	No	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes	Yes

Source: Based on table 20 of the CS[1]
CS = company submission; ERG = Evidence Review Group; ITT = intention-to-treat

ERG comments: As discussed in Section 4.1.4, while not explicitly stated, the ERG assumes that Cochrane risk of bias tool was used.[38]

Appendix 7 of the CS states that an interactive voice/web response system (IVRS/IWRS) was employed to manage subject randomisation and treatment assignment.[36] Demographic and baseline clinical characteristics were generally well balanced. Procedures for blinding of patients, care providers and outcome assessors appear to be appropriate. It is noted that unblinding occurred when participants entered an open-label long-term extension period in the UNCOVER-3 trial. The ERG also notes that the proportion of patients who discontinued for any reason was dissimilar between the groups in the UNCOVER-2 and UNCOVER-3 trials. In the UNCOVER-2 trial, as the proportion was lowest in the population of interest, ixekizumab Q2W (2.6%), compared to the placebo, etanercept and ixekizumab Q4W groups (6.0%, 7.0%, and 5.5%, respectively), the ERG does not consider this a relevant difference. In UNCOVER-3, the proportion of patients discontinuing treatment was two times lower in the active comparator, etanercept (3.4%), than in the ixekizumab Q4W, ixekizumab Q2W and placebo groups (6.7%, 5.7% and 5.2%, respectively). However, the ERG notes that the numbers of discontinuations from study drug due to AE, including death are relative low in all treatments (Table 4.11).

ITT analysis was reported for the main efficacy outcomes. Appropriate methods were used to account for missing data.[1] The ERG could find no evidence that outcomes had been collected but not reported.

Overall, the ERG agrees that there is a low risk of bias, i.e. introduced in the treatment effects.

Results of the study

The UNCOVER studies included the following outcome measures to assess the outcomes defined in the final scope (see Table 3.1):

- PASI 75/90/100
- sPGA
- Relapse rate
- Health-related quality of life
- Psoriasis of the nails, scalp and palmoplantar areas
- Adverse events, including deaths.

These results are presented below. Efficacy analyses were performed using the ITT population. Evidence from the UNCOVER studies for each of these outcomes is presented below in separate tables.

Severity of psoriasis and response rate

The primary outcomes were sPGA (0,1) and PASI 75 at week 12. In all three UNCOVER studies, there were statistically significant increases in sPGA (0,1) and PASI 75 response rates for patients treated with ixekizumab compared with placebo at week 12 ($p<0.001$ for all comparisons). Similar results were also observed when comparing ixekizumab with active comparator etanercept 50 mg twice weekly at week 12 ($p<0.001$ for all comparisons) in the UNCOVER-2 and -3 studies. The results are summarised in Table 4.8.

At week 12, the proportion of patients achieving complete clearance (PASI 100) and high-level responses (PASI 90) were significantly greater with ixekizumab compared with etanercept (UNCOVER-2 and -3 only) and placebo ($p<0.001$ for all comparisons) in all three studies.

Rapid onset of efficacy was also noted: in the UNCOVER-2 study, 18.2% of patients treated with ixekizumab Q2W achieved PASI 75 at week 2, compared with 0.6% of patients who received placebo, and 0.6% of patients who received etanercept, respectively.[40] Similar results in favour of ixekizumab Q2W were also found in the UNCOVER-3 study with 22.9% in the ixekizumab Q2W group, 0% in the placebo group and 2.4% of etanercept group, respectively.[40]

Relapse rate

The relapse rate was assessed based on the maintenance of response at week 60 according to the definition in the final scope.[31] The UNCOVER-1 and UNCOVER-2 included maintenance dosing periods (week 12-60) and study results both indicated that ixekizumab Q4W group had significant benefit over placebo in achieving or maintaining sPGA (0,1) and PASI response (including PASI 75, 90, 100) at week 60 (Table 4.9).

Health-related quality of life

Health-related quality of life, as measured by change from baseline dermatology life quality index (DLQI), also significantly improved in the ixekizumab groups compared with etanercept and placebo groups ($p<0.001$) (Table 4.8).

The proportions of patients who had baseline itch NRS ≥4 and achieved itch NRS ≥4 point reduction from baseline to week 12 in the ixekizumab groups were also significant higher than etanercept and placebo groups (Table 4.8).

Psoriasis symptoms on the face, scalp and nails

Nail Psoriasis Severity Index (NAPSI), Psoriasis Scalp Severity Index (PSSI) and Palmoplantar Psoriasis Severity Index (PPASI), which evaluate the severity of psoriasis in difficult-to-treat area, were measured across all UNCOVER studies.

At week 12, statistically significant improvements were observed in NAPSI scores for patients in the ixekizumab groups compared with the placebo group in the UNCOVER-1 and UNCOVER-3 ($p<0.001$) but not in the UNCOVER-2 (Table 4.8). Ixekizumab were statistically significantly superior to etanercept (UNCOVER-2 and -3 only) and placebo (UNCOVER-1, -2 and -3) at improving scalp psoriasis as measured by the proportion of patients achieving PSSI=0 and the LSM changes from baseline in the PSSI scores. Numerical improvements in PPASI score were observed for both ixekizumab groups compared with etanercept (UNCOVER-2 and UNCOVER-3), however these differences were not-significant in the UNCOVER-3 (Table 4.8).

At week 60, in general, maintenance treatment with ixekizumab Q4W was statistically significantly superior to placebo (UNCOVER-1 and -2) in the proportion of patients who achieved NAPSI, PSSI and PPASI clearance rates although the outcomes of the least squares mean (LSM) changes from baseline in PPASI scores were not significantly different in the UNCOVER-1 and UNCOVER-2 (Table 4.8).

Table 4.8: Summary of results for clinical endpoints (ITT population, 12 weeks)

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
Severity of psoriasis (sPGA)											
sPGA (0,1), n (%)	14 (3.2)	330 (76.4)†	354 (81.8)†	4 (2.4)	129 (36.0)†	253 (72.9)†‡	292 (83.2)†‡	13 (6.7)	159 (41.6)†‡	291 (75.4)†‡	310 (80.5)†‡
OR vs. PBO (95%CI) p-value	-	102.89 (57.52, 184.04) <0.001	146.51 (81.02, 264.92) <0.001	-	27.58 (9.40, 80.98) <0.001	120.29 (39.95, 362.22) <0.001	282.24 (76.03, 1047.7) <0.001	-	11.30 (6.01, 21.25) <0.001	40.84 (21.10, 79.03) <0.001	50.47 (26.54, 95.98) <0.001
OR vs. ETN (95% CI) p-value	-	-	-	-	-	5.37 (3.82, 7.56) <0.001	10.70 (7.23, 15.85) <0.001	-	-	4.80 (3.46, 6.67) <0.001	6.47 (4.55, 9.20) <0.001
sPGA (0), n (%)	0 (0.0)	149 (34.5)	160 (37.0)	1 (0.6)	21 (5.9)	112 (32.3)†‡	147 (41.9)†‡	0 (0.0)	33 (8.6)	139 (36.0)‡	155 (40.3)‡
OR vs. PBO (95%CI) p-value	-	N/A	N/A	-	10.87 (1.42, 83.08) 0.005	86.49 (11.60, 644.87) <0.001	118.34 (17.18, 815.05) <0.001	-	N/A	N/A	N/A
OR vs. ETN (95% CI) p-value	-	-	-	-	-	8.28 (4.95, 13.85) <0.001	14.72 (8.57, 25.29) <0.001	-	-	6.23 (4.08, 9.52) <0.001	7.98 (5.16, 12.33) <0.001
Response rate											
PASI 75											
PASI 75, n (%)	17 (3.9)	357	386	4 (2.4)	149	269	315	14 (7.3)	204	325	336

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
		(82.6)[†]	(89.1)[†]		(41.6)[†]	(77.5)[†‡]	(89.7)[†‡]		(53.4)[†‡]	(84.2)[†‡]	(87.3)[†‡]
OR vs. PBO (95%CI) p-value	-	125.54 (72.26, 218.10) <0.001	223.94 (125.05, 401.03) <0.001	-	30.73 (10.83, 87.16) <0.001	160.50 (51.33, 501.87) <0.001	997.29 (173.11, 5,745.5) <0.001	-	13.71 (7.61, 24.72) <0.001	68.95 (34.53, 137.68) <0.001	72.29 (36.11, 144.73) <0.001
OR vs. ETN (95% CI) p-value	-	-	-	-	-	5.05 (3.60, 7.09) <0.001	13.28 (8.66, 20.34) <0.001	-	-	4.91 (3.46, 6.98) <0.001	6.46 (4.42, 9.45) <0.001
PASI 90											
PASI 90, n (%)	2 (0.5)	279 (64.6)[†]	307 (70.9)[†]	1 (0.6)	67 (18.7)[†]	207 (59.7)[†‡]	248 (70.7)[†‡]	6 (3.1)	98 (25.7)[†‡]	252 (65.3)[†‡]	262 (68.1)[†‡]
OR vs. PBO (95%CI)	-	411.70 (101.09, 1,676.63) <0.001	562.34 (137.80, 2,294.7) <0.001	-	40.31 (5.59, 290.89) <0.001	223.76 (31.67-1,581.0) <0.001	434.42 (56.60, 3,334.3) <0.001	-	12.25 (5.07, 29.61) <0.001	81.81 (29.56, 226.42) <0.001	72.49 (28.39, 185.09) <0.001
OR vs. ETN (95% CI)	-	-	-	-	-	6.55 (4.61, 9.31) <0.001	12.18 (8,28, 17.91) <0.001	-	-	5.68 (4.11, 7.86) <0.001	6.56 (4.70, 9.14) <0.001
PASI 100											
PASI 100, n (%)	0 (0.0)	145 (33.6)	153 (35.3)	1 (0.6)	19 (5.3)	107 (30.8)[†‡]	142 (40.5)[†‡]	0 (0.0)	28 (7.3)	135 (35.0)[‡]	145 (37.7)[‡]
OR vs. PBO (95%CI)	-	N/A	N/A	-	9.89 (1.28,	75.44 (10.49,	113.79 (16.20,	-	N/A	N/A	N/A

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
					76.15) 0.008	542.60) <0.001	799.34) <0.001				
OR vs. ETN (95% CI)	-	-	-	-	-	8.46 (4.97, 14.42) <0.001	14.27 (8.25, 24.68) <0.001	-	-	6.96 (4.46, 10.87) <0.001	8.48 (5.35, 13.45) <0.001
Health-related quality of life											
Itch NRS											
Patients with >4 point reduction from baseline (NRI), n (%)	58 (15.5)	305 (80.5)†	336 (85.9)†	[redacted]	[redacted]	[redacted]	[redacted]	33 (20.9)	200 (64.1)†	250 (79.9)†‡	264 (82.5)†‡
OR vs. PBO (95%CI)	-	22.90 (15.65, 33.51) <0.001	34.39 (22.97, 51.49) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	7.15 (4.47, 11.44) <0.001	14.58 (8.89, 23.91) <0.001	16.70 (10.04, 27.80) <0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	2.27 (1.58, 3.28) <0.001	2.72 (1.86, 3.97) <0.001
DLQI											
Change from baseline, LSM (SE)	-0.7 (0.29)	-10.3 (0.29)†	-10.7 (0.28)†	[redacted]	[redacted]	[redacted]	[redacted]	-1.5 (0.32)	-8.1 (0.23)†	-9.6 (0.23)†‡	-10.0 (0.23)†‡
Patients with DLQI (0,1) (NRI), n (%)	20 (4.6)	258 (59.7)†	287 (66.3)†	[redacted]	[redacted]	[redacted]	[redacted]	15 (7.8)	167 (43.7)†	246 (63.7)†‡	249 (64.7)†‡
OR vs. PBO (95%CI)	-	31.16 (19.09,	41.54 (25.37,	[redacted]	[redacted]	[redacted]	[redacted]	-	10.51 (5.75,	21.05 (11.58,	21.00 (14.1,

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
		50.85) <0.001	68.02) <0.001						19.20) <0.001	38.27) <0.001	27.9) <0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	2.32 (1.72, 3.12) <0.001	2.38 (1.77, 3.20) <0.001
Patients with DLQI (0) (NRI)	2 (0.5)	174 (40.3)†	181 (41.8)†	[redacted]	[redacted]	[redacted]	[redacted]	5 (2.6)	79 (20.7)†	157 (40.7)†‡	163 (42.3)†‡
OR vs. PBO (95%CI)	-	147.46 (36.26, 599.74) <0.001	157.15 (38.64, 639.08) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	10.04 (4.03, 25.03) <0.001	25.60 (10.21, 64.20) <0.001	35.76 (13.21, 96.82) <0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	2.78 (1.99, 3.88) <0.001	2.83 (2.04, 3.92) <0.001
Psoriasis symptoms on the face, scalp and nail											
Face#	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NAPSI score mean change from baseline, LSM (SE)	2.30 (0.736)	-7.14 (0.733)†	-7.12 (0.696)†	[redacted]	[redacted]	[redacted]	[redacted]	1.12 (0.98)	-6.64 (0.68)†	-9.84 (0.70)†‡	-10.41 (0.70)†‡
Patients with NAPSI (0) (NRI), n (%)	10 (3.5)	36 (12.7)†	48 (16.9)†	[redacted]	[redacted]	[redacted]	[redacted]	5 (4.3)	24 (10.2)	45 (19.7)†	40 (17.5)†
OR vs. PBO (95%CI)	-	3.99 (1.94, 8.21)	5.74 (2.84, 11.63)	[redacted]	[redacted]	[redacted]	[redacted]	-	p=0.099	p<0.001	p<0.001

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)
		<0.001	<0.001								
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	p=0.004	p=0.009
PSSI score mean change from baseline, LSM (SE)	-1.5 (0.55)	-18.3 (0.54)†	-19.0 (0.54)†	[redacted]	[redacted]	[redacted]	[redacted]	-5.0 (0.51)	-15.6 (0.37)†	-18.1 (0.37)†‡	-18.6 (0.36)†‡
Patients with PSSI (0) (NRI), n (%)	21 (5.3)	287 (69.5)	290 (73.8)	[redacted]	[redacted]	[redacted]	[redacted]	16 (9.1)	178 (51.1)†	253 (72.5)†‡	264 (75.6)†‡
OR vs. PBO (95%CI)	-	42.24 (25.86, 69.02) <0.001	53.11 (32.25, 87.49) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	<0.001	<0.001	<0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	<0.001	<0.001
PPASI score mean change from baseline, LSM (SE)	0.57 (0.64)	-5.34 (0.63)†	-5.39 (0.59)†	[redacted]	[redacted]	[redacted]	[redacted]	-2.55 (1.02)	-6.13 (0.78)	-7.65 (0.84)†	-7.64 (0.80)†
Patients with PPASI 100 (NRI), n (%)	27 (20.3)	86 (65.6)†	98 (70.0)†	[redacted]	[redacted]	[redacted]	[redacted]	15 (27.8)	57 (60.0)	54 (62.1)†	61 (63.5)†
OR vs. PBO (95%CI)	-	7.68 (4.39, 13.43) <0.001	9.72 (5.52, 17.11) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	-	<0.001	<0.001	<0.001
OR vs. ETN (95% CI)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	p=0.466	p=0.236

Source: Based on Tables 21-25, 29, 31, 33, 34, 37-45 of the CS[1], Griffiths et al. 2015[2] and CSRs for UNCOVER-1 and -2[3, 4]

Data are least squares mean (SE), n (%), or % (CI). Data were analysed with the Cochran-Mantel-Haenszel test with non-responder imputation for response rates and mixed-

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
Endpoint	PBO (N=431)	IXE80 Q4W (N=432)	IXE80 Q2W (N=433)	PBO (N=168)	ETN (N=358)	IXE80 Q4W (N=347)	IXE80 Q2W (N=351)	PBO (N=193)	ETN (N=382)	IXE80 Q4W (N=386)	IXE80 Q2W (N=385)

models repeated-measure analysis for least squares mean change from baseline Itch NRS, DLQI, NAPSI, PSSI and PPASI
† p<0·001 compared with placebo. ‡ p<0·001 compared with etanercept; # Included in the final scope but not reported in any of the studies
ETN = etanercept; ITT = intention to treat; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; n = number of patients in the specified category; N = number of patients in the analysis population; NAPSI = Nail Psoriasis Severity Index; NR = not reported; NRI = non-responder imputation; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PBO = placebo; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; Q2W = once every 2 weeks; Q4W = once every 4 weeks; sPGA = static Physician Global Assessment											

Table 4.9: Summary of results for clinical endpoints (ITT population) at week 60

	UNCOVER-1						UNCOVER-2					
Endpoint	IXE80 Q4W /PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W	IXE80 Q4W/ PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W
Relapse rate – Clinical responses at 60 weeks												
sPGA (0,1), n (%)	8 (7.3%)	78 (70.9%)	9 (7.7%)	89 (74.8%)	17 (7.5%)	167 (72.9%)	4 (4.9)	56 (65.9)	7 (7.4)	84 (82.4)	11 (6.3)	140 (74.9)
OR vs. PBO (95%CI)	-	33.10 (14.33, 76.45) <0.001		38.82 (17.35, 86.87) <0.001	-	35.84 (20.01, 64.20) <0.001	-	37.66 (12.53, 113.16) <0.001	-	58.00 (23.04, 145.99) <0.001	-	44.67 (22.32, 89.41) <0.001
PASI 75, n (%)	9 (8.3)	85 (77.3)	11 (9.4)	93 (78.2)	20 (8.8)	178 (77.7)	6 (7.3)	60 (70.6)	8 (8.5)	91 (89.2)	14 (8.0)	151 (80.7)
OR vs. PBO (95%CI)	-	41.33 (18.12, 94.31) <0.001	-	38.09 (17.64, 82.23) <0.001	-	39.53 (22.45, 68.63) <0.001	-	30.40 (11.72, 78.84) <0.001	-	88.93 (34.14, 231.61) <0.001	-	48.53 (25.19, 93.52) <0.001
PASI 90, n (%)	4 (3.7)	76 (69.1)	6 (5.1)	86 (72.3)	10 (4.4)	162 (70.7)	5 (6.1)	54 (63.5)	4 (4.3)	83 (81.4)	9 (5.1)	137 (73.3)
OR vs. PBO (95%CI)	-	63.29 (21.42, 187.04) <0.001	-	52.64 (20.92, 132.45) <0.001	-	56.65 (28.06, 114.37) <0.001	-	26.83 (9.80, 73.40) <0.001	-	98.29 (32.11, 300.85) <0.001	-	50.84 (24.14, 107.07) <0.001
PASI 100, n (%)	2 (1.8)	57 (51.8)	4 (3.4)	62 (52.1)	6 (2.7)	119 (52.0)	1 (1.2)	40 (47.1)	2 (2.1)	65 (63.7)	3 (1.7)	105 (56.1)
OR vs.	-	59.55	-	31.96	-	41.16	-	72.00	-	80.81	-	73.81

	UNCOVER-1						UNCOVER-2					
Endpoint	IXE80 Q4W /PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W	IXE80 Q4W/ PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W
PBO (95%CI)		(13.97, 253.88) <0.001		(11.03, 92.55) <0.001		(17.52, 96.70) <0.001		(9.58, 541.40) <0.001		(18.81, 347.23) <0.001		(22.75, 239.49) <0.001
Psoriasis symptoms on the scalp and nail												
Face	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NAPSI score *mean change from baseline, LSM (SE)*	-9.32 (1.26)	-18.34 (1.32)†	-8.77 (1.28)	-19.49 (1.28)†	-9.06 (0.90)	-18.93 (0.92)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with NAPSI (0), n (%)	3 (3.8)	33 (44.6)†	0 (0)	38 (50.0)†	3 (1.9)	71 (47.3)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. PBO (95%CI)	-	20.12 (5.80, 69.75) <0.001	-	N/A N/A <0.001	-	46.72 (14.24, 153.30) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSSI score *mean change from*	-12.2 (0.80)	-19.0 (0.81)†	-8.9 (0.81)	-19.5 (0.78)†	-10.6 (0.58)	-19.2 (0.57)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UNCOVER-1						UNCOVER-2					
Endpoint	IXE80 Q4W /PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W	IXE80 Q4W/ PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W
baseline, LSM (SE)												
Patients with PSSI (0), n (%)	5 (4.7)	73 (70.2)†	7 (6.9)	75 (68.2)†	12 (5.7)	148 (69.2)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. PBO (95%CI)	-	48.97 (18.14, 132.17) <0.001	-	29.60 (12.42, 70.51) <0.001	-	37.49 (19.52, 72.01) <0.001	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPASI score mean change from baseline, LSM (SE)	-5.81 (1.07)	-5.88 (1.15)	-2.58 (1.05)	-6.20 (1.09)	-4.17 (0.77)	-6.07 (0.81)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with PPASI 100, n (%)	5 (14.3)	22 (71.0)†	2 (5.4)	21 (63.6)†	7 (9.7)	43 (67.2)†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs. PBO (95%CI)	-	15.09 (4.30, 52.94)	-	42.96 (8.36, 220.77)	-	23.06 (8.70, 61.12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	UNCOVER-1						UNCOVER-2					
Endpoint	IXE80 Q4W /PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W	IXE80 Q4W/ PBO	IXE80 Q4W/ IXE80 Q4W	IXE80 Q2W/ PBO	IXE80 Q2W/ IXE80 Q4W	IXE/PBO	IXE/ IXE80 Q4W
		<0.001		<0.001		<0.001						

Source: Based on Tables 26-28, 30, 32, 35, 36 of the CS[1] and CSRs for UNCOVER-1 and -2[3, 4]

Data are least squares mean (SE), n (%), or % (CI). Data were analysed with the Cochran-Mantel-Haenszel test with non-responder imputation for response rates and mixed-models repeated-measure analysis for least squares mean change from baseline NAPSI, PSSI and PPASI

† p<0·001 compared with placebo. ‡ p<0·001 compared with etanercept; # Included in the final scope but not reported in any of the studies-

IXE = ixekizumab; IXE80 = ixekizumab 80 mg; n = number of patients in the specified category; N = number of patients in the analysis population; NAPSI = Nail Psoriasis Severity Index; NNT = number needed to treat; NR = not reported; NRI = non-responder imputation; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PBO = placebo; PPASI = Palmoplantar Psoriasis Severity Index; PSSI = Psoriasis Scalp Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician Global Assessment

PASI response rate during open-label long-term extension period (up to week 108)

[redacted] v(Figures 4.1 to 4.3).[1]

Figure 4.1: [redacted]

Source: CSR for UNCOVER-3[41]

[redacted]

CSR = clinical study report; ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 90 = at least a 90% improvement from baseline in Psoriasis Area and Severity Index score; Q2W = once every 2 weeks; Q4W = once every 4 weeks

Figure 4.2: [redacted]

Source: CSR for UNCOVER-3[41]

[redacted]CSR = clinical study report; ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 90 = at least a 90% improvement from baseline in Psoriasis Area and Severity Index score; Q2W = once every 2 weeks; Q4W = once every 4 weeks

Figure 4.3: [redacted]

Source: CSR for UNCOVER-3[41]

[redacted]

CSR = clinical study report; ITT = intent to treat; IXE80 = ixekizumab 80 mg; NRI = non-responder imputation; PASI 90 = at least a 90% improvement from baseline in Psoriasis Area and Severity Index score; Q2W = once every 2 weeks; Q4W = once every 4 weeks

ERG comment: The majority of evidence presented on the efficacy of ixekizumab in the CS was derived from three methodologically similar UNCOVER studies comparing 80 mg every two weeks (Q2W) and 80 mg every four weeks (Q4W) against placebo (UNCOVER-1, -2 and -3) and etanercept 50 mg twice weekly (UNCOVER-2 and UNCOVER-3 only).

The available data suggest that ixekizumab is a more effective treatment than placebo and etanercept over the short period (Table 4.8) in terms of achieving major clinical responses (sPGA and PASI), and these benefits are likely to persist for at least 60 weeks (Table 4.9). In general, all other secondary objectives were met, with both dose regimens of ixekizumab showing greater efficacy than placebo and etanercept.

The relative performance of ixekizumab in difficult-to-treat areas, including nails, scalp and palmoplantar region are broadly more efficacious than placebo and etanercept. However, the improvement of psoriasis symptoms of the face which is included in the final scope has not been reported in any of the UNCOVER studies.

Subgroup analysis

The final scope issued by NICE requested evidence in subgroups of patients previously treated by systematic non-biological or biological therapies and in patients with different severity of psoriasis (moderate, severe) if data were available. The company pre-specified a number of subgroup analyses including: age, gender, race, body weight, PASI baseline severity, plaques location, concurrent psoriatic arthritis, previous treatment with systemic biologic and non-biologics systemic therapy and the number of previous exposures to biologic therapy. The company also examined post hoc efficacy of ixekizumab in patients eligible for biologic therapy under current NICE criteria (based on previous treatments and disease severity). The results illustrate the consistently high PASI 75 response rates

observed in patients treated with ixekizumab than in patients treated with placebo regardless of previous exposure to systemic non-biologic and biologic therapies.

ERG comment: The subgroup analyses were performed to explore any differences in outcomes between patient demographics, disease-related variables and previous therapies, on the PASI 75 endpoint at week 12. The company was asked to provide measures of heterogeneity for the subgroup analyses. In response to a clarification request by the ERG, the company provided additional tables to show low heterogeneity across the UNCOVER studies by the results of study treatment interaction.[33] The table of analyses of selected subgroups for each of the individual studies is reproduced as Table 4.12 below.

Subgroup analyses of UNCOVER demonstrated ixekizumab to be consistently efficacious in systemic treatment-naive, biologic-naive, biologic/anti-TNF-α-exposed and biologic/anti-TNF-α-failure patients during the induction dosing period.

Table 4.10: Proportion of patients achieving PASI 75 at week 12 (NRI, ITT). Pooled and subgroup results

Subgroup	p-value (interaction)[a]	PBO n/N_x (%)	IXE80 Q4W n/N_x (%)	IXE80 Q2W n/N_x (%)	All IXE n/N_x (%)
Gender					
Pooled results		N=792	N=1,165	N=1,169	N=2,334
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-1		N=431	N=432	N=433	N=865
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-2		N=168	N=347	N=351	N=698
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-3		N=193	N=386	N=385	N=771
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female		[redacted]	[redacted]	[redacted]	[redacted]
Age					
Pooled results		N=791	N=1,161	N=1,167	N=2,328
<40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥40 years		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-1		N=431	N=432	N=433	N=865
<40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥40 years		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-2		N=167	N=347	N=350	N=697
<40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥40 years		[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	p-value (interaction)[a]	PBO n/N_x (%)	IXE80 Q4W n/N_x (%)	IXE80 Q2W n/N_x (%)	All IXE n/N_x (%)
UNCOVER-3		N=193	N=382	N=384	N=766
<40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥40 years		[redacted]	[redacted]	[redacted]	[redacted]
Disease severity					
Pooled results		N=792	N=1,165	N=1,169	N=2,332
PASI <20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI ≥ 20		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-1		N=431	N=432	N=433	N=865
PASI <20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI ≥ 20		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-2		N=168	N=347	N=351	N=698
PASI <20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI ≥ 20		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-3		N=193	N=386	N=385	N=771
PASI <20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI ≥ 20		[redacted]	[redacted]	[redacted]	[redacted]
Previous non-biologic systemic therapy (NBST): inadequate response, intolerance or contraindication					
Pooled results		N=792	N=1,162	N=1,169	N=2,331
<3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-1		N=431	N=432	N=433	N=865
<3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3		[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	p-value (interaction)[a]	PBO n/N_x (%)	IXE80 Q4W n/N_x (%)	IXE80 Q2W n/N_x (%)	All IXE n/N_x (%)
UNCOVER-2		N=168	N=347	N=351	N=698
<3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3		[redacted]	[redacted]	[redacted]	[redacted]
UNCOVER-3		N=193	N=383	N=385	N=768
<3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3		[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 9 of the response to request for clarification.[33]
Footnotes: b p<0.001 versus PBO; c p<0.001 versus 80 mg Q4W; d p≤0.05 versus 80 mg Q4W, e p≤0.05 versus PBO
ITT = intention to treat; IXE = ixekizumab, IXE80 = ixekizumab 80 mg; NA = not available; NBST = Non-biologic systemic therapies; NRI = non-responder imputation; PASI = psoriasis area and severity index; PBO = placebo; Q2W = once every 2 weeks; Q4W = once every 4 weeks

Safety

The CS provided detailed information on adverse events for the UNCOVER studies. Adverse effects of treatment during the 12-week induction and maintenance dosing periods, are shown in Table 4.11 (all three UNCOVER studies) and Tables 4.12 (UNCOVER-1 and UNCOVER-2), respectively.

During the 12-week induction dosing period, there were more subjects with any treatment-emergent AE (TEAE) treated with ixekizumab than with placebo (see Table 4.11). The discontinuation rates due to AEs were similar in the patients who received ixekizumab and those who received placebo or etanercept. No deaths were recorded for the induction dosing period. The most frequent adverse events of special interest (AESIs) observed in the UNCOVER studies were infections and injection site reactions.

Similar results were observed in the maintenance dosing period (see Table 4.12). It is noted that there were two deaths during the maintenance dosing period occurring in the ixekizumab groups in the UNCOVER-1 trial; one by myocardial infarction and the other of unknown cause.

Table 4.11: Overview of AEs – safety population (Induction Dosing Period, to week 12)

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
	PBO (N=431) n (%)	**IXE80 Q4W (N=432) n (%)**	**IXE80 Q2W (N=433) n (%)**	**PBO (N=167) n (%)**	**ETN (N=357) n (%)**	**IXE80 Q4W (N=347) n (%)**	**IXE80 Q2W (N=350) n (%)**	**PBO (N=193) n (%)**	**ETN (N=382) n (%)**	**IXE80 Q4W (N=382) n (%)**	**IXE80 Q2W (N=384) n (%)**
Patients with ≥1 TEAE	210 (48.7%)	264 (61.1%)	257(59.4%)	89 (53.3)	211 (59.1)	204 (58.8)	216 (61.7)	70 (36.3%)	187 (49.0%)	215 (56.3%)	205 (53.4%)
Discontinuations from Study Drug due to AE (including death)	6 (1.4%)	10 (2.3%)	10 (2.3%)	1 (0.6)	5 (1.4)	5 (1.4)	6 (1.7)	2 (1.0%)	4 (1.0%)	8 (2.1%)	9 (2.3%)
Deaths	0	0	0	0	0	0	0	0	0	0	0
SAEs	5 (1.2%)	12 (2.8%)	6 (1.4%)	2 (1.2)	8 (2.2)	8 (2.3)	5 (1.4)	5 (2.6%)	5 (1.3%)	6 (1.6%)	9 (2.3%)
TEAEs possibly related to study drug	49 (11.4)	111 (25.7)	127 (29.3)	30 (18.0)	91 (25.5)	92 (26.5)	117 (33.4)	24 (12.4)	85 (22.3)	83 (21.7)	103 (26.8)
Treatment-Emergent AE of Special Interest											
Cytopenias	6 (1.4)	3 (0.7)	4 (0.9)	1 (0.6)	5 (1.4)	4 (1.2)	5 (1.4)	1 (0.5)	6 (1.6)	5 (1.3)	3 (0.8)
Hepatic	6 (1.4)	7 (1.6)	4 (0.9)	0 (0)	6 (1.7)	3 (0.9)	6 (1.7)	1 (0.5)	9 (2.4)	4 (1.0)	8 (2.1)
Infection	106 (24.6)	128 (29.6)	124 (28.6)	46 (27.5)	98 (27.5)	100 (28.8)	104 (29.7)	27 (14.0)	59 (15.4)	99 (23.0)	82 (21.4)
Injection-site reactions	13 (3.0)	52 (12.0)	69 (15.9)	7 (4.2)	62 (17.4)	42 (12.1)	69 (19.7)	6 (3.1)	59 (15.4)	55 (14.4)	58 (15.1)
Allergic reactions/ Hypersensitivities	10 (2.3)	19 (4.4)	14 (3.2)	3 (1.8)	12 (3.4)	15 (4.3)	14 (4.0)	4 (2.1)	7 (1.8)	12 (3.1)	13 (3.4)
Anaphylaxis†	2 (0.5)	2 (0.5)	2 (0.5)	(0)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)
Non-Anaphylaxis	8 (1.9)	17 (3.9)	12 (2.8)	3 (1.8)	11 (3.1)	14 (4.0)	13 (3.7)	4 (2.1)	7 (1.8)	11 (2.9)	12 (3.1)
Cerebrocardiovascular events	0 (0)	3 (0.7)	0 (0)	0 (0)	2 (0.6)	5 (1.4)	1 (0.3)	1 (0.5)	0 (0)	1 (0.3)	0 (0)
Malignancies	2 (0.5)	3 (0.7)	0 (0)	0 (0)	1 (0.3)	0 (0)	3 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Depression	3 (0.7)	2 (0.5)	1 (0.2)	1 (0.6)	5 (1.4)	1 (0.3)	2 (0.6)	1 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)
Pneumocystis	0	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	UNCOVER-1			UNCOVER-2				UNCOVER-3			
	PBO (N=431) n (%)	**IXE80 Q4W (N=432) n (%)**	**IXE80 Q2W (N=433) n (%)**	**PBO (N=167) n (%)**	**ETN (N=357) n (%)**	**IXE80 Q4W (N=347) n (%)**	**IXE80 Q2W (N=350) n (%)**	**PBO (N=193) n (%)**	**ETN (N=382) n (%)**	**IXE80 Q4W (N=382) n (%)**	**IXE80 Q2W (N=384) n (%)**
pneumonia (PCP)											
Interstitial lung disease	1 (0.2)	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Crohn's Disease	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Ulcerative Colitis	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Based on Tables 57, 59 and 61 of the CS[1]

† Anaphylaxis as shown here refers to potential cases using broadly-defined Sampson criteria. There were no confirmed cases of anaphylaxis in the Induction Dosing Period

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; ETN = etanercept; ISE = injection-site reaction; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Table 4.12: Overview of AEs – safety population (Maintenance Dosing Period, week 12-60)

	UNCOVER-1						UNCOVER-2					
	IXE80 Q4W/ PBO (N=109) n (%)	IXE80 Q4W/ IXE80 Q4W (N=110) n (%)	IXE80 Q2W/ PBO (N=117) n (%)	IXE80 Q2W/ IXE80 Q4W (N=119) n (%)	IXE/PBO (N=226) n (%)	IXE/ IXE80 Q4W (N=229) n (%)	IXE80Q4W /PBO (N=82) n (%)	IXE80Q4W/ IXE80Q4W (N=85) n (%)	IXE80Q2W/ PBO (N=94) n (%)	IXE80Q2W/ IXE80Q4W (N=102) n (%)	IXE/PBO (N=176) n (%)	IXE/ IXE80Q4W (N=187) n (%)
Patients with ≥1 TEAE	65 (59.6)	87 (79.1)	58 (49.6)	95 (79.8)	123 (54.4)	182 (79.5)	50 (61.0)	66 (77.6)	58 (61.7)	72 (70.6)	108 (61.4)	138 (73.8)
Discontinuations from Study Drug due to AE (including death)	4 (3.7)	5 (4.5)	0 (0.0)	4 (3.4)	4 (1.8)	9 (3.9)	2 (2.4)	2 (2.4)	2 (2.1)	1 (1.0)	4 (2.3)	3 (1.6)
Deaths	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	3 (2.8%)	8 (7.3%)	4 (3.4%)	7 (6.0%)	7 (3.1%)	15 (6.6%)	2 (2.4)	8 (9.4)	6 (6.4)	2 (2.0)	8 (4.5)	10 (5.3)
TEAEs possibly related to study drug	22 (20.2)	38 (34.5)	17 (14.5)	33 (27.7)	-	-	18 (22.0)	28 (32.9)	24 (25.5)	30 (29.4)	42 (23.9)	58 (31.0)
Treatment-Emergent AE of Special Interest												
Cytopenias	1 (0.9)	3 (2.7)	1 (0.9)	4 (3.4)	2 (0.9)	7 (3.1)	1 (1.2)	2 (2.4)	1 (1.1)	1 (1.0)	2 (1.1)	3 (1.6)
Hepatic	3 (2.8)	5 (4.5)	1 (0.9)	7 (5.9)	4 (1.8)	12 (5.2)	3 (3.7)	3 (3.5)	2 (2.1)	3 (2.9)	5 (2.8)	6 (3.2)
Infection	41 (37.6)	63 (57.3)	33 (28.2)	66 (55.5)	74 (32.7)	129 (56.3)	31 (37.8)	44 (51.8)	37 (39.4)	58 (56.9)	68 (38.6)	102 (54.5)
Injection-site reactions	2 (1.8)	11 (10.0)	0	5 (4.2)	2 (0.9)	16 (7.0)	2 (2.4)	5 (5.9)	4 (4.3)	16 (15.7)	6 (3.4)	21 (11.2)
Allergic reactions/ Hypersensitivities	6 (5.5)	8 (7.3)	1 (0.9)	13 (10.9)	7 (3.1)	21 (9.2)	3 (3.7)	3 (3.5)	2 (2.1)	6 (5.9)	5 (2.8)	9 (4.8)
Anaphylaxis†	0	0	0		0	0	0	0	0	0	0	0
Non-Anaphylaxis	6 (5.5)	8 (7.3)	1 (0.9)	0 13 (10.9)	7 (3.1)	21 (9.2)	3 (3.7)	3 (3.5)	2 (2.1)	6 (5.9)	5 (2.8)	9 (4.8)
Cerebrocardiovascular	0	2 (1.8)	1 (0.9)	1 (0.8)	1 (0.4)	3 (1.3)	1 (1.2)	1 (1.2)	0	0	1 (0.6)	1 (0.5)

	UNCOVER-1						UNCOVER-2					
	IXE80 Q4W/ PBO (N=109) n (%)	IXE80 Q4W/ IXE80 Q4W (N=110) n (%)	IXE80 Q2W/ PBO (N=117) n (%)	IXE80 Q2W/ IXE80 Q4W (N=119) n (%)	IXE/PBO (N=226) n (%)	IXE/ IXE80 Q4W (N=229) n (%)	IXE80Q4W /PBO (N=82) n (%)	IXE80Q4W/ IXE80Q4W (N=85) n (%)	IXE80Q2W/ PBO (N=94) n (%)	IXE80Q2W/ IXE80Q4W (N=102) n (%)	IXE/PBO (N=176) n (%)	IXE/ IXE80Q4W (N=187) n (%)
events												
Malignancies	0	0	0	0	0	0	1 (1.2)	0	0	1 (1.0)	1 (0.6)	1 (0.5)
Depression	0	1 (0.9)	0	0	0	1 (0.4)	1 (1.2)	2 (2.4)	1 (1.1)	0	2 (1.1)	2 (1.1)
PCP	0	0	0	0	0	0	0	0	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0	0	0	0	0	0	0
Crohn's Disease	0	0	1 (0.9)	0	1 (0.4)	0	0	0	2 (2.1)	0	2 (1.1)	0
Ulcerative Colitis	0	0	0	0	0	0	0	1 (1.2)	0	0	0	1 (0.5)

Source: Based on Tables 58 and 60 of the CS[1]

Footnotes: † Anaphylaxis as shown here refers to potential cases using broadly-defined Sampson criteria. There were no confirmed cases of anaphylaxis in the Maintenance Dosing Period

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; ETN = etanercept; ISE = injection-site reaction; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event

ERG comment: The ERG notes that safety results for all ixekizumab studies were not included in the CS. However, the ERG extracted these results from Gordon et al. 2016 (see Table 4.13).[40] The integrated safety data set included pooled data from 3,736 patients who participated in the UNCOVER studies. The most frequently reported events (more than 5% across all three studies) were nasopharyngitis and injection site reactions. The three deaths in the study group were judged unrelated to the study drug: "*Among all patients in the UNCOVER trials who received ixekizumab during weeks 0 through 60, there were two confirmed deaths from vascular causes. The third death in the UNCOVER program was reported as being due to unknown causes (the patient had received ixekizumab every 4 weeks in both the induction and maintenance periods)*".[40]

It is noted that the safety profile of longer-term treatment with ixekizumab, beyond 60 weeks, is not yet available.

Table 4.13: Adverse events during the induction periods and the total ixekizumab exposure in the three UNCOVER trials

Adverse Event	**Weeks 0–12**			**Weeks 0–60**
no. of patients (%)	Placebo (N = 791)	Ixekizumab Every 4 wk (N = 1,161)	Ixekizumab Every 2 wk (N =1,167)	All Patients with ixekizumab Exposure (N = 3,736)
Any adverse event†	370 (46.8)	683 (58.8)	681 (58.4)	3021 (80.9)
Serious adverse event	12 (1.5)	26 (2.2)	20 (1.7)	250 (6.7)
Discontinuation of study regimen because of an adverse event	9 (1.1)	24 (2.1)	25 (2.1)	165 (4.4)
Death	0	0	0	3 (0.1)
Common adverse events‡				
Nasopharyngitis	69 (8.7)	104 (9.0)	111 (9.5)	733 (19.6)
Injection-site reaction	9 (1.1)	89 (7.7)	117 (10.0)	387 (10.4)

Source: Based on Gordon et al. 2016[40]
Footnotes: † Adverse events included here are those that appeared or worsened during the treatment periods; ‡ Common adverse events occurring during treatment were defined as those that had an incidence rate of at least 5% among all the patients with ixekizumab exposure and occurred in a greater number of patients who received ixekizumab than patients who received placebo during the induction period.

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

In the CS, the base-case network meta-analysis (NMA) included 31 randomised controlled trails. However, the ERG detected one study, Gordon 2006[49], missing in the NMA which in the CS has been described to meet all inclusion criteria. This study has been added by the ERG. A summary of each of the main characteristics of the RCTs included in the NMA are shown in Table 4.14 while results are presented in Table 4.15. The baseline PASI scores of the overall study population are also reproduced here for comparison.

The company also conducted quality assessment of the studies included in the NMA, based upon randomisation, allocation concealment, blinding, incomplete outcome data and whether there were other sources of bias in Appendix 9 of the CS.[1]

Table 4.14: Summary of trials used to conduct the base-case NMA

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
Study included in CS NMA											
UNCOVER 1 Lilly CSR 2015[3]	2015	A multicentre study with a randomised, double-blind, placebo-controlled induction dosing period followed by a randomised maintenance dosing period and a long-term extension period to evaluate the efficacy of LY2439821 in patients with moderate to severe plaque psoriasis. IF-MC-RHAZ Clinical Study Report (UNCOVER 1)	Ixekizumab 80 mg Q2W Ixekizumab 80 mg Q4W Placebo	PASI 50 PASI 75 PASI 90 PASI 100 DLQI sPGA Itch NRS Safety	This study met all the inclusion criteria	subgroup analysis could be conducted	IXE 80 mg Q2W	63.7/NR	40	20.1	8
							IXE 80 mg Q4W	55.1/NR	38.9	20	7.3
							PBO	56.1/NR	42	20.3	8.6
UNCOVER 2 Griffiths 2015[2]	2015	Comparison of ixekizumab with etanercept or placebo in moderate to severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials	Ixekizumab 80 mg Q2W Ixekizumab 80 mg Q4W Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PASI 100 DLQI sPGA Itch NRS Safety	This publication was included, although most data were gathered from the ixekizumab CSR.	subgroup analysis could be conducted	IXE 80 mg Q2W	51/46	24	19	7
							IXE 80 mg Q4W	51/46	25	20	7
							PBO	48/44	26	21	8
UNCOVER 3 Griffiths 2015[2]	2015	Comparison of ixekizumab with etanercept or placebo in	Ixekizumab 80 mg Q2W	PASI 50 PASI 75	This publication	subgroup analysis	IXE 80 mg Q2W	44/39	15	21	8

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
		moderate to severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials	Ixekizumab 80 mg Q4W Etanercept 50 mg BIW Placebo	PASI 90 PASI 100 DLQI sPGA Itch NRS Safety	was included, although most data were gathered from the ixekizumab CSR.	could be conducted	IXE 80 mg Q4W	47/40	15	21	8
							PBO	43/31	17	21	8
CHAMPION Saurat 2008	2008	Efficacy and safety results from the randomised controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION)	Adalimumab 40 mg EOW Methotrexate 7.5 mg Placebo	PASI change from baseline PGA BSA PASI 50 PASI 75 PASI 90 PASI 100	This study met all inclusion criteria.	No DLQI not reported	ADA 40 mg EOW	82.2	NR	20.2	7.5
							PBO	90.4	NR	19.2	6.9
NCT01483599 Gordon 2015[50]	2015	A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis	Guselkumab 50 mg Guselkumab 100 mg Guselkumab 200 mg Adalimumab 40 mg EOW Placebo	PGA 0,1 PASI 75 PASI 90 PASI 100 DLQI	Although guselkumab was excluded, the adalimumab treatment arm was on-label. The study was included, but the guselkumab	No DLQI not reported	ADA 40 mg EOW	40/27.5	60	20.2	7.6
							PBO	50/21.4	36	21.8	10

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
					arms were excluded.						
NCT00940862 Bissonette 2013[51]	2013	Effects of the Tumour Necrosis Factor-α Antagonist Adalimumab on Arterial Inflammation Assessed by Positron Emission Tomography in Patients With Psoriasis Results of a Randomised Controlled Trial	Adalimumab 40 mg EOW Control (no treatment, topical psoriasis treatments or PUVA)	Carotid artery and ascending aorta inflammation PASI change from baseline	This study met all inclusion criteria.	No DLQI not reported	ADA 40 mg EOW	NR	NR	11.6	5.3
							PBO	NR	NR	13.1	5.7
REVEAL Menter 2008[52]	2008	Adalimumab therapy for moderate to severe psoriasis: a randomised, controlled phase III trial	Adalimumab 40 mg EOW Placebo	PASI 90 PASI 100 PASI change from baseline PGA Adverse events Infections Serious adverse events	This study met all inclusion criteria.	No DLQI not reported	ADA 40 mg EOW	23.1/17.0	11.9	19	7.1
							PBO	22.1/14.8	13.3	18.8	7.1

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
				Withdrawals							
Asahina 2010[53]	2010	Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomised controlled study	Adalimumab 40 mg EOW (with loading dose) Adalimumab 40 mg EOW (without loading dose) Adalimumab 80 mg EOW Placebo	PASI 50 PASI 75 PASI 90 PGA Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria. Adalimumab 40 mg without loading dose and adalimumab 80 mg were excluded.	No Mean Baseline DLQI 8.4 Placebo 8.4 ADA 40 mg EOW	ADA 40 mg EOW	41.9/23.3	NR	30.2	10.9
							PBO	37.0/41.3	NR	29.1	11.8
Gottlieb 2003[54]	2003	A Randomised Trial of Etanercept as Monotherapy for Psoriasis	Etanercept 25 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PGA DLQI Adverse events Serious adverse	This study met all inclusion criteria.	No DLQI not reported	ETN 25 mg BIW	MTX 39/37	NR	17.8	SE+1.1
							PBO	MTX 36/42	NR	19.5	SE+1.3

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
				events Withdrawals							
Leonardi 2003[55]	2003	Etanercept as Monotherapy in Patients with Psoriasis	Etanercept 25 mg QW Etanercept 25 mg BIW Etanercept 50 mg BIW Placebo	PASI 50 PASI 75 PASI 90 PGA DLQI Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria. Etanercept 25 mg QW was excluded.	No Mean (SE) Baseline DLQI was reported: 12.8 (0.6) Placebo 12.7 (0.5) ETN	ETN 25 mg BIW	NR	NR	18.5	SE+0.7
							PBO	NR	NR	18.3	SE+0.6
Papp 2005[56]	2005	A global phase III randomised controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction.	Etanercept 25 mg BIW Etanercept 50 mg BIW	PASI 50 PASI 75 PASI 90 sPGA	This study met all inclusion criteria.	No DLQI not reported	ETN 25 mg BIW	MTX 35/35	NR	16.9	NR (4.0-51.2)

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
			Placebo	Adverse events Infections Serious adverse events Withdrawals			PBO	MTX 39/34	NR	16	NR (7.0-62.4)
van de Kerkhof 2008[57]	2008	Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate to severe plaque psoriasis: a randomised controlled trial with open-label extension	Etanercept 50 mg QW Placebo	PASI 50 PASI 75 PASI 90 PGA Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.	No DLQI not reported	ETN 50 mg QW	49.0/69.8	NR	21.4	9.3
							PBO	47.8/69.6	NR	21	8.7
ERASURE Langley 2014 (EMA 2015)[58]	2015	ERASURE study	Secukinumab 300 mg Secukinumab 150 mg	PASI 50 PASI 75 PASI 90	This study met all inclusion criteria. Secukinumab	No Mean	SEC 300 mg	52.2/NR	28.6	22.5	9.2

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
			Placebo	PASI 100 Adverse events Serious adverse events Withdrawals	150 mg was excluded.	Baseline DLQI 12.0 Placebo 13.9 SEC	PBO	43.5/NR	29.4	21.4	9.1
FEATURE Blauvelt 2015 (EMA 2015)[59]	2015	FEATURE study	Secukinumab 300 mg Secukinumab 150 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.	No	SEC 300 mg	33.9/NR	39	20.7	8
							PBO	49.2/NR	44.1	21.1	8.5
FIXTURE Langley 2014 (EMA 2015)[58]	2015	FIXTURE study	Secukinumab 300 mg Secukinumab 150 mg	PASI 50 PASI 75 PASI 90	This study met all inclusion criteria.	No Mean	SEC 300 mg	59.6/NR	11.6	23.9	9.9

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
			Etanercept 50 mg BIW Placebo	PASI 100 Adverse events Serious adverse events Withdrawals		Baseline DLQI 13.4 Placebo 13.3 SEC	PBO	61.0/NR	10.7	24.1	10.5
JUNCTURE Paul et al 2015 (EMA 2015)[60]	2015	JUNCTURE study	Secukinumab 300 mg Secukinumab 150 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.	No DLQI not reported	SEC 300 mg	50.0/NR	25	18.9	6.4
							PBO	47.5/NR	21.3	19.4	6.7
CLEAR Thaci 2015[61]	2015	Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomised	Secukinumab 300 mg Ustekinumab 45 mg Ustekinumab 90	PASI 75 PASI 90 PASI 100 IGA	This study met all inclusion criteria.	No DLQI not reported	SEC 300 mg	64.7	14.2	21.7	8.5

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
		controlled trial	mg	DLQI Itch NRS Adverse events Serious adverse events Withdrawals			UST 45 mg	65.8	13	21.5	8.07
EXPRESS Reich 2005[62]	2005	Infliximab induction and maintenance therapy for moderate to severe psoriasis: a phase III, multicentre, double-blind trial	Infliximab 5 mg/kg Placebo	PASI 50 PASI 75 PASI 90	This study met all inclusion criteria.	No DLQI not reported	INF 5 mg	MTX 41.9 /42.5	NR	22.9	9.3
							PBO	MTX 45.5/45.5	NR	22.8	8.7
EXPRESS 2 Menter 2007[63]	2007	A randomised comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate to severe plaque psoriasis	Infliximab 3 mg/kg (continuous) Infliximab 5 mg/kg (continuous) Infliximab 3 mg/kg (as needed) Infliximab 5 mg/kg (as needed) Placebo	PASI 75 PASI 90	Only 5 mg/kg continuous arm included.	No Mean (SD) Baseline DLQI 13.4 (7.3) Placebo 12.8 (6.9) Infliximab 3mg 13.1 (7.0) Infliximab 5 mg	INF 5 mg	34.7/27.4	14.3	20.4	7.5
							PBO	33.7/29.8	13	19.8	7.7

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
						Has PASI 75 results for baseline PASI </>20					
Chaudhari 2001[64]	2001	Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: A randomised trial	Infliximab 5 mg/kg Placebo	PASI 75 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.	No DLQI not reported	INF 5 mg	NR	NR	22.1	11.5
							PBO	NR	NR	20.3	5.5
SPIRIT Gottlieb 2004[65]	2004	Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomised, double-blind, placebo-controlled trial	Infliximab 3 mg/kg Infliximab 5 mg/kg Placebo	PASI 50 PASI 75 PASI 90 PGA Adverse events Infections Serious adverse events Withdrawals	Only the 5 mg/kg arm included.	No Median (IQR) baseline DLQI score 14 (9, 18) Placebo 11 (6, 17) Infliximab 3mg	INF 5 mg	88.9/68.7	33.3	20†	
							PBO	82.4/66.7	31.4	18†	

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
						12 (8, 17) Infliximab 5 mg					
Torii et al. 2010[66]	2010	Infliximab monotherapy in Japanese patients with moderate to severe plaque psoriasis and psoriatic arthritis. A randomised, double-blind, placebo-controlled multicenter trial.	Infliximab 5 mg/kg Placebo	PASI 50 PASI 75 PASI 90 PGA DLQI Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.	No Mean (SD) Baseline DLQI 10.5 (6.8) Placebo 12.7 (6.8) Infliximab	INF 5 mg	94.3/34.3	NR	31.9	12.8
							PBO	94.7/36.8	NR	33.1	15.6
Yang 2012[67]	2012	Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomised, double-blind, placebo-controlled multicenter trial	Infliximab 5 mg/kg Placebo	PASI 75 PGA DLQI Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.	No Mean (SD) Baseline DLQI 14.4 (6.3) Placebo 14.4 (6.2) Infliximab	INF 5 mg	NR	NR	23.9	10.7
							PBO	NR	NR	25.3	12.7

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
ACCEPT Griffiths 2010[68]	2010	Comparison of Ustekinumab and Etanercept for Moderate to severe Psoriasis	Ustekinumab 45 mg Ustekinumab 90 mg Etanercept BIW 50 mg	PASI 75 PASI 90 Adverse events Serious adverse events Withdrawals	This study met all inclusion criteria.	No DLQI not reported	UST 45 mg	61.7/66.0	12.4	20.5	9.2
							UST 90 mg	52.4/66.3	10.4	19.9	8.4
Igarashi 2012[69]	2012	Efficacy and safety of ustekinumab in Japanese patients with moderate to severe plaque-type psoriasis: Long-term results from a phase 2⁄3 clinical trial	Ustekinumab 45 mg Ustekinumab 90 mg Placebo	PASI 50 PASI 75 PASI 90 PASI change from baseline PGA VAS DLQI PDI SF-36	This study met all inclusion criteria.	No N with baseline DLQI < 10 16 (50%) Placebo 30 (46.9%) UST 45 mg 32 (51.6%) UST 90 mg	UST 45 mg	73.4/56.3	1.6	30.1	12.9
							UST 90 mg	83.9/82.3	0	28.7	11.2
							PBO	65.6/62.5	0	30.3	11.8
LOTUS Zhu 2013[70]	2013	Efficacy and Safety of Ustekinumab in Chinese Patients with Moderate to severe Plaque-type Psoriasis:	Ustekinumab 45 mg Placebo	PASI 50 PASI 75 PASI 90	This study met all inclusion criteria.	No Mean (SD)	UST 45 mg	39.4/37.5	11.9	23.2	9.5

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
		Results from a Phase 3 Clinical Trial (LOTUS)		PASI 100 Adverse events Serious adverse events Withdrawals		Baseline DLQI 13.1 (7.5) Placebo 13.7 (7.6) UST 45 mg	PBO	42.6/37.0	6.8	22.7	9.5
PEARL Tsai 2011[71]	2011	Efficacy and safety of ustekinumab for the treatment of moderate to severe psoriasis: a phase III, randomised, placebo-controlled trial in Taiwanese and Korean patients (PEARL)	Ustekinumab 45 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 PASI change from baseline PGA DLQI Adverse events Infections Serious adverse events Withdrawals	This study met all inclusion criteria.	No Mean (SD) Baseline DLQI 15.2 (7.0) Placebo 16.1 (6.1) Infliximab	UST 45 mg	70.5/80.3	21.3	25.2	11.9
							PBO	71.7/86.7	15	22.9	8.6

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
PHOENIX 1 Leonardi 2008[72]	2008	Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised double-blind, placebo-controlled trial (PHOENIX 1)	Ustekinumab 45 mg Ustekinumab 90 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 PASI change from baseline PGA DLQI	This study met all inclusion criteria.	No Mean (SD) baseline DLQI 11.8 (7.4) Placebo 11.7 (7.1) UST 45 mg 11.6 (6.9) UST 90 mg	UST 45 mg	55.3/67.8	52.5	20.5	8.6
							UST 90 mg	55.1/66.0	50.8	19.7	7.6
							PBO	55.7/58.8	50.2	20.4	8.6
PHOENIX 2 Papp 2008[73]	2008	Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)	Ustekinumab 45 mg Ustekinumab 90 mg Placebo	PASI 50 PASI 75 PASI 90 PASI 100 PASI change from baseline Adverse events Infections Serious adverse events Withdrawa	This study met all inclusion criteria.	No Mean (SD) baseline DLQI 12.3 (6.9) Placebo 12.2 (7.1) UST 45 mg 12.6 (7.3) UST 90 mg	UST 45 mg	54.5/69.9	38.4	19.4	6.8
							UST 90 mg	54.5/65.0	36.5	20.1	7.5
							PBO	58.8/67.3	38.8	19.4	7.5

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
				ls							
AMAGINE 2 Lebwohl 2015[74]	2015	Phase 3 studies comparing brodalumab with ustekinumab in psoriasis	Ustekinumab 45 mg Ustekinumab 90 mg Brodalumab 140 mg Brodalumab 210 mg Placebo	PASI 75 PASI 90 PASI 100 sPGA PSI	Ustekinumab data only included	No DLQI not reported	UST 45 mg, 90 mg	75	28	20	8.4
							PBO	74.4	29.1	20.4	8.2
AMAGINE 3 Lebwohl 2015[74]	2015	Phase 3 studies comparing brodalumab with ustekinumab in psoriasis	Ustekinumab 45 mg Ustekinumab 90 mg Brodalumab 140 mg Brodalumab 210 mg Placebo	PASI 75 PASI 90 PASI 100 sPGA PSI	Ustekinumab data only included	No DLQI not reported	UST 45 mg, 90 mg	70.3	24	20.1	8.4
							PBO	65.4	24.1	20.1	8.7
Study defined met all inclusion criteria but not in CS NMA											
Gordon 2006[49]	2006	Clinical response to adalimumab treatment in patients with moderate to	Adalimumab 40 mg EOW Adalimumab 40	PASI 75 Adverse	This study met all inclusion criteria.	No	ADA 40 mg EOW	NR	NR	16.7	(5.4-39.0)

Study	Year	Title	Intervention(s) and comparator(s)	Outcomes reported	Rationale for inclusion	Results reported for PASI>10 and DLQI>10	Treatment	Baseline characteristics			
								Previous systemic and/or PUVA (%)	Prior biologic (%)	Mean PASI score	±SD (range)
		severe psoriasis: Double-blind, randomised controlled trial and open-label extension study	mg QW Placebo	events Serious adverse events Withdrawals	Adalimumab 40 mg QW was not included.	DLQI not reported	PBO	NR	NR	16.0	(5.5-40.4)

Source: Tables 48, 49 of the CS[1] and Gordon et al. 2006[49]

ADA = Adalimumab; BID = twice daily; BIW = twice weekly; BSA = body surface area; CSR = Clinical Study Report; DLQI = Dermatology Life Quality Index; EMA = European Medicines Agency; EOW = every other week; ETN = Etanercept; HAM-D = Hamilton Rating Scale for Depression; INF = Infliximab; IXE = Ixekizumab; MTX = Methotrexate; NMA = network meta-analysis; NR = not reported; PASI = Psoriasis Area And Severity Index; PASI 50 = ≥50% improvement psoriasis area and severity index score; PASI70 = ≥70% improvement psoriasis area and severity index score; PASI 75 = ≥75% improvement psoriasis area and severity index score; PASI 90 = ≥90% improvement psoriasis area and severity index score; PASI 100 = 100% improvement psoriasis area and severity index score; PBO = placebo; PDI = Psoriasis Disability Index; PGA = physician's global assessment; PSI = psoriasis symptom inventory; PUVA = Psoralen plus ultraviolet light; QW = once weekly; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SD = Standard deviation; SE = Standard error; SEC = Secukinumab; sPGA = static physician global assessment score; UST = Ustekinumab; VAS = visual analogue scale

ERG comments: As discussed in Section 4.1.4, while not explicitly stated, the ERG assumes that the Cochrane risk of bias tool was used.[38] The trials are generally similar in terms of patients' characteristics: percentage male, age, race, weight, duration of psoriasis. The ERG agrees that there are no major imbalances of the baseline characteristics across the included studies.

The ERG acknowledges that there is no agreed consensus on the definition of moderate and severe psoriasis. According to the clinical expert the ERG consulted, it is preferable to define the population based on PASI score > 10 as well as DLQI score > 10 because this also takes into account the patients view.

The ERG notes there were some variations in baseline PASI score between the included trials which included a proportion of patients with a PASI score <10 (Table 4.14) while the company states *"the median PASI score supports the findings that the baseline PASI scores are homogeneously distributed across the studies included in the psoriasis base case NMA (median PASI score=20.4)".*[1] Furthermore none of the trials included the DLQI scores as eligibility requirement but few studies did report baseline DLQI scores (Table 4.14).

There were some differences in the proportion of patients had received prior systemic and/or biologic treatments between the trials. Where reported, the UNCOVER-1, FEATURE, NCT01483599, PHOENIX 1 and PHOENIX 2 trials had higher percentages of patients who had received biologic treatments before.[3, 59, 72, 73, 75] According to NICE clinical guideline CG153, the effectiveness of biologic therapy is lower when it is used as second treatment in a treatment sequence.[76] Thus, there might be potential uncertainty associated with these analyses.

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

ERG comment: A description of the methods used for the NMA are presented in Section 4.1.5. Thirty-one studies were included in the base case analysis.

The ERG identified an additional 10 studies which were identified but not included in the NMA. As detailed in Table 4.15, the ERG thinks that Gordon 2006[49] should also have been included, so conducted an analysis including these data.

The model is a multinomial model which is jointly modelling the probability of a PASI 50, 75, 90 or 100 response (using binary outcomes). This is appropriate as it allows for the correlation between these outcomes, as a patient who achieves one level of response is more likely to achieve another level so on a per patient basis these outcomes are correlated.

The base-case NMA model was slow to run and crashed after 13,000 iterations when using chain 1 only, it crashed after 2,300 iterations when using the two chains. The ERG results are therefore based on 10,000 iterations and not the 10,000 burn-in followed by 30,000 iterations as specified in the CS.

Table 54 presents the base case results of the CS and the ERG check (in red). As described before, the ERG results will differ slightly as they are based on fewer iterations and chains than the original model. The ERG results represent the median value, it is not clear if the values reported in the submission were mean or median values. The analysis check concentrates on the probability results rather than the relative risks as the probabilities were used in the economic model. The results for Table 4.16 with the addition of Gordon 2006 are given below. The ERG results, including Gordon 2006, are in line with the base case presented in the CS.

Table 4.15: Overview of studies identified for but not included in the NMA

Author	Year	Title	Interventions	Outcomes	CS: Included in			Rationale for inclusion/ exclusion
					Table 48	Table A10	Tables 49-50	
Not connect due to intervention not being licensed or not recommended by NICE								
Apremilast EMA report	2015	ESTEEM 1 study	Apremilast 30 mg BID Placebo	PASI 50 PASI 75 PASI 90 AEs SAEs Withdrawals	No	Yes	No	Apremilast was excluded from the analysis as it is not recommended by NICE
Apremilast EMA report	2015	ESTEEM 2 study	Apremilast 30 mg BID Placebo	PASI 50 PASI 75 PASI 90 AEs SAEs Withdrawals	No	Yes	No	Apremilast was excluded from the analysis as it is not recommended by NICE
Gordon, K. B.; Kimball, A. B.; Chau, D.; Viswanathan, H. N.; Li, J.; Revicki, D. A.; Kricorian, G.; Ortmeier, B. G.	2014	Impact of brodalumab treatment on psoriasis symptoms and health-related quality of life: use of a novel patient-reported outcome measure, the Psoriasis Symptom Inventory	Brodalumab 70 mg Brodalumab 140 mg Brodalumab 210 mg	PSI DLQI	No	Yes	No	This study was excluded as brodalumab does not have a license for the treatment of psoriasis

Author	Year	Title	Interventions	Outcomes	CS: Included in			Rationale for inclusion/ exclusion
					Table 48	Table A10	Tables 49-50	
			Brodalumab 280 mg Placebo					
Papp, K.; Reich, K.; Leonardi, C. L.; Kircik, L.; Chimenti, S.; Langley, R. G. B.; Hu, C.; Stevens, R. M.; Day, R. M.; Gordon, K. B.; Korman, N. J.; Griffiths, C. E. M.	2015	Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate-to-severe plaque psoriasis: Results of a phase III, randomised, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1)	Apremilast 10 mg QID Apremilast 20 mg QID Apremilast 30 mg QID Placebo	PASI change from baseline PASI 75 AEs SAEs Infections	No	Yes	No	Apremilast was excluded from the analysis as it is not recommended by NICE
Papp, K., Cather, J. C. Rosoph, L., Sofen, H., Langley, R. G., Matheson, R. T., Hu, C., Day, R. M.	2012	Efficacy of apremilast in the treatment of moderate-to-severe psoriasis	Apremilast 10 mg BID Apremilast 20 mg BID Apremilast 30 mg BID Placebo	PASI 75 AEs SAEs Withdrawals	No	Yes	No	Apremilast was excluded from the analysis as it is not recommended by NICE
Paul, C., Cather, J., Gooderham, M., Poulin, Y., Mrowietz, U., Ferrandiz, C., Crowley, J., Hu, C., Stevens, R. M., Shah, K., Day, R. M., Girolomoni, G., Gottlieb, A. B.	2015	Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomised controlled trial (ESTEEM 2)	Apremilast 30 mg BID Placebo	PASI50 PASI 75 PGA DLQI AEs SAEs Withdrawals	No	Yes	No	Apremilast was excluded from the analysis as it is not recommended by NICE

Author	Year	Title	Interventions	Outcomes	CS: Included in			Rationale for inclusion/ exclusion
					Table 48	Table A10	Tables 49-50	
Nakagawa, H., Niiro, H., Ootaki, K.	2015	Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: Efficacy and safety results from a phase II randomised controlled study	Brodalumab 70 mg Brodalumab 140 mg Brodalumab 210 mg Placebo	PASI 75 PASI 90 sPGA AEs SAEs Withdrawals	No	Yes	No	This study was excluded as brodalumab does not have a license for the treatment of psoriasis
Insufficient details on PASI								
Flytstrom I., Stenberg B., Svensson A., Bergbrant I-M.	2007	Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomised controlled trial.	Cyclosporin 3-5 mg/kg Methotrexate 7.5 mg/kg	DLQI SF-36 VAS PASI change from baseline	No	Yes	No	The study did not provide relevant data for in the PASI base case analysis but DLQI data was presented in a manner which could be used in the NMA.
Reich K., Segaert S., Van de Kerkhof P., Durian C., Boussuge MP., Paolozzi L., Wajdula J., Boggs R.	2009	Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis	Etanercept 50 mg QIW Placebo	DLQI EQ-5D	No	Yes	No	This study met all inclusion criteria. PASI data already captured in Van de Kerkhof

Author	Year	Title	Interventions	Outcomes	CS: Included in			Rationale for inclusion/ exclusion
					Table 48	Table A10	Tables 49-50	
								2008.
Should be included in the NMA								
Gordon, K. B.Langley, R. G.Leonardi, C.Toth, D.Menter, M. A.Kang, S.Heffernan, M.Miller, B.Hamlin, R.Lim, L.Zhong, J.Hoffman, R.Okun, M. M.	2006	Clinical response to adalimumab treatment in patients with moderate-to-severe psoriasis: Double-blind, randomised controlled trial and open-label extension study	Adalimumab 40 mg EOW Adalimumab 40 mg QIW Placebo	PASI 75 AEs SAEs Withdrawals	Yes	Yes	No	This study met all inclusion criteria. Adalimumab 40 mg QIW was not included.

Source: Table 48 of the CS[1], Table 10 of Appendix 8[36]

AE = adverse event; BID = twice daily; CS = company submission; DLQI = Dermatology Life Quality Index; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; QID = four times a day; QIW = Four times a week; SAE = serious adverse event; SF-36 = Short form 36

Table 4.16: PASI base-case NMA random-effects model - absolute probabilities of achieving ≥50%, ≥75%, ≥90% or 100% PASI symptom relief for each treatment (CS base-case and ERG calculation)

	PASI 50			PASI 75			PASI 90			PASI 100		
	Probability	95% CrI		Probability	95% CrI		Probability	95% CrI		Probability	95% CrI	
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	93.2% 93.3%	89.5% 89.4%	96.1% 96.2%	81.8% 81.9%	74.9% 74.6%	88.1% 88.2%	59.6% 59.6%	50.0% 49.7%	69.3% 69.6%	28.6% 28.4%	20.7% 20.6%	37.9% 38.0%
Infliximab 5 mg/kg	92.8% 93.0%	88.1% 88.2%	96.1% 96.2%	81.1% 81.4%	72.6% 72.6%	88.1% 88.3%	58.7% 58.8%	47.2% 47.3%	69.4% 69.8%	27.8% 27.7%	18.7% 18.9%	38.0% 38.5%
Ustekinumab 45 mg	87.1% 87.1%	81.4% 81.1%	91.7% 91.5%	71.0% 70.8%	62.2% 61.6%	78.8% 78.5%	45.6% 45.2%	36.0% 35.4%	55.2% 54.7%	17.9% 17.4%	12.0% 11.7%	24.7% 24.3%
Ustekinumab 90 mg	89.6% 89.5%	84.2% 83.9%	93.7% 93.5%	75.1% 74.8%	66.2% 65.8%	82.7% 82.4%	50.6% 50.0%	40.1% 39.6%	60.7% 60.2%	21.4% 20.7%	14.3% 14.0%	29.5% 28.9%
Ustekinumab 45 mg<100kg & 90 mg>100kg	82.8% 82.7%	75.3% 75.2%	89.0% 88.7%	64.4% 64.1%	54.0% 53.8%	73.9% 73.5%	38.4% 37.9%	28.4% 28.3%	48.8% 48.4%	13.5% 13.1%	8.3% 8.2%	20.0% 19.7%
Adalimumab 80 mg/40 mg EOW	77.8% 78.3%	68.9% 68.9%	85.5% 85.8%	57.5% 57.9%	46.4% 46.4%	68.2% 68.7%	31.7% 31.8%	22.3% 22.4%	42.2% 42.7%	10.0% 9.9%	5.7% 5.7%	15.6% 16.0%
Etanercept 50 mg weekly/ 25 mg BIW	63.9% 64.3%	52.8% 53.3%	74.3% 74.1%	41.3% 41.4%	30.3% 30.7%	52.8% 52.6%	18.9% 18.8%	11.8% 12.0%	27.5% 27.2%	4.6% 4.4%	2.3% 2.3%	7.9% 7.8%
Placebo	13.7% 13.6%	10.1% 10.0%	17.9% 17.7%	4.7% 4.6%	3.1% 3.1%	6.6% 6.6%	1.0% 1.0%	0.6% 0.6%	1.5% 1.5%	0.1% 0.1%	0.0% 0.0%	0.1% 0.1%

Source: Table 52 of the CS[1] and ERG figures (marked in red)
BIW = twice weekly; CrI = credible intervals; CS = company submission; EOW = every other week; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement in Psoriasis Area and Severity Index; PASI 75 = ≥75% improvement in Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in Psoriasis Area and Severity Index; PASI 100 = 100% improvement in Psoriasis Area and Severity Index; Q2W = once every 2 weeks; Q4W = once every 4 weeks

4.5 Additional work on clinical effectiveness undertaken by the ERG

Given the company's later clarification that non-RCT evidence was not actively sought, the ERG conducted a small independent clinical effectiveness search combining the condition and drugs facets with a validated RCT filter. Screening a sample of 600 titles and abstracts of identified references, the ERG did not identify any further relevant papers.

4.6 Conclusions of the clinical effectiveness section

The CS reported the clinical efficacy of ixekizumab in the treatment of psoriasis consists of three pivotal RCTs (UNCOVER trials). The primary outcomes were sPGA (0,1) and PASI 75 at week 12. In all three UNCOVER trials, there were statistically significant increases in sPGA (0,1) and PASI 75 response rates for patients treated with ixekizumab compared with placebo and etanercept at week 12. Furthermore, the improvements in PASI response rate appeared to be maintained for up to 60 weeks during of the long-term extension period. The improvement in health-related quality of life of patients was significantly higher with ixekizumab than with placebo and etanercept. The relative performance of ixekizumab in difficult-to-treat areas, including nails, scalp and palmoplantar areas is broadly more efficacious than placebo and etanercept. However, the improvement of psoriasis symptoms of the face which is included in the final scope has not been reported in any of the UNCOVER studies.

Ixekizumab was generally well-tolerated in the UNCOVER trials. Overall, the adverse event profile appears to be similar incidences of adverse events as with the active comparator etanercept. The discontinuation rates due to AEs did not differ between the ixekizumab, etanercept or placebo treatment groups at week 12.

Subgroup data were reported for patients who had been treated with systemic non-biologic and biologic therapies. The results showed that ixekizumab was consistently efficacious across all subgroups in the UNCOVER trials.

Although the pivotal trial results for the primary outcomes appear robust and the selection of studies for inclusion in the NMA appears to be appropriate, the ERG felt that there are several areas of uncertainty regarding the clinical efficacy with respect to the decision problem considered in the submission.

- The participants in the pivotal RCTs (PASI score ≥ 12) were not entirely representative of the population for the moderate to severe psoriasis patients which was defined as a total PASI score ≥ 10 and a DLQI score ≥ 10 by the company submission. The ERG acknowledges that there is no agreed consensus on the terminology used to clarify the severity of psoriasis with various PASI thresholds suggested to define moderate to severe or severe psoriasis, respectively. However, according to the response of the clinical expert ERG consulted, PASI score of more than 10 (or 12) is used as the cut off for moderate/severe psoriasis combined when using systematic therapy rather than topical therapy. Therefore, it seems as the population in the UNCOVER trials did not fully match the population defined in the scope and there is an issue with generalisability.
- In addition, a proportion of the patients in the UNCOVER trials and the other studies used to inform the NMA were exposed to biologic therapy before. According to NICE clinical guideline CG153, the effectiveness of biologic therapy is lower when it is used as second treatment in a treatment sequence. Thus, there may lead to bias in the results.
- The evidence of the improvement of facial psoriasis which was required in the final scope is not available in any of the UNCOVER trials. The ERG considers that this to be a potential limitation of the PASI and subsequently the trials ideally should have included some relevant measures to detect clinical improvement of facial psoriasis.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

The searches reported in Appendix 11 were well reported and easily reproducible.[36] Additional searches included hand searching the reference list of included studies, and searches of the Centre for Reviews and Dissemination (CRD) HTA database and 11 individual HTA agencies. Page 198 of the CS[1] reported that searches were designed for each of the databases required by NICE however the recommended NHS EED search appears to have been replaced by a search of the Health Economics Evaluations Database (HEED) and no search of Econlit is reported. However, the ERG feels that these omittances are unlikely to have affected the overall recall of results and notes that these requirements have since been removed from the latest submission template produced by NICE.[77]

The ERG noted that an economics and costs filter was included in the HEED search. As this is an economics database the ERG believes it is not necessary to include this facet, as this may result in unnecessarily restricting the results retrieved. Although a validated filter does not appear to have been used or referenced when searching Medline and Embase, a wide range of relevant terms was included.

5.1.2 Inclusion/exclusion criteria used in the study selection

Eligibility criteria for the cost effectiveness SLR are presented in Table 5.1.

Table 5.1: Inclusion and exclusion criteria for identification of cost effectiveness and model input studies

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adult populations with moderate to severe psoriasis	Non-adult populations
Intervention and Comparators	Conventional systemic therapies (fumaric acid, methotrexate, ciclosporin and acitretin) and biologic therapies (efalizumab, etanercept, adalimumab, infliximab, ustekinumab, secukinumab and apremilast) for psoriasis.	Therapies other than conventional and biologic systemic therapies
Outcomes	Only studies focused on CEMs using quality-adjusted life years (QALY) as outcome measure. For studies on model inputs, this review focused on health utilities (irrespective of study countries), UK-specific healthcare resource utilisation and costs.	CEMs without QALYs
Study type	Appraisals/assessments from HTA agencies and published studies presenting CEMs for which only full publications were available. For studies on model inputs (i.e., health utilities, UK-specific healthcare resource utilisation and costs), all types of publications were of interest, including abstracts or posters reporting the outcomes of interest.	Economic evaluations for which full publications were not available.
Other restrictions	Study language was restricted to English, French, German, Italian and Spanish. Studies published after January 1 2000.	Other study languages. Studies published before January 1, 2000 (original review) and studies published before September 22, 2014 (updated review)
Source: Table 63 of the CS[1] CEM = cost-effectiveness model; HTA = health technology assessment; QALY = quality-adjusted life year; UK = United Kingdom		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the objective of the company's SLR.

5.1.3 Included/excluded studies in the cost effectiveness review

Nine studies met the inclusion criteria,[78-86] three of them were UK-based studies, and six were NICE TA's. Quality assessments of those studies are provided in Appendix 11 of the CS.[36]

ERG comment: The rationales for excluding studies after full paper reviewing seem appropriate given the defined in- and exclusion criteria. The company did not identify any study investigating the cost effectiveness of ixekizumab in the population of interest for the current decision problem.

5.1.4 Conclusions of the cost effectiveness review

The CS provides an overview of the included studies but no specific conclusion is formulated.

ERG comment: The ERG thinks the company could have argued why the included studies were not relevant for the current decision problem.

5.1.5 Objective of the HRQoL and resources use and costs review

Searches were reported for Medline, Medline in process, Embase, Econlit and Cochrane library databases, including NHS EED. The host and search dates were reported for all resources and searches were well reported and easily reproducible. Additional hand searches of conference proceedings, clinical trials resources and HTA agencies were also reported.

The ERG had some queries regarding the points at which results were exported from the Cochrane Library search (Table 34, Appendix13).[1] The Company confirmed in their response to clarification that results from NHS EED were exported from Line #4 using the economic evaluations limit and that the results of a search combining psoriasis terms with HRQoL terms were exported from all Cochrane Library databases at Line #12.[33]

5.1.6 Inclusion/exclusion criteria used in the study selection for the HRQoL and resources use and costs review

Title and abstract screening was performed in duplicates by two independent reviewers. After this first screening phase, full text screening was performed on the potentially relevant articles. The following eligibility criteria were used for the study selection during these screening phases (Table 5.2).

Table 5.2: Inclusion and exclusion criteria for identification of HRQoL inputs

Parameter	Inclusion criteria	Exclusion criteria
Population	Adult patients with moderate to severe plaque psoriasis	Non-adult, non-human, non-moderate to severe plaque psoriasis
Intervention and comparators	Interventions of interest include biological therapies recommended by NICE: Adalimumab Etanercept Secukinumab Ustekinumab Infliximab	Interventions not of interest: Phototherapy alone Non-biological therapies alone (acitretin, ciclosporin, methotrexate) Topical treatments Online management, writing exercises, counselling, etc.
Outcomes	Patients utility scores and quality-of-life data Costs and resource use Any relevant economic evidence	Not outcome of interest
Study type	Health economic evaluations Observational studies Retrospective chart reviews Clinical trials Population-based studies	Not study type of interest
Publication time frame	Last 10 years (2006-present)	Studies published prior to 2006
Additional restriction	Country of focus for observational, and economic evaluation studies is UK	Countries other than the UK

Source: Table 71 of the CS[1]
HRQoL = health-related quality of life; NICE = National Institute for Health and Clinical Excellence; UK = United Kingdom

ERG comment: The ERG does not agree with the exclusion of studies investigating phototherapy alone and non-biological therapies alone (acitretin, ciclosporin, methotrexate) as these were listed as comparators in the NICE scope (Section 3).

5.1.7 Included/excluded studies in the HRQoL and resources use and costs review

In total, 4,899 studies were identified through the electronic search and 12 through hand searches. After removal of duplicates (n=316), 309 studies were identified as potentially relevant through title and abstract screening. Six studies[87-92] were included in the HRQoL review (CS Tables 72 to 78) and six other studies[93-98] were included in the resources use and costs review (CS Tables 82 and 83) after full text screening. All included resources use and costs studies were UK specific, which was not the case for the included HRQoL studies. Quality assessment of the included studies is provided in Appendix 13 of the CS.[36]

ERG comment: In the HRQoL review, 11 studies, which also contained European Quality of Life-5 Dimensions (EQ-5D) data, were excluded due to limited information in the abstracts or incomparable assessment time points (see Appendix 13).[36]

In addition, the overview of included studies in the resource use and costs review contains the summary of only five studies instead of six. The omitted study is an abstract which provides travel time and costs of patients attending a clinic for follow-up visit.[98] The ERG does not consider these cost estimates as relevant for the current assessment.

5.1.8 Conclusions of the HRQoL and resources use and costs review

The company underlines that the utility values provided by the studies identified in the HRQoL review are not comparable to the utility values used in the cost effectiveness model because they are not stratified by PASI health states.

No specific conclusion has been formulated for the studies included in the resources use and costs review.

ERG comment: The HRQoL studies identified in the systemic literature review were not used in the company's cost effectiveness model. An overview of the identified studies is provided in Section 5.2.8.

No comment on the resource use and costs review since the company did not formulate any specific conclusions of the SLR. One of the six resources use and costs study is used in the company cost effectiveness model: Fonia et al. 2010 is a retrospective UK cohort study which provides resource use and costs estimates of moderate to severe psoriasis patients before and after the initiation of biologic treatment.[93]

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.3: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A de novo Markov state-transition model was developed in Visual Basic for Applications (VBA) with a Microsoft Excel interface.		CS section 5.2.2
States and events	Four treatment-related health states are incorporated: • Induction (trial) period; • Maintenance period;	The model structure is similar to that of the York model which has been used	CS section 5.2.2

	Approach	Source / Justification	Signpost (location in CS)
	• BSC and; • Death. These treatment-related states are considered for 3 lines of biological therapy and BSC. PASI response categories were used to determine treatment response and HRQoL.	in all NICE submissions subsequent to the York model publication.[99]	
Comparators	Different treatment sequences were considered by the company, all consisting of three lines of biologic treatment and subsequent BSC. • 1) Ixekizumab; 2) Ustekinumab 90 mg; 3) Infliximab; 4) BSC • 1) Adalimumab; 2) Ustekinumab 90 mg; 3) Infliximab; 4) BSC • 1) Etanercept 50 mg; 2) Ustekinumab 90 mg; 3) Infliximab; 4) BSC • 1) Infliximab; 2) Ustekinumab 90 mg; 3) Adalimumab; 4) BSC • 1) Secukinumab; 2) Ustekinumab 90 mg; 3) Infliximab; 4) BSC • 1) Ustekinumab 45 mg; 2) Adalimumab; 3) Infliximab; 4) BSC • 1) Ustekinumab 90 mg; 2) Adalimumab; 3) Infliximab; 4) BSC	The biologic treatments included are recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies or for patients who are intolerant or have a contraindication to these treatments.[88] Infliximab is only recommended for very severe psoriasis, but nevertheless included in the treatment sequences.[88] The dosing regimens for each treatment are in line with their marketing authorisation. Each biologic treatment is assessed as first-line in a treatment sequence. In addition, in the absence of national guidance on the positioning of biologic treatments in a sequence, the company selected the treatments and their ordering predominantly based on the basis of market shares	CS section 5.2.3
Population	Biological-naïve patients who have failed to respond to prior	The company states *"it is anticipated*	CS section 5.2.1

	Approach	Source / Justification	Signpost (location in CS)
	conventional systemic therapies, and are eligible for biologic therapies approved in the UK. This population is further specified into: *"patients who have failed to respond to, or are unable to be treated with conventional systemic therapies who have a PASI score of ≥ 10 and a DLQI > 10"*	*that ixekizumab will be used in the population currently eligible for biological therapies"*	
Treatment effectiveness	Based on PASI response categories the proportion of treatment responders (eligible for maintenance therapy) is determined.	Based on the York model.[99]	CS section 5.2.2
Adverse events	The impact of adverse events of treatments on HRQOL is not incorporated in the model, the impact on costs is only explored in a scenario analysis.	Justified by a lack of evidence. More specifically, the company argued that it would be difficult to trace back malignancies to specific treatments in the context of a treatment sequencing approach.	CS section 5.4.4, 5.4.5 and 5.6.2
Health related QoL	Estimated based on the EQ-5D-5L questionnaire which was administered to patients in the UNCOVER-1, 2 and 3 trials at baseline and at week 12. The base-case considered the patient group with DLQI>10.	DLQI>10 was used in accordance with the definition of moderate to severe psoriasis as described in NICE CG153.[76]	CS section 5.4
Resource utilisation and costs	The following costs categories were considered in the company cost effectiveness model: • drug costs; • administration costs; • monitoring costs; • non-responder costs and; • BSC costs.		CS section 5.5
Discount rates	Discount of 3.5% for utilities and costs	As per NICE scope	CS section 5.2.2
Sub groups	No clinically defined subgroup analysis reported in the CS.	The company argued that subgroup analyses by	CS section 4.8

	Approach	Source / Justification	Signpost (location in CS)
		clinically defined subgroups was not warranted because treatment response to ixekizumab was consistent across these groups	
Sensitivity analysis	Both DSA and PSA are performed		CS section 5.8

BSC = best supportive care; CG = clinical guideline; CS = company submission; DLQI = Dermatology Life Quality Index; DSA = deterministic sensitivity analysis; EQ-5D-5L = European Quality of Life-5 Dimensions and 5 levels HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; mg = milligram; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted Life Year

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Partly	The population in the base-case economic evaluation is labelled as biological-naïve patients who have failed to respond to prior conventional systemic therapies, and are eligible for biologic therapies approved in the UK, e.g. as a first line biologic therapy. This is not in line with the scope, as the scope covers all patients under the licensed indication which includes conventional systemic treatments. Moderate to severe psoriasis is preferably defined as PASI > 10 and DLQI > 10. This definition has not been used consistently for all estimates of input parameters in the model.
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	Not all possible treatment sequences have been considered. Most importantly, ixekizumab has only been considered as a first line therapy in the base-case analysis.
Type of economic evaluation	Cost effectiveness analysis	Y	
Perspective on costs	NHS and Personal Social Services (PSS)	Y	
Perspective on outcomes	All health effects on individuals	Y	
Time horizon	Sufficient to capture differences in costs and outcome	Y	Lifetime (45- 99.9 years)
Synthesis of evidence in outcomes	Systematic review	Y	
Measure of health effects	Quality adjusted life years (QALYs)	Y	

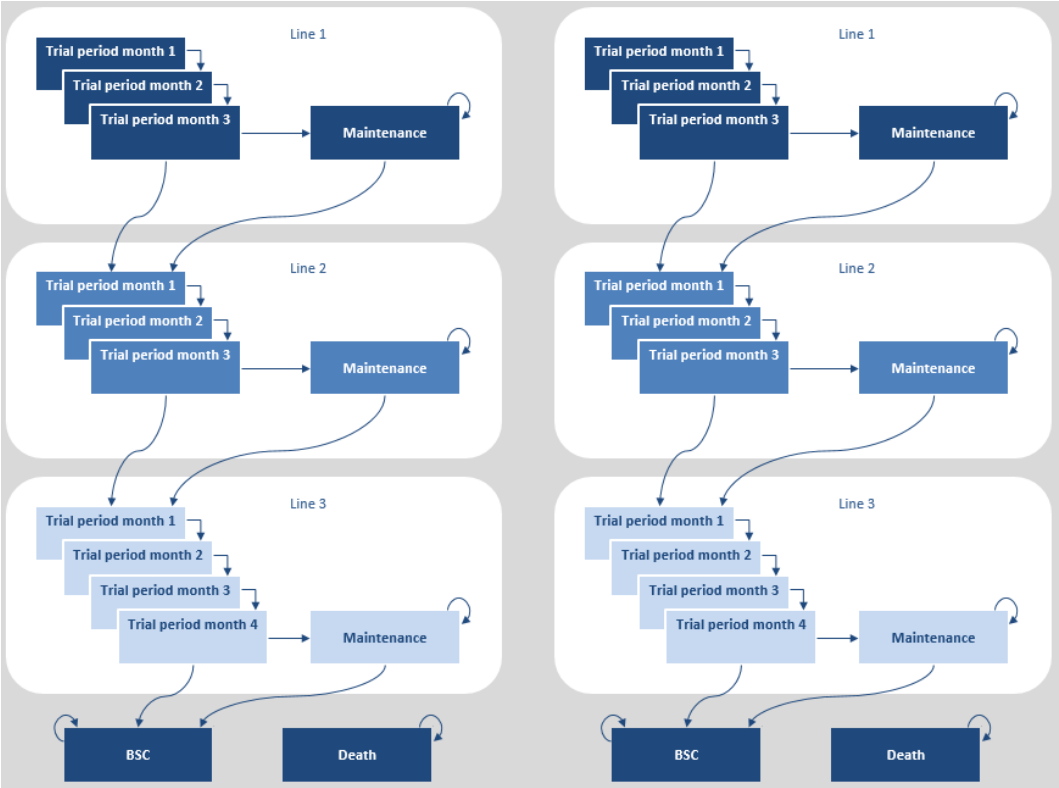
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Y	
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Y	Valuation of HRQoL based on public preferences from a representative sample of the UK (3L) or English (5L) population using choice-based methods: time trade-off (TTO) for the 3L and a hybrid of TTO and discrete choice experiments (DCE) for the 5L.
Discount rate	An annual rate of 3.5% on both costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	
Sensitivity analysis	Probabilistic modelling	Y	

EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Clinical Excellence; PSA = probablistic sensitivity analysis; quality-adjusted life years; PSS = Personal Social Services; TTO = Time trade off; UK = United Kingdom

5.2.2 Model structure

A de novo Markov state-transition model was developed in Visual Basic for Applications (VBA) with a Microsoft Excel interface. The company states that the model consists of five PASI response categories (PASI<50 (no response), PASI 50-74, PASI 75-89, PASI 90-99, and PASI 100 (complete clearance of symptoms)) and four treatment-related health states. The PASI response states determine utility gains. The four treatment states determine the cost impact of a treatment in the model as they are associated with specific resource use rates: Induction (trial) period, Maintenance period, BSC and Death. The induction period consists of tunnel states, and the total length is dependent on the particular biologic and can last from 10 to 16 weeks in alignment with the response assessment time points reported in CG153.[76] At the end of the induction period, patients are assessed on the basis of PASI response and assigned in the model to one of the five PASI response health states. Patients who meet the minimum base case response criterion of PASI 75 continue treatment in the maintenance state. If patients do not have an adequate level of response, they enter another induction period upon initiating the next treatment line, either active treatment or BSC. At the end of the subsequent induction period, these patients are once again assessed for response. During the maintenance period, patients continue to receive the active therapy and are assumed to maintain their level of response until discontinuation due to any cause, such as loss of effectiveness or AEs. Upon discontinuing, a patient is assumed to revert to their baseline PASI score. Similar to the patients without adequate response to the induction therapy, these patients proceed to the induction period of the subsequent treatment in the sequence and are assumed to experience no improvement from baseline HRQoL until the next response assessment for the subsequent biologic therapy or BSC. BSC is the final treatment in the sequence, consisting of a bundle of non-biologic supportive therapies. The impact of adverse events of treatments on HRQoL is not incorporated in the model, the impact on costs is only explored in a scenario analysis. All patients, including non- or partial responders, continue to receive BSC and maintain the level of response until death. Patients can die from the induction, maintenance and BSC health states. Mortality is not conditioned on treatment or treatment response and has been derived from life tables for the UK. The cycle length is one month. The company did not apply a half-cycle correction because the cycle length was relatively short.

Figure 5.1: Model structure



Source: Figure 38 CS [1]
Note: Arrows to the death state from all other states are removed to simplify the Figure.

ERG comment: In the base-case analysis the model compares treatment sequences rather than single treatments. It has been argued that economic evaluations of psoriasis treatments are sensitive to assumptions about treatment sequencing and the choice and effectiveness of subsequent treatment regimens.[100] The ERG agrees that the treatment sequencing approach is superior to comparing single treatments. The content of the sequences included in the assessment is discussed in Section 5.2.4.

According to the ERG, the PASI response categories are called health states by the company, but are not actual health states in the sense that transitions between each of them are not possible. PASI response is only used to determine the probability of going to maintenance or to the next induction period, and to determine the utility gain patients experience while on maintenance.

The model structure is developed around a relative PASI response. The ERG acknowledges that this approach is common in this disease area and that relative PASI response is the most used outcome measure in the clinical trials. There is however an important drawback associated with this approach. In health state transition models, the health states are supposed to be homogeneous with regard to consequences for health and costs. When relative measures are used to define health states, this aspect may well be violated. Patients in a specific PASI relative response state may differ substantially with regard to health-related quality of life, further disease progression as well as resource consumption. The observation that adjusting the regression model to estimate change in utility per PASI response category for baseline utility improved the model fit considerably (explained variance 0.512 relative to 0.052 for the unadjusted model) may indicate that this is indeed the case. The possible implication is that the true impact of a treatment on quality of life and costs is not captured. This may bias the comparative effectiveness (for instance, the quality of life and costs of patients with 75% PASI response on one treatment is not the same as on another treatment), but the direction and magnitude of

this issue is difficult to determine. PASI 100, full clearance, was incorporated as a separate response category in this model, while models in previous TAs used a PASI response category of 90-100%. The ERG asked the company to conduct a scenario analysis with PASI 90-100. The results are presented in Section 5.2.11.

The treatment specific PASI response is kept constant over the different treatment lines. This assumption was relaxed in a scenario analysis, labelled 'effect modification' by the company. See Section 5.2.6 for a discussion of this topic.

The ERG asked the company to perform an analysis incorporating the impact of AEs on not only costs but also on HRQoL. The company responded that this was not modelled because health utility information on adverse events was lacking, and because it would be difficult to trace back malignancies to specific treatments in the context of a treatment sequencing approach (response to question B11,[33]). According to the ERG the absence of evidence does not justify the exclusion of a plausible consequence of treatment. The ERG agrees that in the situation where patients are treated with a large variety of multiple lines of treatments it may be challenging to contribute the occurrence of long-term adverse events to single treatments, which may lead to uncertainty in model parameter estimates. This does however not justify neglecting these adverse events. In the ERG base-case the costs of AEs are included. Due to time constraints, and the complexity and lack of transparency of the model the ERG was unable to incorporate estimates of the impact of AEs on HRQoL.

Furthermore, the ERG considers that applying an induction phase, in which no utility gain can be generated, is implausible. The duration of the induction phase differs between treatments, so this may impact on comparative effectiveness. The company performed a scenario analysis in which utility gain was instantaneously applied in the induction phase (from the start of the induction phase patients experience the utility gain of the PASI response they acquire after the induction phase). In addition, the model allows for a scenario analysis with a linear utility gain during the induction phase. According to the ERG this model assumption is the most plausible assumption.

Finally, it is assumed that discontinuation rates are equal for all treatments and constant over time. As the treatments differ with respect to adverse effects the ERG thinks it is not plausible to assume equal discontinuation rates. The estimation of the discontinuation rates is further discussed in section 5.2.6.

5.2.3 Population

Ixekizumab has market authorisation for patients with moderate to severe plaque psoriasis who are candidates for systemic therapy. The base-case economic evaluation considers biological-naïve patients who have failed to respond to prior conventional systemic therapies, and are eligible for biologic therapies approved in the UK, e.g. as a first line biologic therapy. This is not in line with the scope, as the scope covers all patients under the licensed indication. The company states "*it is anticipated that ixekizumab will be used in the population currently eligible for biological therapies*".[1] This population is defined by the company as *"patients who have failed to respond to, or are unable to be treated with conventional systemic therapies who have a PASI score of ≥ 10 and a DLQI > 10"*.[1]

The population in the UNCOVER trials does not exactly match the "PASI score of ≥ 10 and a DLQI > 10" definition of moderate to severe psoriasis used in UK clinical guidelines.[76] The company argues that although the UNCOVER trials included patients with a PASI score of ≥12, the population in the trials can be classified as moderate to severe psoriasis.[99] In the UNCOVER trials the baseline pooled DLQI score was 12.5. The company used the subset of patients with DLQI>10 at baseline to calculate utility estimates.

ERG comment: The ERG acknowledges that there is no agreed consensus on the definition of moderate and severe psoriasis. According to the clinical expert consulted by the ERG, it is preferable to define the population based on PASI score >10 as well as DLQI score >10 because this also takes into account the patient experience. The ERG questions the inconsistent use of definitions for moderate to severe psoriasis to inform treatment response (only PASI >10, the ITT population from the UNCOVER trials) and utility gain per PASI response category (patients with DLQI>10 at baseline from the UNCOVER trials).

The company labels the population in the base case analyses as 'biological naïve', but this is not in line with the patients included in the UNCOVER trials and the other studies used to inform the NMA. These studies did include patients who have used biologic treatments (see Section 4.3). Nor is it in line with the scope. In response to clarification question B3, the company states "*patients are biological-naïve in the sense that they are modelled as initiating the first of three biological treatment sequences*".[33] The ERG disagrees with this view, as it is not in line with the evidence used to inform the input parameters, and hence the model results do not reflect a biological naïve population, but a population for whom biologic therapy is considered.

5.2.4 Interventions and comparators

In the base-case analysis, ixekizumab as a first line therapy in a biologic treatment sequence is compared to each currently approved biologic as first line therapy followed by subsequent second and third line biologic therapies (similar treatment sequences for all comparators). The biologic treatments included are: adalimumab, etanercept, ustekinumab, secukinumab and infliximab. Each of these treatments are recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or for patients who are intolerant or have a contraindication to these treatments.[101] Infliximab is only recommended for very severe psoriasis, but nevertheless included in the treatment sequences.[101] The dosing regimens for each treatment are in line with their marketing authorisation.

All treatment sequences consist of four treatments, with the fourth treatment being BSC in each treatment sequence (Table 5.5). Each biologic treatment is assessed as first line in a treatment sequence. It is assumed that a patient who has not responded to treatment is not given a different dosage of the same treatment or its biosimilar counterpart later in the sequence. In addition, in the absence of national guidance on the positioning of biologic treatments in a sequence, the company selected the treatments and their ordering on the basis of market shares in second line; alternating between mechanisms of action following failure on an initial biologic treatment, where possible and maintaining a common treatment algorithm between sequences for easier comparison. The company states that BSC as a standalone comparator is not included in the full comparator set in the base-case analysis because it is unlikely that patients who would be eligible to receive a sequence of biologic treatments are treated with BSC following failure on conventional systemic or first biologic therapy for the remainder of their lifetime.

Table 5.5: Intervention and comparators as first line in treatment sequence

Sequence	1st Line	2nd Line	3rd Line	4th Line
1A	Ixekizumab	Ustekinumab 90 mg	Infliximab	BSC
1B	Adalimumab	Ustekinumab 90 mg	Infliximab	BSC
1C	Etanercept 50 mg	Ustekinumab 90 mg	Infliximab	BSC
1D	Infliximab	Ustekinumab 90 mg	Adalimumab	BSC
1E	Secukinumab	Ustekinumab 90 mg	Infliximab	BSC
1F	Ustekinumab 45 mg	Adalimumab	Infliximab	BSC
1G	Ustekinumab 90 mg	Adalimumab	Infliximab	BSC

Source: Based on Table 69 of the CS[1]
BSC = best supportive care; CS = company submission

The model has the flexibility to assess the cost effectiveness of ixekizumab positioned in second line within a treatment sequence. This is assessed in a scenario analysis.

ERG comment: An appropriate assessment of cost effectiveness requires a comparison against all relevant and feasible treatment options for the population listed in the scope. According to the ERG that is not the case in this assessment.

1. In each treatment sequence, BSC is positioned as a fourth line treatment, with costs based on systemic and supportive treatments received in the year prior to initiating biologic therapy, but effectiveness based on placebo (while patients on placebo were not allowed to receive some of the treatments included in the BSC costs, such as methotrexate, see response to clarification question A9;[33]. According to the clinical expert consulted by the ERG, patients who have failed on non-biological systemic therapies before starting a biologic therapy are not likely to respond to these treatments, after four lines of biologic therapies, but phototherapy is an option. Phototherapy can be provided alongside a biological therapy. The evidence on this is however scarce.
2. Non-biologic systemic therapies such as ciclosporin, methotrexate and phototherapy are not included in the treatment sequences, while these treatments are options for patients in the population described in the scope. This seems reasonable if patients have failed those treatments before starting biologic therapy. According to the ERG's clinical expert this will be the case for the majority of patients.
3. The treatment sequences are informed by market share. According to the ERG sequences containing ixekizumab should be compared to not only treatment patterns that are currently the most widely used, but also the most optimal treatment sequence currently available, based on available trial evidence.
4. Ixekizumab is only positioned as a first line biologic treatment, while different positions for ixekizumab and a comparison of sequences where ixekizumab either extends a proposed sequence or displaces a therapy seem plausible as well. The ERG considers it important not to assume that ixekizumab will be a first line biologic treatment, but to formally demonstrate this is more cost effective than other positions. According to the clinical expert consulted by the ERG, at this time, clinicians are likely to be inclined to use ixekizumab as a second line of therapy because more experience and safety data with TNF α inhibitors and ustekinumab are available than with ixekizumab. Ixekizumab may be a first line treatment for patients with comorbid arthritis, for whom ustekinumab is less suitable.

5.2.5 Perspective, time horizon and discounting

The analysis takes a NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The time horizon is lifetime.

ERG comment: The approach is in concordance with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

Treatment responses in the cost effectiveness model were taken from the NMA (Section 4.3). More specifically, PASI change scores were estimated using data from the UNCOVER trials (ixekizumab and etanercept) and indirect evidence (other biologics). Treatment effectiveness in the UNCOVER trials was based on patients with moderate to severe psoriasis (PASI≥12, no DLQI restriction) who were candidates for systemic therapy and/or phototherapy (Section 5.2.3). A comparison of treatment response to ixekizumab and etanercept in the UNCOVER trials and the NMA was presented (Table 5.6). Furthermore, it was assumed that response rates for BSC were equivalent to placebo in the UNCOVER trials. In a scenario analysis alternative rates for BSC effectiveness were used, which were obtained from a study on inpatient management with phototherapy, systemic therapy and/or topical therapy.[97]

It is important to note that response was estimated in the NMA in terms of the cumulative percentage, i.e. the percentage achieving at least 50% or at least 75% which overlap. This contrasts with how the company estimated utility, which is a function of mutually exclusive categories:

- PASI <50 (no response)
- PASI 50-74
- PASI 75-89
- PASI 90-99
- PASI 100 (complete clearance of symptoms)

Table 5.6: Summary of clinical outcomes in model compared with clinical data

Outcome	UNCOVER-1	UNCOVER-2	UNCOVER-3	Model*
Ixekizumab 80 mg Q2W	N=433	N=351	N=385	
PASI 50	93.8%	94.9%	93.8%	[redacted]
PASI 75	89.1%	89.7%	87.3%	[redacted]
PASI 90	70.9%	70.7%	68.1%	[redacted]
PASI 100	35.3%	40.5%	37.7%	[redacted]
Etanercept	N/A	N=358	N=382	
PASI 50	N/A	62.8%	78.0%	63.9%
PASI 75	N/A	41.6%	53.4%	41.3%
PASI 90	N/A	18.7%	25.7%	18.9%
PASI 100	N/A	5.3%	7.3%	4.6%
Ustekinumab 45 mg	N/A	N/A	N/A	
PASI 50	N/A	N/A	N/A	87.1%
PASI 75	N/A	N/A	N/A	71.0%
PASI 90	N/A	N/A	N/A	45.6%
PASI 100	N/A	N/A	N/A	17.9%

Outcome	UNCOVER-1	UNCOVER-2	UNCOVER-3	Model*
Adalimumab 80 mg/ 40 mg EOW	N/A	N/A	N/A	
PASI 50	N/A	N/A	N/A	77.8%
PASI 75	N/A	N/A	N/A	57.5%
PASI 90	N/A	N/A	N/A	31.7%
PASI 100	N/A	N/A	N/A	10.0%
Ustekinumab 90 mg	N/A	N/A	N/A	
PASI 50	N/A	N/A	N/A	89.6%
PASI 75	N/A	N/A	N/A	75.1%
PASI 90	N/A	N/A	N/A	50.6%
PASI 100	N/A	N/A	N/A	21.4%
Infliximab 5 mg/kg	N/A	N/A	N/A	
PASI 50	N/A	N/A	N/A	92.8%
PASI 75	N/A	N/A	N/A	81.1%
PASI 90	N/A	N/A	N/A	58.7%
PASI 100	N/A	N/A	N/A	27.8%
Secukinumab 300 mg	N/A	N/A	N/A	
PASI 50	N/A	N/A	N/A	93.2%
PASI 75	N/A	N/A	N/A	81.8%
PASI 90	N/A	N/A	N/A	59.6%
PASI 100	N/A	N/A	N/A	28.6%
Placebo	N/A	N=358	N=382	
PASI 50	11.6%	6.5%	15.5%	13.7%
PASI 75	3.9%	2.4%	7.3%	4.7%
PASI 90	0.5%	0.6%	3.1%	1.0%
PASI 100	0.0%	0.6%	0.0%	0.1%

Source: Based on Tables 52 and 92 of the CS[1]
Footnote: *Model estimates are based on the NMA in which UNCOVER data was combined with indirect evidence for other comparators.
BSC = best supportive care; N/A = not applicable; PASI = Psoriasis Area and Severity Index; Q2W = once every 2 weeks

Treatment response in biologic-experienced patients, i.e. after first line in the sequence

Treatment responses that were used in the NMA were based on single treatments. In the base-case analysis, it was assumed that prior biologic treatment did not modify treatment response. Therefore, treatment effectiveness was assumed not to vary with the place in the treatment sequence.

The company argued that an NMA subgroup analysis of treatment response in patients with prior biologic failure could not be carried out due to a lack of robust evidence. In addition, in the UNCOVER trials no statistically significant differences were found when comparing treatment response (PASI 75) between biologic-naïve and biologic-experienced patients (85.8% and 83.5% respectively; Table 45 of the CS).[1] In a scenario analysis treatment effectiveness was adjusted for

prior biologic failure.[102] Here, a decrease in treatment response was only applied to biologics in the second and third line as it was assumed that patients were biological-naïve at baseline.

Response criterion

The PASI 75 cut-off was used to define treatment responders who subsequently maintained treatment. The company justified the use of this threshold by stating that PASI 75 was the most commonly used primary effectiveness measure and response criterion for treatment continuation in previous NICE TAs on psoriasis.[103] PASI 90 and PASI 50 were included as response criteria for treatment continuation in scenario analyses. The latter was used as a proxy of the definition (PASI 50 and five-point increase in the DLQI) mentioned in clinical guidelines for psoriasis.[76, 94]

Discontinuation

A constant annual discontinuation rate of 20% was applied in the maintenance period to capture all drop-out due to loss of effectiveness and adverse events. The discontinuation rate was obtained from a British observational cohort study (BADBIR) in which loss of effectiveness was reported as major reason for discontinuation.[26] The company used an annual discontinuation rate of 20% during treatment maintenance which corresponded to the 53% overall drug survival rate after three years.[26] Moreover, it was used in previous TAs on psoriasis. In a sensitivity analysis the discontinuation rate was varied between 4.7% and 42.8 % (based on 95% CI). The level of discontinuation was assumed to be constant over time, supported by the findings of a Danish cohort study.[102] Furthermore, discontinuation was not conditioned on the level of treatment response or type of treatment. In a scenario analysis the discontinuation rate of biologics in the second and subsequent lines was adjusted for prior biologic failure.

ERG comment: Several issues are raised by the ERG regarding treatment effectiveness.

1. It was not clear to the ERG whether the treatment responses used in the cost effectiveness model were related to the specific population being addressed. The company clarified that the population in the base-case analyses consisted of patients with prior systemic failure, PASI>10 and DLQI>10 who are biologic-naïve (Section 5.2.3, Clarification Question B2). However, treatment responses in the cost effectiveness model were informed by the NMA, which was based on the UNCOVER trials (ixekizumab and etanercept) and indirect evidence (other comparators). In the UNCOVER trials on average 35.2% of all patients (Table 4.5) were previously treated with systemic therapies. Therefore, only 35.2% of the patient population could have experienced prior systemic failure. For the other comparators treatment responses of patients with prior systemic failure were not obtained. Secondly, the company justified that the use of UNCOVER data was appropriate to reflect a biological-naïve population by stating that "only 26.4% of patients enrolled in UNCOVER-1, -2 and -3 had received either only prior biologic or prior biologic and non-biologic systemic therapy".[33] For the other comparators treatment responses for only biological-naïve patients could not be obtained. Thirdly, treatment responses in the NMA were not based on the DLQI>10 subpopulation as data could not be obtained for all comparators. Based on the NMA, treatment response for ixekizumab was [redacted] (PASI 75), [redacted] (PASI 90), and [redacted] (PASI 100). In the DLQI>10 subpopulation (UNCOVER trials, Clarification Question B1) treatment response was lower: [redacted] (PASI 75), [redacted] (PASI 90), and [redacted] (PASI 100). According to the clinical expert the ERG consulted, it is preferable to define the population based on PASI and DLQI score because it takes patient experience into account (Section 5.2.3). Overall, the ERG concludes that treatment responses did not relate to the specific population being

addressed as response rates were not solely based on biological-naïve patients with prior systemic failure and DLQI >10.

2. The ERG questions the assumption that treatment response for BSC is equal to placebo. It was mentioned that BSC, positioned as a fourth line treatment in the economic model, included systemic and supportive drugs, and inpatient and outpatient admissions (Clarification Question B4). In addition, the company explained that, *"systemic and supportive therapies in the study encompass acitretin, ciclosporin, fumaric acid esters, hydroxycarbamide, methotrexate, mycophenolate mofetil, amoxicillin, erythromycin, flucloxacillin and prednisolone".*[33] In contrast, patients in the placebo arm of the UNCOVER trials were not allowed to receive some of those systemic treatments. The clinical expert consulted by the ERG confirmed that BSC is often unsuccessful after failure on systemic and three lines of biologic treatments, but phototherapy may be an option. The ERG acknowledges that the evidence on BSC after failing three lines of biologic treatment is scarce. In a scenario analyses, the company used treatment responses in moderate to severe psoriasis patients who received inpatient management with phototherapy, systemic treatment and topical therapy. It was however unclear whether these inputs were related to patients who previously failed on systemic and biologic treatments.[97]
3. A decrease in treatment effectiveness for biologics in the second and subsequent lines was not included in the base-case analysis. The effect modifier that was used in the scenario analysis (Danish study) was considered not to be sufficiently robust. Furthermore, an NMA subgroup analysis of treatment effectiveness for biologic-experienced patients was not conducted because treatment responses for all comparators could not be obtained. No significant differences were found when comparing treatment response to ixekizumab in biologic naïve patients and biologic-experienced patients (UNCOVER trials) (Table 45 CS, Clarification Question B8). According to the clinical expert consulted by the ERG, effect modification may be present after failing a biologic due to inefficacy, but this will not be the case if biologics differ in mode of action. In the cost effectiveness model (Section 5.2.4), biologics in the sequence are based on different modes of action (i.e. TNF-α, IL-12/13 inhibitors and IL-17 inhibitors) (Figure 9 CS).[1] Given this finding and the small evidence base, the ERG excluded effect modification in its base-case, but assessed its impact in an explorative analysis.
4. A constant annual discontinuation rate of 20% was applied in the base-case analysis as it was used in previous TAs and supported by observational data. As treatments differ with respect to adverse effects the ERG thinks it is not plausible to assume equal discontinuation rates. In response to the clarification letter, the company provided treatment-specific discontinuation rates (Table 5.7). Sensitivity analyses using varying discontinuation rates over time were not conducted by the company because evidence could not be obtained for all comparators.

Table 5.7: Biologic therapy-specific discontinuation rates

Biologic	Year 1 discontinuation rate	Source
Ixekizumab	5.3%	UNCOVER-3 long term extension period
Adalimumab	21%	Warren 2015[26]
Etanercept	30%	Warren 2015[26]
Infliximab	35%	Warren 2015[26]
Ustekinumab 45 mg, 90 mg	11%	Warren 2015[26]
Secukinumab	11.7%	TA350[21]
Source: Table 14 response to request for clarification[33] TA = Technology appraisal		

The ERG noted that discontinuation rates were informed by studies that had different study designs. Discontinuation rates for adalimumab, etanercept, infliximab and ustekinumab were obtained from the BADBIR study, an observational cohort study (Table 5.7). Discontinuation rates for ixekizumab and secukinumab were obtained from controlled trials (UNCOVER trial and FIXTURE, ERASURE trials). In general, drop-out rates in observational or real-life studies are higher compared to trials, for instance because patients are able to switch to alternative biologic therapies. Therefore, the ERG thinks that the use of equal discontinuation rates for the different biological treatments was more plausible than using the values from the BADBIR study for comparators.

5.2.7 Adverse events

The consequences of AEs were not modelled in the base-case analysis because of their small cost impact and a lack of evidence on AE rates for several biologics. Furthermore, the company argued that AEs may exceed the duration of treatment with any given biologic and given the delayed onset of malignancies, there would be uncertainty in identifying which element of the treatment sequence may have been associated with the AE. In a scenario analysis, only the costs of AEs requiring hospitalisation were modelled. AEs included non-melanoma skin cancer (NMSC), malignancies other than NMSC and severe infections. The inclusion of these AEs was in concordance with the secukinumab submission.

AE rates for ixekizumab were taken from phase III RCTs (Table 5.8).[40] Rates for NMSC and other malignancies were informed by SmPC reports (adalimumab and ustekinumab)[104, 105], product information (etanercept)[106], and Reich et al. 2015 (infliximab).[107] AE rates for NMSC and other malignancies for secukinumab were assumed to be equal to ixekizumab Q2W. Rates for severe infections were taken from Dixon et al. 2006 (adalimumab, etanercept, infliximab) [108] and from the SmPC reports (ustekinumab and secukinumab).[105, 109]

Table 5.8: AE rates

Treatment	NMSC (rate/patient year)	Malignancies other than NMSC (rate/ patient year)	Severe infections (rate/patient year)	Reference:
Ixekizumab Q2W	0.0070	0.0040	0.0190	Gordon 2016 [40]
Adalimumab	0.0097	0.0098	0.0519	SmPC [104]; Dixon (2006) [108]
Etanercept 50 mg	0.0354	0.00093	0.0513	Enbrel product information [106]; Dixon (2006) [108, 110, 111]
Infliximab	0.0050	0.0000	0.0552	Reich (2015) [107]; Dixon (2006) [108]
Secukinumab	0.0070	0.0040	0.0150	NMSC and other malignancies: assumed equal to ixekizumab Q2W; Infection: SmPC[112]
Ustekinumab 45 mg	0.0065	0.0016	0.0100	SmPC [109]
Ustekinumab 90 mg	0.0065	0.0016	0.0100	SmPC [105]

Source: based on Table 108 of the CS [1]
AE = adverse event; NMSC = non-melanoma skin cancer; Q2W = every 2 weeks; SmPC = summary of product characteristics

ERG comment: AEs were included in a scenario analysis and consisted of AE-related costs for NMSC, other malignancies, and severe infections. The ERG noted that the company had used the incorrect reference for AE rates of ustekinumab 45 mg. The company referred to the SmPC of ustekinumab 90 mg while the SmPC of ustekinumab 45 mg should have been used.[113] However, this did not result in different AE rates. After recalculating the AE rates of adalimumab, the ERG came up with a slightly different rate for non-melanoma skin cancer (NMSC; 0.0096 instead of 0.0097) and used this in its base-case.[104] The ERG agrees with the company on the assumption that AE rates of NMSC and other malignancies for secukinumab are likely to be similar. According to the clinical expert, equal AE rates can be assumed as both biologics have comparable mode of actions.

5.2.8 Health-related quality of life

Searches intended to identify relevant HRQoL studies as well as cost and resource use data were reported for Medline, Medline in process, Embase, Econlit and Cochrane library databases, including NHS EED. The host and search dates were reported for all resources and searches were well reported and easily reproducible. Additional hand searches of conference proceedings, clinical trials resources and HTA agencies were also reported.

The ERG had some queries regarding the points at which results were exported from the Cochrane Library search (Table 34, Appendix13).[1] The company confirmed in their response to clarification that results from NHS EED were exported from Line #4 using the economic evaluations limit and that the results of a search combining psoriasis terms with HRQoL terms were exported from all Cochrane Library databases at Line #12.[33]

Estimation of health-related quality-of-life data from UNCOVER trials

The EQ-5D-5L questionnaire was administered to patients in the UNCOVER-1, 2 and 3 trials at baseline and at week 12.[3, 4, 41] The base-case HRQoL analysis considered the patient group with DLQI>10 at baseline, which the company based on the definition of moderate to severe psoriasis as described in NICE Clinical Guidelines 153.[76] For this patient group EQ-5D-5L data were available for 2,085 of a total of 3,731 patients (56%). For use in a scenario analysis, the company considered all patients in the UNCOVER trials.

For patients who discontinued before the end of the induction period, the EQ-5D-5L value at the visit prior to drop-out was used as a proxy for the week 12 value following the last-observation carried forward (LOCF) approach. The change in EQ-5D-5L derived utility, using the England tariff, from baseline to week 12 was calculated for each patient. The utility scores were pooled across all treatment arms in the UNCOVER trials, including the placebo arms. A least squares regression model was used to estimate the change from baseline EQ-5D-5L utility as a linear function of PASI response at week 12 and baseline EQ-5D-5L (Table 5.9, CS equation 2[1]). PASI 100 is the reference category, hence the intercept and baseline EQ-5D-5L correspond to the change from baseline EQ-5D-5L associated with complete psoriasis clearance and coefficients represent changes in EQ-5D-5L for achieving a response level that is less than complete clearance. Adjustment for baseline EQ-5D-5L was performed with the rationale that patients with a response category of PASI 100 at week 12 started with a slightly higher mean baseline EQ-5D-5L score than patients with a lower PASI response category. Furthermore, due to the ceiling effect associated with the EQ-5D-5L utility upper bound of one, the change in EQ-5D-5L depends on where the patient started from. Adjusting the model for baseline EQ-5D-5L utility resulted in explained variance of 0.512, as opposed to 0.052 for the unadjusted model.

Table 5.9: Parameter coefficients and EQ-5D-5L utility values

PASI category	Model coefficients (DLQI >10)		Mean change at week 12 from baseline EQ-5D-5L	
			DLQI>10 (Company base-case)	ITT population (Company sensitivity analysis)
Intercept	α	0.6465086155		
No Response	β1	-0.1408543935	0.012	0.005
PASI 50-74	β1	-0.0529486119	0.100	0.071
PASI 75-89	β1	-0.0224581658	0.131	0.083
PASI 90-99	β1	-0.0086372007	0.144	0.102
PASI 100	β1	0 (reference)	0.153	0.104
Baseline EQ-5D-5L	β2	-0.6490599844		

Source: Based on Tables 70, 80 and 114 of the CS[1] and the response to the request for clarification[33]
Mean utility change from baseline can be calculated using a mean baseline EQ5D-5L of 0.7608 following equation 2 from the CS (Change from baseline EQ-5D-5L= $\alpha + \beta_1$*(PASI – response at 12 weeks) + β_2 * baseline EQ-5D-5L) + ε).
CS = company submission; DLQI = Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life-5 Dimensions, five-level scale; ITT = intention to treat; PASI = Psoriasis Area and Severity Index

ERG comment: In their base-case the company used the subset of patients from the UNCOVER trials with DLQI>10 at baseline to calculate utility estimates (see Section 5.2.3 Population). This is not consistent with the ITT population used to estimate PASI response. PASI response is slightly lower in the DLQI>10 subset (see response to clarification question B1[33]), while utility gains per PASI response category are larger than in the ITT population (CS Table 114[1]). Based on the advice of our clinical expert, the ERG agrees with the use of the DLQI>10 subset, as it describes the population in the scope better, but is concerned about the inconsistency with using the total ITT population to calculate PASI response.

The ERG has concerns about the quality of the least square regression model with baseline EQ-5D-5L and PASI response categories as covariates. Many other choices could have been made regarding the model and covariates. In the clarification letter the ERG requested to explore several alternative modelling choices (Table 5.10).[33] The company provided several additional analyses with alternative modelling choices, which may have an impact on the ICER if these were applied in the cost effectiveness analysis.[33] Some of these alternatives included significant alternative or additional covariates, which may therefore result in better model performance. However, as none of these alternative modelling choices, performance statistics or model diagnostics were provided, the ERG could not assess whether the original linear regression model, used in the company base-case, is the most appropriate method for the calculation of utility gains or whether any of the alternatives would provide a better fit. Therefore, the ERG is uncertain about the estimates of utility gains per PASI response category applied in the model.

Table 5.10: Summary of requested alternatives for utility change estimation

ERG request	Response and result	Source
Alternative model shapes, such as a gamma model (using a log-link) using transformed utility (1-utility).	All covariates except PASI 90 had [redacted].	Table 16 of RRfC
Baseline PASI instead of baseline	All covariates except PASI 75 & 90, but	Table 17+18 of

ERG request	Response and result	Source
EQ5D-5L.	including baseline PASI had [redacted]. Mean utility changes differed slightly.	RRfC
Add interaction term between PASI response and baseline EQ-5D-5L to assess whether the assumption of constant utility gain over time is justified.	Company responds that "assumption that the utility gain based on initial PASI response at the end of the trial period (week 12) is consistent with previous modelling approaches and is the only feasible assumption given the available data". Company feels that there is insufficient data, but without justification. Interaction terms between baseline EQ-5D-5L and No response, PASI 50 and PASI 75 had [redacted].	Table 19 of RRfC
PASI response 90-100% reduction subgroup (instead of 90-99% and 100% separately) for consistency with previous TAs.	Mean utilities changes using 4 categories only differs slightly; [redacted] for PASI 90-100 vs. 0.144 for PASI 90-99 (Table 5.9). Not much influence on (deterministic) ICER vs. Etanercept sequence 1C; £34,547 for 90-100% subgroup vs. £33,858 for base-case (90-99% and 100% subgroup).	Table 20+21 of RRfC CS Table 91
Inclusion of age as a covariate as HRQoL was assumed constant while EQ-5D-3L population norms for the UK general population are known to decrease with age.[114]	Company explains that prior models submitted to NICE for psoriasis followed a similar process not taking into account age-adjustment in utility. Age covariate had [redacted]. Mean change in utilities was similar.	Table 22+23 of RRfC
Source: Based on Table 91 of the CS[1] and Tables 16-23 of the CL response[33] EQ-5D = European Quality of Life – 5 Dimensions; PASI = Psoriasis Area and Severity Index; RRfC = response to request for clarification; TA = technology appraisal		

For all patients who discontinued the study before the end of the induction period (week 12), the last EQ-5D-5L value, if collected at the visit prior to discontinuation, was used as an estimate for the week 12 value using the last-observation-carried-forward (LOCF) approach. The company explained that in the UNCOVER 1, 2 and 3 studies EQ-5D-5L data was collected at baseline and at week 12. If a patient discontinued the study before 12 weeks, EQ-5D-5L was collected (if possible) at the last visit, which was used for LOCF imputation.[33] Values missing for any other reason were not imputed as no previous post baseline observations were available. The LOCF method underestimates variance, and is therefore inferior to multiple imputation methods. To be able to judge whether it is reasonable to assume that the EQ-5D-5L score at the last visit would be representative for the score at week 12, pattern and reasons of discontinuation need to be known. The ERG requested this information, but the company did not provide it. As a result, it is unknown in how many patients LOCF was used to obtain a utility value at week 12, and whether the LOCF method was reasonably appropriate. In conclusion, the application of the LOCF approach to an unknown number of patients that discontinued for unknown reasons further increased the ERGs uncertainty about the estimates of utility gain applied in the model.

Health-related quality of life literature

A SLR was conducted to identify relevant HRQoL studies that report utilities in patients with moderate to severe plaque psoriasis in the UK. Six studies with HRQoL outcomes based on EQ-5D-

5L questionnaires were included in this STA submission (see Sections 5.1.5-5.1.8). The utility values derived from the EQ-5D-5L data from UNCOVER trials lie within the wide range of estimates identified from the SLR and in previous NICE TAs (CS Table 78[1], Table 5.11). Utility values identified from the SLR were not included in the base-case analysis, because data from those studies were not stratified by PASI responses, were based on non-UK populations, or were reported without uncertainty estimates. The alternative utility estimates were used in scenario analyses (CS Table 112[1]).

ERG comment: The estimates of utility gain per PASI response category used in the base-case are within the range of estimates reported in previous TA, and on the conservative side.

Implementation of health-related quality of life data in cost effectiveness analysis

In the base-case analysis, patients were assumed to accrue no health utility gains within the induction period. Utility gains were only assigned to responder patients on biologic therapy, hence having a minimum PASI of 75, in the maintenance period (CS equation 3[1]). However, at the end of the BSC induction period, all patients, including non-responders, accrue utility gains according to PASI response associated with placebo (CS equation 4[1]). The company explained that as ixekizumab is probably associated with a higher weighted average utility gain in the induction period due to the rapid onset of response in patients, the approach assuming no utility gain in the induction period likely provided a conservative estimate of the HRQoL gains associated with ixekizumab. Instantaneous health utility gain at the start of the induction period or applying health utility gain that changes linearly with time each model cycle during the induction period were applied in a scenario analysis (see also Section 5.2.11 Sensitivity analyses).

ERG comment: The ERG agrees with the application of an induction period for active treatment and BSC. As the treatment effect will probably occur gradually over time the ERG considers the linear approach of assigning utility gain to the induction period to be most plausible.

Table 5.11: Comparison of EQ-5D utilities from previous TAs and UNCOVER data

Reference source	Reference	Results				
		No PASI response	**PASI 50-74**	**PASI 75-89**	**PASI ≥ 90**	**PASI 100**
Previous STA	Secukinumab (TA350) (DLQI > 10)	0.109	0.193	0.226	0.264	NR
Previous STA	Ustekinumab (TA180) (DLQI > 10)	0.04	0.17	0.22	0.25	NR
Previous STA	Infliximab (TA134) (4th quartile DLQI)	0.12 (SE 0.03)	0.29 (SE 0.06)	0.38 (SE 0.08)	0.41 (SE 0.09)	NR
Previous STA	Adalimumab (TA146)	0.054 (SE 0.017)	0.14 (SE 0.016)	0.14 (SE 0.016)	0.219 (SE 0.021)	NR
Previous STA	Adalimumab (TA146) (DLQI ≤ 10)	0.045 (SE 0.024)	0.102 (SE 0.022)	0.102 (SE 0.022)	0.13 (SE 0.031)	NR
Previous STA	Adalimumab (TA146) (DLQI > 10)	0.063 (SE 0.025)	0.178 (SE 0.023)	0.178 (SE 0.023)	0.308 (SE 0.027)	NR
Previous STA	Etanercept and Efalizumab (TA103)	0.05 (SE 0.01)	0.17 (SE 0.04)	0.19 (SE 0.04)	0.21 (SE 0.05)	NR
Previous STA	Etanercept and Efalizumab (TA103) (4th quartile DLQI)	0.12 (SE 0.03)	0.29 (SE 0.06)	0.38 (SE 0.08)	0.41 (SE 0.09)	NR
Present STA	Ixekizumab (DLQI > 10, Company base-case)	0.0123 (SE 0.006)	0.100 (SE 0.010)	0.131 (SE 0.008)	(PASI 90-99) 0.144 (SE 0.007)	0.153 (SE 0.007)
	Ixekizumab (Total population, Company sensitivity analysis)	0.005	0.071	0.083	0.102	0.104
	Ixekizumab (4 categories)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 78 and 114 of the CS[1] and Table 20 of the response to the request for clarification[33]
CI = confidence interval; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life – 5 Dimensions; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; SE = standard error; STA = single technology appraisal; TA = technology appraisal

Health-related quality-of-life of adverse events

Consequences of AEs regarding HRQoL were not modelled in the base-case analysis because of lack of evidence on AE rates for several biologics (see also Section 5.2.7 Adverse events). The serious AEs of interest requiring hospitalisation in the model are aligned with those included in the secukinumab submission and encompass non-melanoma skin cancer (NMSC), malignancies other than NMSC and severe infections.[115] The company acknowledges that each of these AEs is likely to be associated with significant HRQoL impacts, but as AEs may exceed the duration of treatment with any given biologic and given the delayed onset of malignancies, there would be uncertainty in identifying which element of the treatment sequence may have been associated with the AE.

ERG comment: The ERG requested a sensitivity analysis to show the impact of adverse events on utility on the results of the model, which was not performed because of the arguments concerning lack of data and difficulty in tracing AEs to treatments, explained above. The ERG was unable to technically implement adjustments for HRQoL of AEs. In line with the TA for secukinumab HRQoL of AEs have not been incurred in the additional ERG analyses.[115]

5.2.9 Resources and costs

The following health care resource use and costs were considered in the company cost effectiveness model: drug costs, administration costs, monitoring costs, non-responder costs and BSC costs.

Drug costs were obtained from the Monthly Index of Medical Specialities (MIMS) (Table 5.12).[116] The list price of all biologic therapies were used in the base-case cost effectiveness analysis, except for ixekizumab for which a Patient Access Scheme (PAS) has been agreed upon and ustekinumab 90 mg (administrated to patients weighing more than 100 kg) which was allocated the same costs as ustekinumab 45 mg (PAS price). The costs of infliximab, which is weight-based, was calculated based on a mean weight of 91.56 kg (mean weight of UNCOVER patients at baseline). The biosimilar price of infliximab and etanercept were used in the base-case analysis.

Table 5.12: Drug acquisition prices

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (induction period)	Total annual cost (maintenance period)	Source
Ixekizumab	1	80 mg	[redacted]	[redacted]	[redacted]	[redacted]	PAS price
Adalimumab (Humira)	2	40 mg/ 0.8ml	£704.28	£352.14	£3,521.40	£9,155.64	MIMS, June 2016[116]
Etanercept (Enbrel)	4	50 mg	£715.00	£178.75	£2,145.00	£9,295.00	MIMS, June 2016[116]
Biosimilar etanercept (Benepali)	4	50 mg	£656.00	£164.00	£1,968.00	£8,528.00	MIMS, June 2016[116]
Infliximab (Remicade)	1	100 mg	£419.62	£1,921.02*	£5,763.06*	£12,486.63*	MIMS, June 2016[116]
Biosimilar infliximab	1	100 mg	£377.66	£1,728.93*	£5,186.78*	£11,238.03*	MIMS, June

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (induction period)	Total annual cost (maintenance period)	Source
(Remsima)							2016[116]
Secukinumab (Cosentyx)	2	150 mg	£1218.78	£1,218.78	£8,531.46	£15,844.14	MIMS, June 2016[116]
Ustekinumab 45 mg (Stelara)	1	45 mg	£2,147.00	£2,147.00	£4,294.00	£9,303.67	MIMS, June 2016[116]
Ustekinumab 90 mg (Stelara)	1	90 mg	£2,147.00	£2,147.00	£4,294.00	£9,303.67	MIMS, June 2016[116]; NICE TA 180[117]
Source: Table 84 of the CS[1] Footnote: *Infliximab dose based on a baseline weight of 91.56 kg MIMS = Monthly Index of Medical Specialities; PAS = Patient Access Scheme							

Drug administration costs were also incorporated in the cost effectiveness analysis. All biologic therapies, except for infliximab, are administrated through subcutaneous (SC) injections. For these, a three hours nurse training was taken into account during each induction period. It was subsequently assumed that all patients were able to administrate these SC injections individually, and no further administration costs were taken into account during the maintenance period. Infliximab is administrated through an intravenous (IV) injection and was assumed to require three outpatient visits during the induction period and 6.5 per year during the maintenance period. Prices were based on NHS reference costs[118] and the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care 2015 (Table 5.13).[119]

Table 5.13: Drug administration costs

Administration method	Administration cost	Number of administrations in the induction period	Total cost: induction period	Number of administrations annually in the maintenance period	Total annual cost in the maintenance period	Source
SC self-injection: three 1-hour nurse training sessions	£36.00	3	£108.00	0	£0.00	PSSRU, Unit Costs of Health and Social Care 2015, Nurse (GP practice), wage cost per hour[119]
IV infusion*, outpatient procedure	£97.08	3	£291.24	6.5	£631.02	NHS Reference Cost 2014-2015, Outpatient Procedure (Currency Code: WF01A, "Non-Admitted Face to Face Attendance, Follow-up". Dermatology).[118]

Source: Table 85 of the CS[1]
Footnote: *Infliximab only
GP = general practitioner; IV = intravenous; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; SC = subcutaneous

In addition, the cost effectiveness model included monitoring costs during the induction and maintenance periods (Table 5.14). Resource use estimates were based on NICE CG153[76] and prices were obtained from NHS reference costs.[118] Monitoring costs consisted of physician visits and monitoring tests. Monitoring costs for all subcutaneously administrated comparators, including ixekizumab, were assumed to be the same. Resource use was based on the costing template accompanying CG153[76] and prices were obtained from the NHS reference costs 2014/2015 (CS Table 86).[118]

Table 5.14: Resource use and costs for SC and IV monitoring during the induction and maintenance periods

Treatment period	Physician visits (£101.58)	Full blood count (£3.01)	Liver function test (£1.19)	Test for urea & electrolytes (£1.19)	Total costs
SC administration					
Induction	2	2	2	2	£ 213.94
Maintenance (annual)	4	4	4	4	£ 427.88
IV administration*					
Induction	1	3	3	3	£ 117.75
Maintenance (annual)	0	4	4	4	£ 21.56

Sources: Tables 86-87 of the CS[1]
Footnote: * Infliximab only
CS = company submission; IV = intravenous; SC = subcutaneous

Induction and maintenance costs concern only outpatient resources use and costs. 'Non-responder' costs are applied to patients that do not respond to treatment, which comprises of inpatient resources use and costs. The non-responder costs were obtained from Fonia et al. 2010[93] and assumed equal to the inpatient costs incurred by moderate to severe psoriatic patients 12 months before the initiation of biologic therapy. These costs were applied to the *"next subsequent induction period in the sequence"* (i.e. this includes only the induction periods of the second and third treatment lines when patients do not respond in the company base-case).[1] Non-responder costs were assumed to be £274.27 per monthly cycle.

In the BSC state, patients incur health care costs of £423.52 per monthly cycle (CS Table 88).[1] This estimate is also based on Fonia et al. 2010[93] and represents health care costs incurred by moderate to severe psoriatic patients before the initiation of biologic therapy (drug costs, inpatients admission and outpatient care). In a sensitivity analysis, the company explored the influence of BSC costs on the cost effectiveness results by replacing the estimate from Fonia et al. 2010[93] with an estimate based on NICE CG 153 (£938.10 per monthly cycle)[76]. Costs were inflated to 2015 values if needed.

AE costs were not considered in the company base-case analysis but included in a scenario analysis. In this sensitivity analysis, the serious adverse events costs requiring hospitalisation were included (i.e. NMSC, malignancy other than NMSC, and severe infections). These costs were obtained from the NHS reference costs 2014/2015 (Table 5.15). The costs of severe infections were based on an average of six types of infection (i.e. sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection, and urinary tract infection) and the costs of malignancy other than non-melanoma skin cancer was based on an average of lymphoma and melanoma.[118] Weighted averages were calculated if multiple reference codes were used. Total AE annual costs (Table 5.16) for each comparator is calculated by multiplying the average unit cost of each AE by their treatment-specific annual rates (Table 5.8).

Table 5.15: Health care costs incurred by AEs (recalculated by the ERG)

Adverse reactions	AE	Cost per unit (as in CS)	Average unit cost (as in CS)	Cost (recalculated by the ERG)	Average unit cost (recalculated by the ERG)	Reference in submission
NMSC		£2,461.59	£2,461.59	£2,462	£2,462	National Schedule of Reference Costs Year 2014-15 : JC42A[118]
Malignancy other than NMSC:	Lymphoma (hospital costs)	£1,942.39	£2,201.99	£4,908	£3,685	National Schedule of Reference Costs Year 2014-15 : SA31A-F[118]
	Melanoma (hospital costs)	£2,461.59		£2,462		National Schedule of Reference Costs Year 2014-15 : JC42A[118]
Severe Infection:	Sepsis	£2,149.02	£2,602.93	£2,708	£3,379	National Schedule of Reference Costs Year 2014-15 : WJ05A-B; WJ06A-J[118]
	Tuberculosis	£2,570.71		£3,618		National Schedule of Reference Costs Year 2014-15 : DZ14F-J[118]
	Pneumonia	£2,066.42		£2,726		National Schedule of Reference Costs Year 2014-15 : DZ23H-N[118]
	Skin and soft tissue infection	£3,453.45		£3,946		National Schedule of Reference Costs Year 2014-15 : JD07A-

Adverse reactions	AE	Cost per unit (as in CS)	Average unit cost (as in CS)	Cost (recalculated by the ERG)	Average unit cost (recalculated by the ERG)	Reference in submission
						D[118]
	Bone and joint infection	£3,550.54		£4,706		National Schedule of Reference Costs Year 2014-15 : HD25D-H[118]
	Urinary tract infection	£1,827.46		£2,567		National Schedule of Reference Costs Year 2014-15 : LA04H-S[118]

Source: Table 109 of the CS[1]
AE = adverse event; CS = company submission; ERG = Evidence Review Group; NMSC = non-melanoma skin cancer

Table 5.16: Annual AE costs per treatment regimen

Treatment	Malignancies other than NMSC (£2,461.59)	NMSC (£2,201.99)	Severe infections (£2,602.93)	Total annual cost
Ixekizumab Q2W	£17.23	£8.81	£49.46	£75.49
Adalimumab	£23.88	£21.58	£135.09	£180.55
Etanercept 50 mg	£87.14	£2.05	£133.53	£222.72
Infliximab	£12.31	£0.00	£143.68	£155.99
Secukinumab	£17.23	£8.81	£39.04	£65.08
Ustekinumab 45 mg	£16.00	£3.52	£26.03	£45.55
Ustekinumab 90 mg	£16.00	£3.52	£26.03	£45.55

Source: Table 110 of the CS[1]
AE = adverse event; CS = company submission; NMSC = non-melanoma skin cancer; Q2W = once every two weeks

ERG comment: The ERG had concerns about the representativeness of the UNCOVER mean weight for the calculation of infliximab treatment costs, the suitability of the evidence underlying resources use and costs of monitoring during the induction and maintenance period and the possible overlap between monitoring costs and non-responder costs. The ERG requested clarification on all these points.[33] Firstly, the company demonstrated that the mean weight used in the current decision problem was similar to the mean weight in clinical trials informing previous TAs concerning treatments for moderate to severe psoriasis (response to Clarification Question B17).[33] Secondly, the company stated that monitoring resource use estimates were obtained from the Appendix O of the CG153.[76] However, the primary source underlying the frequency of monitoring procedures is not provided in CG153. Thirdly, the company explained that non-responder costs were applied to patients with a PASI response < 50, while patients responding to treatment would incur treatment, administration, and monitoring costs (the percentage with PASI 50-74). Therefore, monitoring costs were not covering part of the non-responder costs. The company further explained that non-responder costs were considered as the *"inpatient admissions, ICU admissions, HDU admissions, A&E visits, day ward admissions and phototherapy incurred 12 months before biologic therapy initiation"*.[33] The ERG considers the approach undertaken by the company concerning these topics as consistent with previous assessments and adequate for the current decision problem.

In addition, the ERG requested the company to provide a sensitivity analysis in which the BSC costs, based on the health care costs before biologic initiation, would be replaced by the health care costs following biologic initiation (both estimates are obtained from Fonia et al. 2010[93]).[37] The company did not provide the requested sensitivity analysis because the health care costs following biologic treatment (based on Fonia et al. 2010[93]) *"would not adequately capture the increase in healthcare resource use due to biologic treatment failure- i.e. the costs from Fonia following biologic therapy initiation would be confounded by the fact that patients were being treated with biologics when the definition of BSC in the economic model precludes the use of biologic treatment."*[33] The ERG agrees with this argument. However, the current estimate is based on a biologic-naïve population (i.e. health care costs incurred before biologic treatment initiation)[93] and does not represent health care resource use and costs after multiple biologic treatment failures. According to the clinical expert consulted by the ERG, Fonia et al. 2010[93] provides a realistic estimates of inpatients and phototherapy resource use

and costs but not of the cost of systemic non-biologic treatment. This is because clinicians are not likely to actively treat patients after several failures to biologic therapies and only sometimes treat patients with therapies on which they already failed. Since there is a discrepancy between the population from Fonia et al.2010[93] and the BSC population in the current assessment, the ERG does not consider the BSC resource use and cost estimates from Fonia et al. 2010[93] as representative for the current decision problem, i.e. after failure to three biologic therapies. The ERG is however not aware of any study providing the required estimate and Fonia et al.2010[93] has the advantage of being a UK-based study which has been considered as most representative in previous assessments.[115, 120] Because of the lack of studies investigating resource use and costs in the population of interest (i.e. after failure to three biologic therapies), the company's estimate will be used in the ERG base-case analysis even though the ERG considers the current BSC estimate as uncertain.

Costs incurred by AEs, based on the NHS reference costs[118] provided by the company were audited by the ERG. The ERG was not able to reproduce the estimates provided by the company and have therefore recalculated cost estimates based on the NHS reference costs[118] reported in the CS (weighted average based on finished consultant episodes (FCEs) were calculated when multiple reference codes were reported). The recalculated estimates by the ERG are higher for 'Malignancy other than NMSC' and 'Severe Infection' than the ones provided in the CS. NMSC costs remained the same. Recalculated AEs costs (Table 5.15) will be used in the ERG base-case analysis.

Finally, the ERG discovered a mistake in the number of annual administration of secukinumab in the company cost effectiveness model. Secukinumab is administrated once monthly during the maintenance period which results in 12 annual administrations. However, the model took 13 annual administrations of secukinumab into account. This has been corrected in the ERG base-case.

5.2.10 Cost effectiveness results

As labelled by the company, deterministic results were provided for biologic naïve patients with prior systemic failure and moderate to severe psoriasis (PASI>10 and DLQI≥10). A fully incremental analysis was conducted with ixekizumab as first line treatment. One should note that secukinumab is available in the NHS under a confidential PAS price arrangement. Consequently, the analyses presented in the current report do not represent the true value for money of secukinumab. A confidential appendix, in which all analyses (both company and ERG analyses) have been reproduced, has been prepared by the ERG.

The company provided disaggregated results of QALYs gained and costs by health state and costs per cost category (Appendix 2). Disaggregated results were not provided for life years (LYs) per treatment sequence. The ixekizumab sequence resulted in higher total QALY gain (1.45 QALY gain) compared to all other sequences (1.30 to 1.42 QALY gain). A substantial part of this QALY gain was acquired in the PASI 100 state. The total costs of the ixekizumab sequence (£150,889) were higher compared to all other sequences, except for the secukinumab sequence (£177,101). A large part of the cost increments were accrued in the PASI 100 state. When comparing the costs of treatment sequences by cost categories, treatment costs and costs of BSC contributed to the largest cost increments. Lowest treatment costs were incurred for the etanercept sequence (£75,935) and highest costs were for the secukinumab sequence (£113,989). BSC costs ranged from [redacted] (ixekizumab sequence) to £62,928 (etanercept sequence).

The ICER for the ixekizumab sequence versus the etanercept sequence was £33,858. Other treatment sequences were dominated (secukinumab sequence) or extendedly dominated by the ixekizumab sequence. When comparing the ixekizumab sequence to other sequences than the referent, the ICER ranged from £4,300 to £19,202 (Table 5.17).

Table 5.17: Base-case results (Biologic-naïve patients with prior systemic failure, PASI >10 and DLQI ≥ 10)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs. comparator
1C	ETN 50 mg weekly	UST 90 mg	INF	BSC	£144,635	1.27	Referent	Referent	Referent	£33,858
1F	UST 45 mg	ADA	INF	BSC	£148,218	1.30	£3,582.91	0.04	Extendedly dominated	£18,278
1B	ADA	UST 90 mg	INF	BSC	£148,350	1.32	£3,714.86	0.05	Extendedly dominated	£19,202
1G	UST 90 mg	ADA	INF	BSC	£148,719	1.32	£4,083.20	0.06	Extendedly dominated	£16,763
1D	INF	UST 90 mg	ADA	BSC	£150,350	1.33	£5,714.25	0.06	Extendedly dominated	£4,300
1A	IXE	UST 90 mg	INF	BSC	£150,889	1.45	£6,253.65	0.18	£33,858	N/A
1E	SEC	UST 90 mg	INF	BSC	£177,101	1.42	£32,465.66	0.15	Dominated	Dominated

Source: Based on Table 91 of the CS [1]
ADA = adalimumab; BSC = best supportive care; DLQI = Dermatology Life Quality Index; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; N/A = not applicable; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

ERG comment: The ERGs main concerns were related to the population for which results were provided, disaggregated results for LYs were not presented, and deterministic results for the base-case analysis were shown.

1. It was mentioned that cost effectiveness results were related to biologic naïve patients with prior systemic failure and moderate to severe psoriasis (PASI>10 and DLQI≥10). However, treatment response in the cost effectiveness model (Section 5.2.6), and thereby also cost effectiveness results, did not reflect a biological-naïve population with prior systemic failure. Moreover, utility estimates were based on patients with DLQI>10, while this was not the case for treatment response (Section 5.2.6).
2. The ERG requested disaggregated results for LYs per treatment sequence because of validity reasons. In response to the clarification, it was stated that disaggregated results were not provided as mortality was not differentiated by type of treatment and incremental results are zero. Although the total LYs do not differ between the treatment sequences, the disaggregated LYs most likely do and are relevant to interpret the QALY gains. Therefore, the ERG remarks that the presentation of disaggregated LYs for each treatment sequence would have contributed to the validity of the cost effectiveness model.
3. Deterministic results were used in the base-case analysis rather than the probabilistic results, which does not align with the NICE reference case.

5.2.11 Sensitivity analyses

A probabilistic sensitivity analysis (PSA) was undertaken including the following parameters:

- Utility gain (per level of treatment response)
- Annual discontinuation rate
- Number of physician visits
- Monitoring frequency during the induction period
- Monitoring frequency during treatment maintenance
- Monitoring costs
- Cost of BSC
- BSC effectiveness
- Response rates

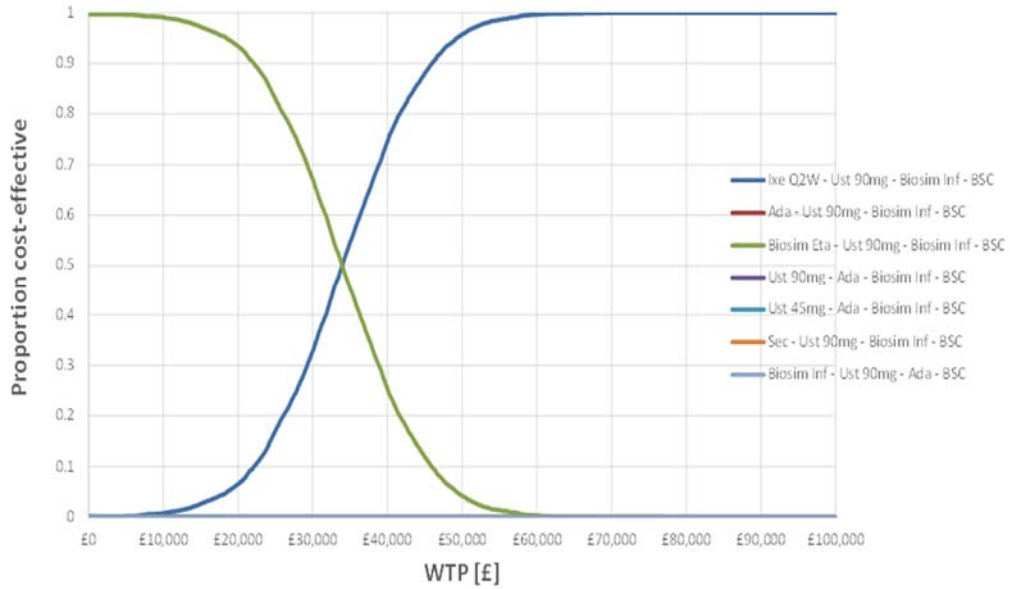
Base-case PSA results are provided (Table 5.18). PSA simulation results were used to draw the PSA scatterplot, the cost effectiveness acceptability curve (CEAC) (Figure 5.2) and the cost effectiveness acceptability frontier (CEAF) (Appendix 3). The results show that the etanercept sequence and the ixekizumab sequence have the highest probability being cost effective. The etanercept sequence is the most cost effective treatment sequence up to a willingness to pay (WTP) threshold of £34,000. For a WTP threshold above £34,000 the ixekizumab sequence had the highest probability of cost effectiveness.

Table 5.18: Probabilistic results

Comparator sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER (cost/QALY) fully incremental	ICER (cost/QALY) IXE sequence vs. comparator
1C: ETN sequence	£145,400	1.30	Referent	Referent	Referent	£32,815
1F: UST 45 mg sequence	£149,050	1.34	£3,650	0.04	Extendedly dominated	£17,025
1B: ADA sequence	£149,174	1.35	£3,774	0.05	Extendedly dominated	£15,841
1G: UST 90 mg sequence	£149,555	1.35	£4,155	0.06	Extendedly dominated	£15,353
1D: INF sequence	£151,391	1.36	£5,991	0.06	Extendedly dominated	£1,447
1A: IXE sequence	£151,575	1.49	£6,175	0.19	£32,815	N/A
1E: SEC sequence	£179,042	1.45	£33,642	0.15	Dominated	Dominated

Source: Based on Table 97 of the CS and cost effectiveness model[1]
ADA = adalimumab; BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Figure 5.2: Company base-case analysis cost effectiveness acceptability curve



Source: Based on figure 41 of the CS [1]
ADA = adalimumab; BSC = best supportive care; CEAC = cost-effectiveness acceptability curves; ETN = etanercept; INF = infliximab; IXE = ixekizumab; SEC = secukinumab; UST = ustekinumab; WTP = willingness to pay

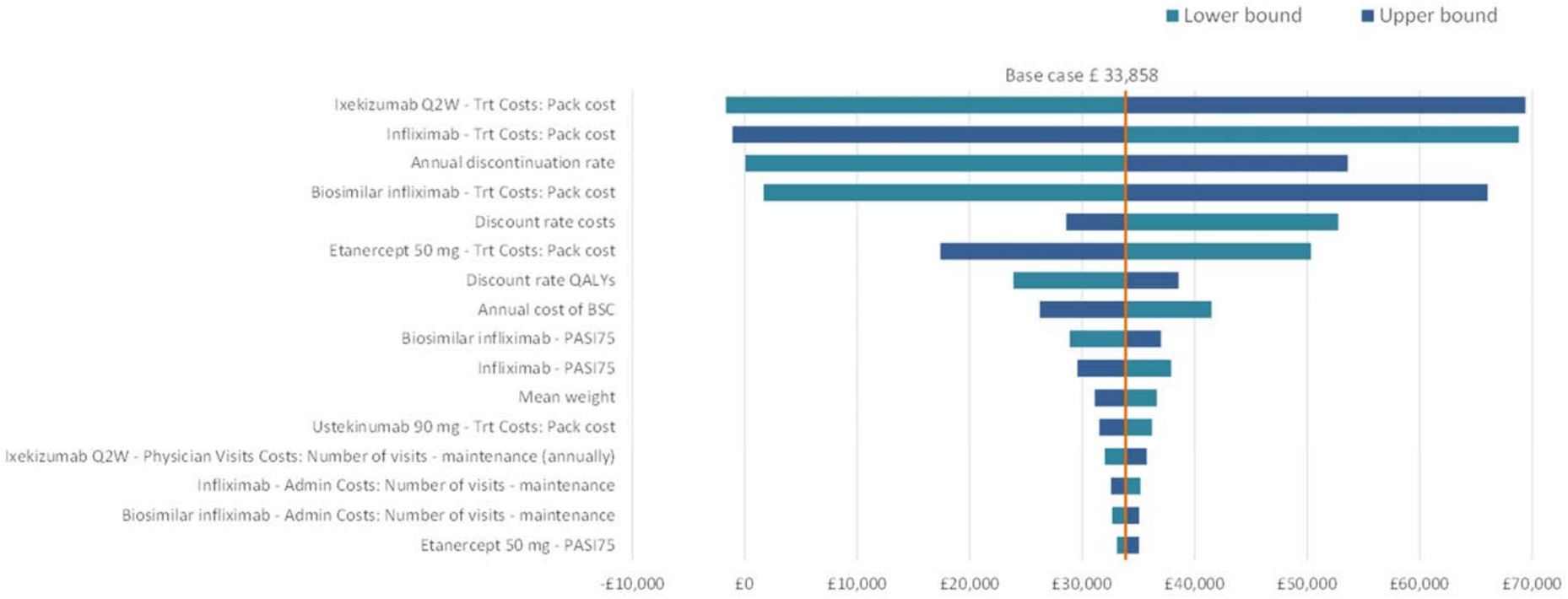
Deterministic sensitivity analyses

One-way sensitivity analyses were carried out for the following input parameters:

- Discount rates *(0%-5%, assumption)*
- Annual discontinuation rate *(lower to upper 95% CI)*
- Number of physician visits *(±1 visit, assumption)*
- Monitoring frequency during the induction period *(±1 test, assumption)*
- Monitoring frequency during treatment maintenance *(±1 test, assumption)*
- Monitoring costs *(±20% of mean value)*
- Cost of best supportive care (BSC) *(±20% of mean value)*
- BSC effectiveness *(lower to upper 95% CI)*
- Response rates *(lower to upper 95% CI)*
- Drug costs *(±20% of mean value)*
- Drug administration *(±1 hour of training / infusion, assumption)*

Sensitivity analyses were conducted for ixekizumab versus etanercept (Figure 5.3) and all other comparisons (Appendix 2). Results were presented in tornado diagrams. The most influential parameters for the pairwise comparisons with etanercept were drug costs, discount rates (both costs and QALYs), and the annual discontinuation rate (Figure 5.3). These results were consistent across all pairwise comparisons (Appendix 2). For the pairwise comparison with the secukinumab sequence, PASI 75 response rates for both ixekizumab and secukinumab were the most influential parameters (ICERs showed dominance).

Figure 5.3: Tornado diagram: ixekizumab sequence versus etanercept sequence



Source: Based on Figure 44 of the CS[1]
BSC = best supportive care; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; Trt = treatment; UST = ustekinumab

Scenario analyses

Structural uncertainty was explored through 12 scenario analyses. Three scenarios modelled alternatives to the sequence approach (scenario A-C) whereas the others maintained the base-case treatment sequencing (scenario D-L). The results of scenario analyses D-L allowed for a direct comparison with the base-case deterministic result as the same sequence approach was maintained (Table 5.19). The ICER of ixekizumab compared to etanercept was most sensitive to alternative response rates for BSC (ICER £50,047) and the use of alternative utility sources. In the latter scenario analysis, the ICER was £16,109 when utilities were based on patients within the fourth quartile DLQI score as used in the York model to £47,235 when utilities were based on all patients in the UNCOVER trials.[99] The company mentioned that in other NICE TAs considering biologic therapies alternative estimates were used for model time horizon, BSC costs, and utility gains (inputs from York model and secukinumab submission, CS Table 114). When using these estimates the ICERs stayed below £30,000.

Table 5.19: Results scenario analyses

Scenario analysis	Details scenario analysis	ICER IXE versus comparator
A: Prior failure on or contraindication to TNF-alpha inhibitor	ADA was used in the first treatment line (based on market share).	IXE sequence (referent) dominated all other sequences
B: Single treatment comparators	Single treatments followed by BSC.	£39,563 (IXE vs. ETN as single treatment)
C: Conventional non-biologic systemic therapies	IXE compared to methotrexate, ciclosporin and BSC as single treatments.	£65,468 (IXE vs. methotrexate)
Deterministic base-case ICER* (IXE vs. ETN)		**£33,858**
D: Model time horizon 10 years		£24,216
E: Effect modification after previous biologic failure	Effect modification (odds ratio 1.24) was used to decrease treatment response and increase monthly discontinuation rates for all biologics from the second-treatment lines onwards. [102]	£38,034
F: Branded prices ETN and INF		£24,923
G: Instantaneously utility gain assignment	Utility gains for responders and non-responders were assigned at the start of the induction period.	£32,337
H: Costs of adverse events	Adverse events included NMSC, other malignancies, and severe infections.	£32,932
I: PASI response criteria: PASI 50 or PASI 90		£30,146; £35,506
J: Alternative utility sources	Utilities based on: 1) all patients in UNCOVER trials (baseline adjusted for EQ-5D-5L); 2) patients with DLQI >10 in UNCOVER trials (baseline unadjusted); 3) utilities based on EQ-PSO bolt-on from patient with DLQI >10 in UNCOVER trials; 4) patients with 4th quartile DLQI score from the	£16,109(York: 4th DLQI) to £47,235 (all patients UNCOVER)

Scenario analysis	Details scenario analysis	ICER IXE versus comparator
	York model; 5) patients with DLQI score >10 from the secukinumab submission	
K: BSC cost	Alternative costing of BSC based on CG153 costing tool 116).[76]	IXE dominated all other sequences
L: BSC effectiveness	Three alternative response rates were included: 1) 0% PASI 50-100; 2) 65% PASI 50 and 0% PASI 75-100; 3) 83% PASI 50 and 0% PASI 75-100.[97]	£30,738 to £50,047 (CS, Table 118)

Source: Based on Table 99-118 of the CS[1]
* Base-case ICER (deterministic result) and ICER of analysis D-L for the ixekizumab sequence versus the etanercept sequence.
ADA = adalimumab; BSC = best supportive care; DLQI = Dermatology Life Quality Index; ETN = etanercept; EQ-PSO = EQ-5D psoriasis bolt-on; ICER = incremental cost-effectiveness ratio; IXE = ixekizumab; NMSC = non-melanoma skin cancer; PASI = Psoriasis Area and Severity Index

Subgroup analyses

The company labelled the population being addressed in the base-case analysis as moderate to severe psoriasis with PASI≥10 and DLQI>10 (Section 5.2.3). In the base-case analysis treatment response was based on the NMA. Because no data could be obtained for all comparators, no restriction was made to DLQI score. The company showed that response rates for ixekizumab in the UNCOVER trials for patients with DLQI>10 did not significantly differ from patients with DLQI ≤10 (CS, Table 46). In addition, a subgroup analysis on utility scores was performed for which a statistically significant different between PASI and baseline DLQI was found (Section 5.2.8).

The company argued that subgroup analyses by clinically defined subgroups was not warranted because treatment response to ixekizumab was consistent across these groups (CS, Section 4.8).[1]

ERG comment: The ERG noted three main issues regarding the company's sensitivity and subgroup analyses.

1. Uncertainty around NHS reference costs was not correctly included in the company's PSA (Clarification Question B18). The company divided the mean value obtained from NHS reference costs by four in order to obtain the standard error (SE) of the estimates. The ERG does not agree with this methodology and asked the company to determine the SE based on the lower and upper bounds of the NHS reference costs. After including this in the PSA, the ICER of ixekizumab compared to etanercept was £32,566, which is comparable to the base-case probabilistic result (£32,815).
2. Probabilistic results for the scenario analyses were not provided which is not in concordance with the NICE methods guide.[121] However, the ERG remarked that it would probably not influence results to a great extent given that the base-case deterministic and probabilistic results are similar (£33,858 and £32,815 respectively).
3. The ERG questioned the use of the DLQI >10 subpopulation for calculating utilities while treatment responses in the model were not based on this subpopulation. A subgroup analysis was performed for the UNCOVER data because DLQI scores and hence subgroup specific estimates were not available for all comparators in the NMA. This analysis showed that PASI response was slightly lower in the DLQI >10 subpopulation (Table 5.20, Clarification Question B1, [33]), while utility estimates per PASI response category were larger (see Table 114 CS, [1]) (Section 5.2.3). The ERG questions the inconsistent use of definitions for moderate to severe psoriasis to inform treatment response and utility gain per PASI response category (Section 5.2.3).

Table 5.20: PASI 75, PASI 90, PASI 100 response rates, primary psoriasis placebo-controlled integrated analysis set by subgroups, ITT population - UNCOVER-1, -2 and -3

Subgroup	p-value (interaction)	PBO N=792 n/Ns (%)	IXE80Q4W N=1,165 n/Ns (%)	IXE80Q2W N=1,169 n/Ns (%)
PASI 75				
DLQI ≤10	[redacted]	[redacted]	[redacted]	[redacted]
DLQI >10		[redacted]	[redacted]	[redacted]
PASI 90				
DLQI ≤10	[redacted]	[redacted]	[redacted]	[redacted]
DLQI >10		[redacted]	[redacted]	[redacted]
PASI 100				
DLQI ≤10	[redacted]	[redacted]	[redacted]	[redacted]
DLQI >10		[redacted]	[redacted]	[redacted]

Footnote: [a] p<0.001 vs. placebo (Risk Difference)
DLQI = Dermatology Life Quality Index; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; Ns = number of patients in each subgroup; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo

In response to clarification questions, additional scenario analyses were performed by the company (Table 5.21). The most influential scenario analysis was the scenario in which treatment specific discontinuation rates were used. This lowered the ICER of the ixekizumab sequence compared to the etanercept sequence to £24,145. The ERG does not consider this analysis plausible as discontinuation rates were not informed properly (Section 5.2.6). Varying the order of biologics within treatment sequences informed by the BADBIR study [26](Tables 5.21 and 5.22) resulted in the highest ICER (£36,885 IXE versus ETN). Not using a separate PASI response category for full clearance (PASI 100), which is more in concordance with previous TAs, increased the ICER to £34,547.

Table 5.21: ICERs of first line ixekizumab versus etanercept (the referent) treatment sequences for additional scenario analyses

Analysis	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER (£) fully incremental
Company base-case*	£150,889	1.45	£6,253.65	0.18	£33,858
Alternative ordering of treatment sequences	£141,116	1.36	£7,317	0.21	£36,885
Treatment specific discontinuation rates	£160,327	2.00	£17,355	0.72	£24,145
Four PASI response categories (PASI 90-100)	£150,889	1.45	£6,254	0.18	£34,547

Source: Based on Tables 13, 15, 21 of the response to the request for clarification [33]
Footnote: * Deterministic results
ICER = incremental cost effectiveness ratio; PASI = Psoriasis Area and Severity Index QALY = quality-adjusted life year

Table 5.22: Alternative ordering of sequences based on BADBIR drug survival rates

1st line	2nd line	3rd line	4th line
Ixekizumab	Ustekinumab 90 mg	Adalimumab	BSC
Adalimumab	Ustekinumab 90 mg	Etanercept	BSC
Etanercept	Ustekinumab 90 mg	Adalimumab	BSC
Infliximab	Ustekinumab 90 mg	Adalimumab	BSC
Secukinumab	Ustekinumab 90 mg	Adalimumab	BSC
Ustekinumab 45 mg	Adalimumab	Etanercept	BSC
Ustekinumab 90 mg	Adalimumab	Etanercept	BSC
BSC = Best supportive care			

5.2.12 Model validation and face validity check

Face validity of the conceptual model was assessed in an advisory board with clinical and health economic experts. The Excel model was developed by an external consultancy company, and internal validation was performed by a second consultancy company. This encompassed a "cell-by-cell technical validation of the model… and the VBA code was checked".1 The company states that cross validation by replicating comparisons from previous submissions are hampered by differences in discount rates, time horizon, treatment sequencing and utility values between submissions, the expansion of the evidence base for biologic treatments and the confidential PAS price for secukinumab. Assessing external and predictive validity is not performed; justified by the absence of relevant trials and observational studies. The company provided an overview of the sources of evidence used to inform input parameters, and states that these sources are ranked highly (1+, 1 or 2, based on the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 13; 122).

ERG comment: The ERG agrees with the general approaches taken to assess face and internal validity. Details regarding results of these checks (what revisions have been made to the conceptual model; what were the results of the check of model concept and VBA code by the second consultancy) are however not provided.

The ERG disagrees with the justifications for omitting cross validation based on the absence of relevant trials and observational studies. Cross validation is a comparison with other cost effectiveness analyses/models, and other TAs are available. In addition, observational studies such as the BADBIR study, contain information on comparators for external validation. The ERG provided a comparison with previous TAs in Table 5.23. It shows that ICERs for single treatment comparisons are higher using the CS model than reported in previous TAs. In comparison with the company's base-case, in TA350 the incremental costs of the biologic therapies versus BSC in the CS are higher, and the incremental QALYs lower.[21] The latter can be explained by the lower utility estimates per PASI response category calculated from UNCOVER data, compared to estimates used in previous TAs. The ERG believes that differences in total and incremental costs between the current and previous assessments might be the consequences of different time horizon and other assumptions which differ between the assessments (e.g. regarding treatment discontinuation rate). Finally, the ERG notes that very little attempt has been undertaken to (statistically) validate the regression model (CS equation 2) that is used to calculate the utility gain. Face validity of the mean utility gains have been checked by comparison to values in the literature and other TAs (Table 5.11).

The model contains information and possibilities that are not used for the current submission, such as the possibility to position ixekizumab in a third or later line for pairwise comparisons, and to compare sequences that consist of more than four lines. Although these possibilities improve the flexibility of

the model, these also increase the complexity of the code considerably. Moreover, the model is programmed in VBA with an Excel user interface, and the variables used in the VBA code were not defined, nor linked to the CS report. This severely hampered the transparency of the model. Upon request by the ERG the company provided a full list of the parameter names used in the Excel model, the VBA code and the description in the CS report. This was helpful in gaining understanding of the technical implementation of the model.

Table 5.23: Single line biologic therapy versus BSC cost effectiveness results from previous TAs compared to the current submission

Comparator versus BSC	Other Technology Appraisal					This submission[3]		
	Source	Estimate from	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Intermittent etanercept	TA103[1]	Company			£37,200			£46,833
		ERG			£65,320			
Infliximab	TA134[1]	Company			£22,240			£73,644
Adalimumab	TA146[1]	Company			£30,500			£53,718
		NICE			£30,500			£53,718
Etanercept		Company			£37,700			£46,833
Infliximab		Company			£42,500			£73,644
Ustekinumab 45 mg	TA180[1]	Company			£41,000			£52,990
Etanercept		Company			£37,200			£46,833
Adalimumab		Company			£37,200			£53,718
Infliximab		Company			£37,200			£73,644
Ustekinumab 45 mg		ERG			£37,200			£52,990
Etanercept	TA350[2]	Company	£2,178	0.156	£13,962	£7,025	0.150	£46,833
Adalimumab		Company	£3,371	0.248	£13,593	£11,818	0.220	£53,718
Infliximab		Company	£19,929	0.384	£51,898	£25,039	0.340	£73,644
Ustekinumab 45 mg		Company	£5,934	0.330	£17,982	£15,703	0.290	£52,990

Footnotes: [1]Taken from table 47 in the ERG report of ID679 (the apremilast TA, Wade et al 2015[120]; [2] Secukinumab ERG report[115]; [3] Calculated by the ERG using the company's base case model[1]

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; QALY = quality adjusted life year; TA = technology appraisal

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from Section 5.2, the ERG defined a new base-case (see Tables 5.26 and 6.1).[1] This base-case included multiple adjustments to the original base-case presented in the CS. These adjustments were subdivided into three categories (derived from Kaltenthaler et al. 2016[123]):

1. Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
2. Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
3. Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

The combination of these corrections/amendments resulted in the ERG base-case (Table 5.24). Additionally, five explorative sensitivity analyses were performed based on the ERG base-case to examine the impact of different assumptions on the model results. The following sections will present the probabilistic results (1,000 simulations) of each amendment and explorative analysis.

One additional treatment sequence, with ixekizumab as second line therapy (adalimumab>ixekizumab Q2W>Biosimilar infliximab>BSC) has been added to the comparators in all ERG amendments and explorative analyses. According to the clinical expert consulted by the ERG, it is plausible that clinicians will more likely use first line treatments with which they have more experience and for which long-term safety data are available (i.e. TNF-α blockers and ustekinumab) before using a new therapy such as ixekizumab (Section 5.2.4). For this additional treatment sequence, Adalimumab has been chosen as first line therapy as it had the largest market share for first line therapy of psoriatic patients in 2014 according to the company.[1]

Table 5.24: Treatment sequence included in ERG base-case and additional analyses

Sequence	1st Line	2nd Line	3rd Line	4th Line
1A	Ixekizumab	Ustekinumab 90 mg	Infliximab	BSC
1B	Adalimumab	Ustekinumab 90 mg	Infliximab	BSC
1C	Etanercept 50 mg	Ustekinumab 90 mg	Infliximab	BSC
1D	Infliximab	Ustekinumab 90 mg	Adalimumab	BSC
1E	Secukinumab	Ustekinumab 90 mg	Infliximab	BSC
1F	Ustekinumab 45 mg	Adalimumab	Infliximab	BSC
1G	Ustekinumab 90 mg	Adalimumab	Infliximab	BSC
1H	Adalimumab	Ixekizumab	Infliximab	BSC
1I*	Adalimumab	Secukinumab	Infliximab	BSC

* only used in an ERG explorative sensitivity analysis, and replace sequence 1G since the multiple treatment comparison allows for a maximum of 8 treatment sequences to be compared simultaneously
BSC = best supportive care; ERG = Evidence Review Group

Fixing errors

1. Inclusion of AEs
    a. Recalculation of AEs unit costs (Section 5.2.9)

       The ERG audited the AEs cost estimates from the company and was not able to reproduce them. Therefore, the ERG recalculated the AEs costs based on the NHS reference costs provided by the company.

    b. Use of correct AEs rates (Section 5.2.7)

       The ERG further audited the AE rates reported by the company and found an error, which was corrected in the ERG base-case.

2. Using lower and upper bounds of NHS reference costs to calculate the standard error (SE) in order to implement costs distribution in the PSA (Section 5.2.11)

   The ERG incorporated the NHS reference costs as probabilistic parameters in the PSA (instead of dividing the mean by 4 as in the company base-case). The SEs obtained in the clarification letter[33] were audited by the ERG. The ERG could not reproduce these SEs, therefore recalculated those (Table 5.25) and implemented these in the PSA.

Table 5.25: Recalculation of SE for the NHS refs costs based on lower and upper quartiles

Currency code	Currency description	Cost in model	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Derived SE	Derived SE (ERG calculation)
WF01A	Non-Admitted Face to Face Attendance, Follow-up (Dermatology)	Intravenous administration (infliximab)	£97.08	£71.87	£106.94	£128.80	£26
-	Dermatology	Physician visit	£101.58	NR*	NR*	£128.80	£26
DAPS05	Haematology	Full blood count	£3.01	£1.87	£3.67	£4.10	£1.33
DAPS04	Clinical Biochemistry	Urea & electrolytes; liver function test, GFR	£1.19	£0.75	£1.38	£1.60	£0.47

* Interquartile range assumed to be equivalent to that of WF01A Non-Admitted Face to Face Attendance, Follow-up (Dermatology)
GFR = glomerular filtration rate; NHS = National Health Service; NR = not reported; SE = standard error

3. Correcting the number of annual administrations of secukinumab in the maintenance period.
   The ERG corrected the number of administrations of secukinumab from 13 to 12 annual administrations in the maintenance period.

Fixing violations

None

Matters of judgement

4. Use of linear utility gains during the induction period instead of assuming no utility gain during the induction period (Section 5.2.2 and 5.2.8)

Table 5.26: Probabilistic company and ERG results

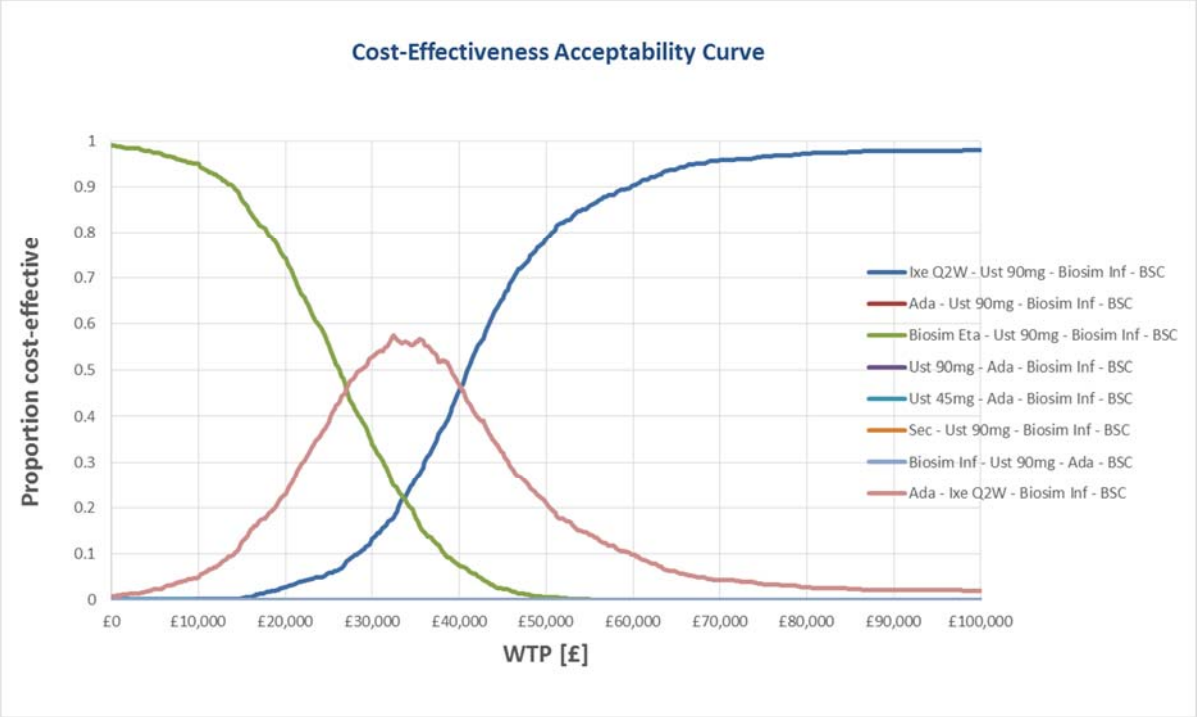
Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
Company base-case								
1C: ETN sequence	£145,831	1.302	-	-	-	£32,541	NR	NR
1F: UST45 sequence	£149,493	1.341	£3,661	0.039	Extendedly dominated	£16,550	NR	NR
1B: ADA sequence	£149,587	1.354	£3,756	0.052	Extendedly dominated	£17,460	NR	NR
1G: UST90 sequence	£149,966	1.357	£4,134	0.055	Extendedly dominated	£15,027	NR	NR
1D: INF sequence	£151,894	1.362	£6,063	0.060	Extendedly dominated	£602	NR	NR
1A:IXE sequence	£151,972	1.491	£6,141	0.189	£32,541	-	NR	NR
1E: SEC sequence	£179,702	1.457	£33,871	0.155	Dominated	Dominated	NR	NR
1H: ADA-IXE sequence	NR	NR	NR	NR	NR	NR	NR	NR
ERG base-case								
1C: ETN sequence	£147,438	1.345	-	-	-	£30,517	£25,532	-
1H:ADA-IXE sequence	£150,574	1.468	£3,136	0.123	£25,532	£39,129	-	£25,532
1F: UST45 sequence	£151,103	1.389	£3,665	0.044	Dominated	£15,024	Dominated	Dominated
1B: ADA sequence	£151,311	1.405	£3,874	0.060	Dominated	£15,281	Dominated	Dominated
1G: UST90 sequence	£151,629	1.408	£4,191	0.063	Dominated	£13,147	Dominated	Dominated
1A: IXE sequence	£153,356	1.539	£5,918	0.194	£39,129	-	-	-
1D: INF sequence	£153,613	1.412	£6,175	0.066	Dominated	Dominated	Dominated	Dominated

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
1E: SEC sequence	£176,999	1.504	£29,561	0.159	Dominated	Dominated	£730,630	£730,630
ADA = adalimumab; ERG = Evidence Review Group; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; NR = not reported; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab								

5.3.1 Probabilistic sensitivity analyses (ERG base-case)

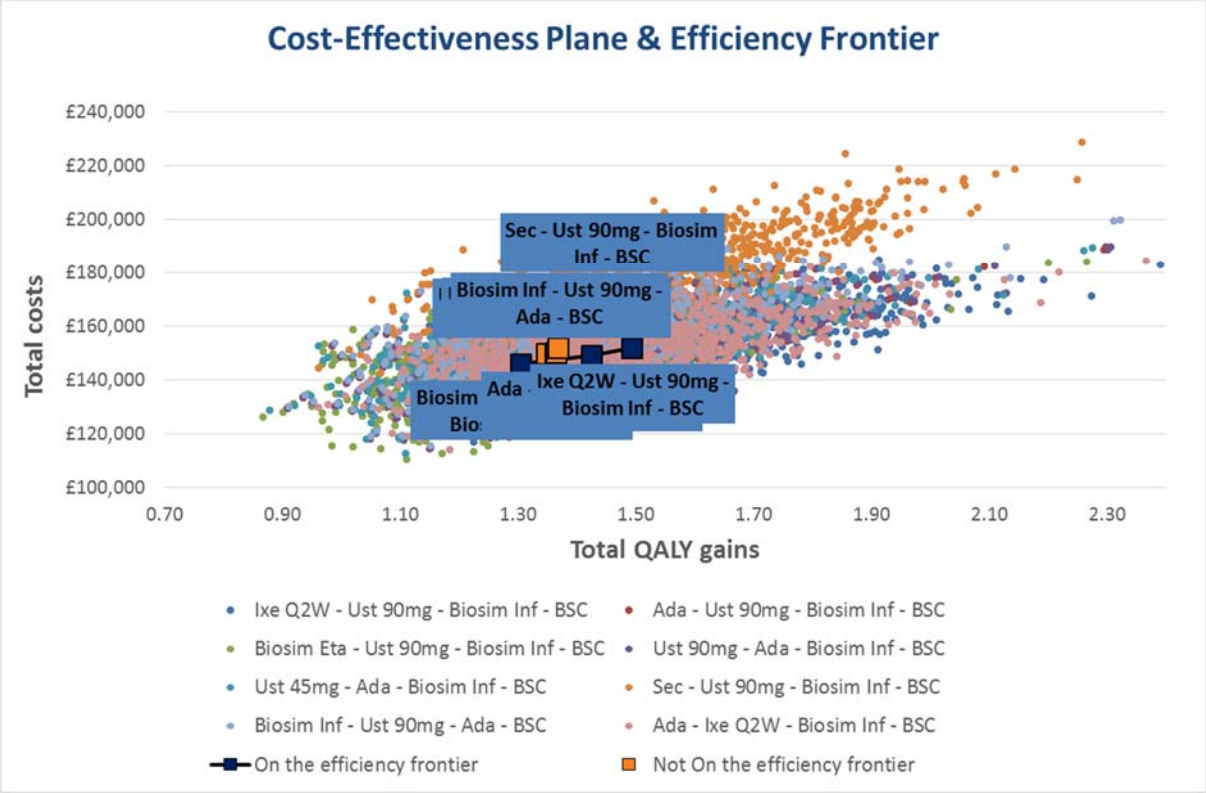
A PSA was performed to capture the parameter uncertainty in the ICER. The scatterplot and CEAC of this analysis are presented in Figures 5.4 and 5.5 respectively. Based on the ERG base-case analysis, thus also including the adalimumab>ixekizumab>infliximab>BSC (sequence 1H), ixekizumab has a probability of 2.8% and 13.2% of being cost effective at the £20,000 and £30,000 thresholds, respectively. Adding the sequence adalimumab>ixekizumab>infliximab>BSC (sequence 1H) provides a cost effective alternative to the treatment sequences proposed by the company. This sequence (sequence 1H) has a 22.8% and 52.9% probability of being cost effective at the £20,000 and £30,000 thresholds, respectively.

Figure 5.4: ERG base-case cost effectiveness acceptability curve



ADA = Adalimumab; BSC = best supportive care; ERG = Evidence Review Group; ETA = Etanercept; INF = infliximab; IXE = ixekizumab; Q2W = once every two weeks; SEC = secukinumab; UST = Ustekinumab; WTP = willingness to pay

Figure 5.5: ERG base-case scatter plot



ADA = Adalimumab; BSC = best supportive care; ERG = Evidence Review Group; ETA = Etanercept; INF = infliximab; IXE = ixekizumab; Q2W = once every two weeks; SEC = secukinumab; UST = Ustekinumab

5.3.2 Exploratory analyses (conditional on ERG base-case)

Additional exploratory sensitivity analyses were performed by the ERG to examine the potential impact of various alternative assumptions on the cost effectiveness estimates. These analyses were performed on the ERG and company base-case and investigated the impact of the following adjustments (Tables 6.2 to 6.4): two of these explorative analyses were already performed by the company on the company base-case analysis and were consequently not reproduced by the ERG (use of the ITT population to estimate utility gains (per PASI response categories) instead of restricting to patients with DLQI>10 and the use of effect modification for second- and third-line biologic treatments) (Table 6.3). The remaining three explorative analyses were performed by the ERG on the company base-case (Table 6.4)

6. Use of the ITT population to estimate utility gains (per PASI response categories) instead of restricting to patients with DLQI>10 (Section 5.2.8)
   The ITT population was used to estimate PASI responses in the NMA while a subset (PASI score > 10 as well as DLQI score > 10) was used to estimate utility gains associated with each PASI response category as it was not possible to perform the NMA for this subset of patients. To mend this inconsistency, an explorative analysis was performed wherein also the ITT population was used for the estimation of utility gains per PASI response category.
7. Use of effectiveness data of ixekizumab Q2W from the DLQI>10 population of the UNCOVER trials
   Similar as the previous explorative analysis, the inconsistency in patient population used to estimate PASI response and utility gain per PASI response category was mended by estimating PASI response for ixekizumab based on the DLQI>10 population of the

UNCOVER trials. It should be noted that the PASI responses for the other biological treatments were still based on the NMA without the DLQI>10 restriction. Therefore, the results should be interpreted with caution.

8. Use of effect modification for second and third line biologic treatments (Section 5.2.6)
   As described in the CS, the effectiveness of biologic therapies might decrease in patients previously treated with biologic therapies. To explore the impact of this assumption, an effect modification is applied to the second-(and subsequent) line of biologic treatments. The same effect modification factor as in the CS is used in this explorative analysis (i.e. 1.24).[1]
9. Varying BSC costs by plus/minus 20%

Since there is a discrepancy between the population from Fonia et al.2010[93] and the BSC population in the current assessment, the ERG does not consider the BSC resource use and cost estimates used in the company base-case (from Fonia et al. 2010[93]) as representative for the current decision problem, i.e. after failure to three biologic therapies. The ERG is however not aware of any study providing the required estimate and Fonia et al.2010[93] has the advantage of being a UK-based study which has been considered as most representative in previous assessments. Given the uncertainty regarding this BSC cost estimate, the impact of varying this variable is explored.

10. Use of alternative treatment sequences
    - Secukinumab as second line therapy in the treatment sequence (sequence 1I (adalimumab>secukinumab>infliximab>BSC) will replace ustekinumab 90 mg sequence 1G)

Given that the treatment sequences were predominantly based on market share and it was uncertain whether this reflected all potentially relevant treatment sequences, an alternative treatment sequence with secukinumab as second line therapy is explored (adalimumab>secukinumab>infliximab>BSC). This treatment sequence has been chosen because adalimumab was the drug with the highest market share as first-line treatment. Furthermore, secukinumab has the same mechanism of action as ixekizumab. This explorative analysis consequently explores whether first or second line ixekizumab provides better value for money than a first or second line treatment with the same mechanism of action on the disease. Another reason to select secukinumab as second line treatment is its high PASI response rates.

The two most influential adjustments on the ERG base-case analysis were the use of the ITT population to determine utility gains and the variation in BSC costs.

5.4 Conclusions of the cost effectiveness section

The economic model described by the company is considered by the ERG to meet the NICE reference case for the most part.

The model structure is similar to models that were submitted in previous assessments and models described in the literature. Although common in this field, the ERG questions the use of relative PASI response to model the cost effectiveness as it may not reflect true differences in costs and health-related quality of life between treatments and treatment sequences. Regarding the model structure, the ERG also questioned the exclusion of the consequences of AEs, the assumption of no utility gain in the induction phase, and equal discontinuation rates for all treatments. Perspective, time horizon and discounting are in concordance with the NICE reference case. The main differences are that the model structure in this assessment considers treatment sequences instead of single treatment, and considered PASI 100, complete clearance of symptoms, as a separate response category. According to the ERG, the treatment sequence approach is superior to considering single treatments as this better reflects the

context in which the treatment will be used. Considering PASI 100 as a separate response category seems an appropriate reflection of the manifestation of the condition. In the base-case this led to a slightly more beneficial ICER than including PASI 100 in the 90-100 category.

The population in the base-case analysis was labelled by the company as biologic naïve patients with prior systemic failure and moderate to severe psoriasis (PASI≥10 and DLQI>10). This is not fully in line with the scope, nor is it fully in line with the populations used to estimate values for input parameters. According to the ERG, the base-case analysis reflects a population for whom biologic treatment is considered. Part of this population will be biologic naïve and the majority of these patients will have failed prior systemic treatment (in the UNCOVER trials combined 74% was biologic naïve and 36% of the patients never used previous systemic therapies).

Each treatment sequence considered in the model consists of three biologic treatments followed by BSC. The biologic treatments included are: adalimumab, etanercept, ustekinumab, secukinumab and infliximab. The ordering of the biologic treatments was based on market share, with the assumption that treatments are not repeated, and alternation of mechanism of action. Ixekizumab was only modelled as a first line treatment. Although the ERG acknowledges that the submission could not possibly include all possible treatment sequences, the ERG thinks it is especially important to also consider a treatment sequence in which ixekizumab is a second line treatment instead of a first line treatment. According to the clinical expert consulted by the ERG, currently, clinicians would likely be inclined to use ixekizumab as a second line of therapy because more experience and safety data with TNF α inhibitors and ustekinumab are available than with ixekizumab.

The difference between the treatment sequences is driven by a difference in PASI response (which determines the proportion of patients eligible for maintenance treatment, and hence utility gain and costs of treatment) and a difference in costs of single treatments. PASI response was based on the NMA, and all usual caveats apply to the validity of comparative effectiveness estimates derived with this methodology. In addition, the ERG concludes that the populations included in the trials in the NMA may not fully reflect the population in the scope, as it was impossible to perform the NMA on patients with PASI≥10 *and* DLQI>10. Furthermore, the assumption that BSC after three lines of biologic treatment equals placebo alongside a (mostly first line) biologic is questionable. It seems however plausible to assume that the treatment response to BSC in that setting, i.e. after failure on three biologic therapies, will be very modest. It is debatable to assume that discontinuation is equal across all treatments, but reliable data to inform treatment specific discontinuation rates were lacking.

Utility gains associated with a PASI response were estimated using regression analysis on the EQ-5D-5L data obtained in the subgroup of patients with DLQI>10 at baseline in the UNCOVER trials. The ERG considered the utility estimates used by the company as uncertain for the following two reasons. First, one regression model was fitted, and alternative models were presented upon request. However, because performance and diagnostic statistics were not provided, the ERG was unable to determine whether the model that was used to determine utility gain per PASI response category is the optimal one. Second, the ERG questions the use of the last-observation-carried-forward method to impute values for patients who discontinued. Because the number of patients this concerned, as well as the reasons for discontinuation, are unknown, the ERG is unable to assess the impact.

In general, the ERG considers the costs to be consistent with previous TAs and adequate for the current decision problem. An area of concern is the costs of BSC. There is a lack of evidence on the costs of BSC in patients who have failed three biologic therapies, which renders the estimate uncertain. In addition, the ERG could not reproduce the estimates of AEs costs. The recalculated

estimates by the ERG are higher for 'Malignancy other than NMSC' and 'Severe Infection' than the ones provided in the CS. The ERG also detected a minor calculation error in the costs of secukinumab.

Although the ERG agrees with the use of the subset of patients with DLQI>10 at baseline from UNCOVER to estimate utility gain, as it describes the population in the scope better, the ERG is concerned about the inconsistency with using the total ITT population to calculate PASI response.

As labelled by the company, base-case results were provided for biologic naïve patients with prior systemic failure and moderate to severe psoriasis (PASI≥10 and DLQI>10). The ICER for the ixekizumab sequence versus the etanercept sequence was £33,858. Other treatment sequences were dominated (secukinumab sequence) or extendedly dominated by the ixekizumab sequence. The PSA was executed and showed that for a WTP threshold above £34,000 the ixekizumab sequence had the highest probability of cost effectiveness.

The ERG fixed some errors in the CS base-case analysis (AEs unit costs and rates, use of lower and upper quartiles of NHS reference costs to implement costs distributions in the PSA, and the number of annual administrations of secukinumab in the maintenance period). In addition, the ERG judged it appropriate to include a sequence with ixekizumab as a second line treatment (adalimumab>ixekizumab Q2W>biosimilar infliximab>BSC; ADA-IXE, sequence 1I), and to apply a linear utility gain during the induction period. In the ERG base-case incremental analysis, the ADA-IXE sequence has an ICER of £25,532 versus the etanercept sequence, and the ixekizumab in the first line sequence has an ICER of £39,129 compared to ADA-IXE. The ADA-IXE sequence has a probability of being cost effective of 22.8% at a threshold of £20,000, and 52.9% at a threshold of £30,000.

Additional exploratory sensitivity analyses were performed to examine the potential impact of various alternative assumptions. These analyses were performed on the ERG base-case, and on the company base-case if the company had not reported the analysis in the CS.

1. Use of the ITT population from the UNCOVER trials to calculate utility gains for PASI responses instead of restricting to patients with DLQI>10,
2. Use of effectiveness data of ixekizumab from the DLQI>10 population of the UNCOVER trials instead of the ITT population (based on the NMA),
3. Use of effect modification (i.e. reduced treatment effectiveness for subsequent treatments),
4. Variation of BSC costs (plus/minus 20%),
5. Replacing the ustekinumab 90 mg sequence with a sequence with secukinumab as second-line therapy (adalimumab>secukinumab>infliximab>BSC)

The choice of utility increment values and BSC costs were the two most influential adjustments on the ERG base-case analysis. All exploratory analyses increased the (fully) incremental ICER of the ixekizumab treatment sequence, except when the BSC costs were increased. In each fully incremental analysis, ADA-IXE was compared to the etanercept sequence, followed by ixekizumab as first line compared to ADA-IXE. All other comparators were (extendedly) dominated. Adding the sequence with secukinumab as second line therapy did not influence this finding. The largest impact on the ICER was observed when using the ITT population from the UNCOVER trials to calculate utility gain per PASI response category. This increased the ICER of the ADA-IXE sequence versus the etanercept sequence to £36,314, and the ICER of ixekizumab in the first line sequence versus ADA-IXE to £55,243. Use of effectiveness data of ixekizumab from the DLQI>10 population of the UNCOVER trials led to higher ICERs for the aforementioned comparisons, £26,499 and £40,308 respectively. Including effect modification increased the ICER of the ADA-IXE sequence versus the etanercept

sequence to £35,191, but decreased the ICER of ixekizumab in the first line sequence versus ADA-IXE to £35,514. Increasing BSC costs decreased both ICERs (£17,532 and £32,673 respectively) and decreasing BSC increased both ICERS (£33,352 and £45,709, respectively). When replacing the ustekinumab 90 mg sequence by the sequence with secukinumab as a second line treatment, the ICERs amount to £25,423 and £38,914, respectively. One should note that secukinumab is available in the NHS under a confidential PAS price arrangement. Consequently, the analyses presented in the current report do not represent the true value for money of secukinumab. A confidential appendix, in which all analyses (both company and ERG analyses) have been reproduced, has been prepared by the ERG.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 shows how each individual change impacts the ICER plus the combined effect of all changes simultaneously. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3. Moreover, the exploratory sensitivity analyses are presented in Table 6.2 (both conditional on the ERG base-case). Appendix 4 and the economic model sent by the ERG contain the technical details on the analyses performed by the ERG.

Table 6.1: ERG base-case, incorporating corrections and amendments identified by the ERG

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
Company base-case								
1C: ETN sequence	£145,831	1.302	-	-	-	£32,541	NR	NR
1F: UST45 sequence	£149,493	1.341	£3,661	0.039	Extendedly dominated	£16,550	NR	NR
1B: ADA sequence	£149,587	1.354	£3,756	0.052	Extendedly dominated	£17,460	NR	NR
1G: UST90 sequence	£149,966	1.357	£4,134	0.055	Extendedly dominated	£15,027	NR	NR
1D: INF sequence	£151,894	1.362	£6,063	0.060	Extendedly dominated	£602	NR	NR
1A:IXE sequence	£151,972	1.491	£6,141	0.189	£32,541	-	NR	NR
1E: SEC sequence	£179,702	1.457	£33,871	0.155	Dominated	Dominated	NR	NR
1H: ADA-IXE sequence	NR	NR	NR	NR	NR	NR	NR	NR
Adding ixekizumab as second-line therapy (sequence 1H)								
1C: ETN sequence	£145,639	1.289	-	-	-	£32,715	£25,081	-
1H: ADA-IXE sequence	£148,473	1.402	£2,835	0.113	£25,081	£44,612	-	£25,081

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
1F: UST45 sequence	£149,188	1.326	£3,550	0.038	Dominated	£17,048	Dominated	Dominated
1B: ADA sequence	£149,334	1.341	£3,695	0.052	Dominated	£17,805	Dominated	Dominated
1G: UST90 sequence	£149,713	1.344	£4,074	0.055	Dominated	£15,298	Dominated	Dominated
1D: INF sequence	£151,554	1.348	£5,916	0.059	Dominated	£1,224	Dominated	Dominated
1A: IXE sequence	£151,709	1.474	£6,070	0.186	£44,612	-		-
1E: SEC sequence	£178,898	1.441	£33,259	0.152	Dominated	Dominated	£777,552	£777,552
Fixing errors 1.to 3.								
1C: ETN sequence	£147,211	1.301	-	-	-	£31,518	£27,456	-
1H: ADA-IXE sequence	£150,315	1.414	£3,104	0.113	£27,456	£37,674	-	£27,456
1F: UST45 sequence	£150,820	1.338	£3,608	0.037	Dominated	£15,304	Dominated	Dominated
1B: ADA sequence	£151,042	1.354	£3,830	0.052	Dominated	£15,401	Dominated	Dominated
1G: UST90 sequence	£151,354	1.357	£4,143	0.055	Dominated	£13,389	Dominated	Dominated

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
1A: IXE sequence	£153,126	1.489	£5,914	0.188	£37,674	-	£37,674	-
1D: INF sequence	£153,291	1.361	£6,080	0.060	Dominated	Dominated	Dominated	Dominated
1E: SEC sequence	£176,543	1.454	£29,332	0.153	Dominated	Dominated	£656,935	£656,935
Matter of judgement: use of linear utility gains during the induction period								
1C: ETN sequence	£145,068	1.331	-	-	-	£32,127	£23,889	-
1H: ADA-IXE sequence	£147,993	1.453	£2,925	0.122	£23,889	£46,501	-	£23,889
1F: UST45 sequence	£148,711	1.376	£3,644	0.045	Dominated	£17,210	Dominated	Dominated
1B: ADA sequence	£148,852	1.391	£3,785	0.060	Dominated	£18,099	Dominated	Dominated
1G: UST90 sequence	£149,233	1.393	£4,166	0.062	Dominated	£15,507	Dominated	Dominated
1D: INF sequence	£151,108	1.397	£6,040	0.066	Dominated	£1,173	Dominated	Dominated
1A: IXE sequence	£151,257	1.524	£6,189	0.193	£46,501	-	£46,501	-
1E: SEC sequence	£178,549	1.489	£33,481	0.158	Dominated	Dominated	£863,207	£863,207

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
ERG base-case								
1C: ETN sequence	£147,438	1.345	-	-	-	£30,517	£25,532	-
1H:ADA-IXE sequence	£150,574	1.468	£3,136	0.123	£25,532	£39,129	-	£25,532
1F: UST45 sequence	£151,103	1.389	£3,665	0.044	Dominated	£15,024	Dominated	Dominated
1B: ADA sequence	£151,311	1.405	£3,874	0.060	Dominated	£15,281	Dominated	Dominated
1G: UST90 sequence	£151,629	1.408	£4,191	0.063	Dominated	£13,147	Dominated	Dominated
1A: IXE sequence	£153,356	1.539	£5,918	0.194	£39,129	-	-	-
1D: INF sequence	£153,613	1.412	£6,175	0.066	Dominated	Dominated	Dominated	Dominated
1E: SEC sequence	£176,999	1.504	£29,561	0.159	Dominated	Dominated	£730,630	£730,630

ADA = adalimumab; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; NR = not reported; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Table 6.2: Exploratory analysis based on the ERG base-case (probabilistic results)

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
1. Use of ITT population for utility increments calculation								
1C: ETN sequence	£147,308	0.875			-	£43,223	£36,314	-
1H:ADA-IXE sequence	£150,523	0.963	£3,215	0.089	£36,314	£55,243	-	£36,314
1F: UST45 sequence	£151,027	0.907	£3,720	0.032	Dominated	£21,515	Dominated	Dominated
1B: ADA sequence	£151,236	0.918	£3,928	0.043	Dominated	£21,761	Dominated	Dominated
1G: UST90 sequence	£151,553	0.919	£4,246	0.045	Dominated	£18,827	Dominated	Dominated
1A: IXE sequence	£153,333	1.014	£6,026	0.139	£55,243	-	-	-
1D: INF sequence	£153,532	0.922	£6,224	0.048	Dominated	Dominated	Dominated	Dominated
1E: SEC sequence	£177,010	0.989	£29,703	0.114	Dominated	Dominated	£1,023,866	£1,023,866
2. Use of effectiveness data of ixekizumab Q2W from the DLQI>10 population of the UNCOVER trials*								
1C: ETN sequence	£147,016	1.328	-	-	-	£31,793	£26,499	-
1H:ADA-IXE sequence	£149,980	1.440	£2,964	0.112	£26,499	£40,308	-	£26,499
1F: UST45 sequence	£150,705	1.374	£3,689	0.045	Dominated	£15,288	Dominated	Dominated
1B: ADA sequence	£150,874	1.388	£3,859	0.060	Dominated	£15,687	Dominated	Dominated
1G: UST90 sequence	£151,192	1.390	£4,176	0.062	Dominated	£13,334	Dominated	Dominated
1A: IXE sequence	£152,783	1.510	£5,768	0.181	£40,308	-	-	-
1D: INF sequence	£153,111	1.394	£6,096	0.066	Dominated	Dominated	Dominated	Dominated
1E: SEC sequence	£176,246	1.486	£29,231	0.157	Dominated	Dominated	£578,608	£578,608
3. Use of effect modification								
1C: ETN sequence	£136,718	1.109			-	£35,330	£35,191	-

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
1H:ADA-IXE sequence	£140,194	1.208	£3,475	0.099	£35,191	£35,514	-	£35,191
1B: ADA sequence	£140,346	1.164	£3,628	0.055	Dominated	£21,026	Dominated	Dominated
1F: UST45 sequence	£140,588	1.163	£3,869	0.054	Dominated	£18,805	Dominated	Dominated
1G: UST90 sequence	£141,077	1.178	£4,358	0.069	Dominated	£16,866	Dominated	Dominated
1A: IXE sequence	£142,838	1.282	£6,119	0.173	£35,514	-		
1D: INF sequence	£143,490	1.185	£6,772	0.076	Dominated	Dominated	Dominated	Dominated
1E: SEC sequence	£162,669	1.252	£25,950	0.143	Dominated	Dominated	£504,000	£504,000
4. Increasing BSC costs by 20%								
1C: ETN sequence	£159,711	1.345			-	£23,083	£17,532	-
1H:ADA-IXE sequence	£161,864	1.468	£2,153	0.123	£17,532	£32,673	-	£17,532
1F: UST45 sequence	£162,964	1.389	£3,254	0.044	Dominated	£8,156	Dominated	Dominated
1B: ADA sequence	£163,037	1.405	£3,326	0.060	Dominated	£8,598	Dominated	Dominated
1G: UST90 sequence	£163,355	1.408	£3,644	0.063	Dominated	£6,339	Dominated	Dominated
1A: IXE sequence	£164,187	1.539	£4,476	0.194	£32,673	-	-	-
1D: INF sequence	£165,339	1.412	£5,628	0.066	Dominated	Dominated	Dominated	Dominated
1E: SEC sequence	£188,056	1.504	£28,345	0.159	Dominated	Dominated	£724,174	£724,174
4. Decreasing BSC costs by 20%								
1C: ETN sequence	£135,135	1.347			-	£37,911	£33,352	
1F: UST45 sequence	£139,167	1.390	£4,032	0.043	Extendedly dominated	£21,769	£246	Extendedly dominated
1H:ADA-IXE	£139,186	1.469	£4,052	0.121	£33,352	£45,709	-	£33,352

Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
sequence								
1B: ADA sequence	£139,483	1.405	£4,348	0.058	Dominated	£21,945	Dominated	Dominated
1G: UST90 sequence	£139,800	1.408	£4,665	0.061	Dominated	£19,948	Dominated	Dominated
1D: INF sequence	£141,806	1.412	£6,671	0.064	Dominated	£4,891	Dominated	Dominated
1A: IXE sequence	£142,432	1.540	£7,297	0.192	£45,709	-	-	
1E: SEC sequence	£165,996	1.505	£30,861	0.158	Dominated	Dominated	£735,625	£735,625
5. Alternative treatment sequence (secukinumab as second-line therapy (sequence 1I))								
1C: ETN sequence	£147,456	1.341			-	£30,485	£25,423	-
1H:ADA-IXE sequence	£150,546	1.462	£3,090	0.122	£25,423	£38,914	-	£25,423
1F: UST45 sequence	£151,062	1.383	£3,606	0.042	Dominated	£15,238	Dominated	Dominated
1B: ADA sequence	£151,287	1.399	£3,831	0.058	Dominated	£15,373	Dominated	Dominated
1A: IXE sequence	£153,386	1.535	£5,931	0.195	£38,914	-	-	-
1D: INF sequence	£153,594	1.405	£6,139	0.064	Dominated	Dominated	Dominated	Dominated
1I: ADA-SEC sequence	£171,508	1.427	£24,053	0.086	Dominated	Dominated	Dominated	Dominated
1E: SEC sequence	£177,036	1.500	£29,581	0.159	Dominated	Dominated	£705,037	£705,037

[*] For this sensitivity analysis, all variables were made probabilistic except the PASI response rates of ixekizumab

ADA = adalimumab; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; NR = not reported; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Table 6.3: Exploratory analyses based on the company base-case (performed by the company, deterministic results)

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs. comparator
1. Use of ITT population for utility increments calculation						
1C: ETN sequence	£144,635	0.82	-	-	-	£47,235
1E: UST45 mg sequence	£148,218	0.85	£3,583	0.03	Extendedly dominated	£25,460
1B: ADA sequence	£148,350	0.86	£3,715	0.04	Extendedly dominated	£26,749
1F: UST 90 mg sequence	£148,719	0.86	£4,083	0.04	Extendedly dominated	£23,366
1D: INF sequence	£150,350	0.87	£5,714	0.04	Extendedly dominated	£6,003
1A: IXE sequence	£150,889	0.95	£6,254	0.13	£47,235	N/A
1G: SEC sequence	£177,101	0.93	£32,466	0.11	Dominated	Dominated
3. Use of effect modification						
1C: ETN sequence	£134,937	1.05	-	-	-	£38,034
1B: ADA sequence	£138,426	1.10	£3,488	0.05	Extendedly dominated	£23,940
1E: UST45 mg sequence	£138,768	1.10	£3,831	0.05	Dominated	£20,974
1F: UST 90 mg sequence	£139,232	1.11	£4,294	0.06	Extendedly dominated	£19,500
1A: IXE sequence	£141,260	1.22	£6,322	0.17	£38,034	N/A
1D: INF sequence	£141,351	1.12	£6,413	0.07	Dominated	Dominated
1E: SEC sequence	£163,488	1.19	£28,551	0.14	Dominated	Dominated

Source: Tables 105 and 115 of the CS[1]

ADA = adalimumab; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; NR = not reported; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

Table 6.4: Exploratory analyses based on the company base-case (performed by the ERG, probabilistic results)

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs. comparator
2. Use of effectiveness data of ixekizumab Q2W from the DLQI>10 population of the UNCOVER trials*						
1C: ETN sequence	£146,134	1.308	-	-	-	£33,246
1E: UST45 sequence	£149,741	1.346	£3,607	0.038	Extendedly dominated	£16,426
1B: ADA sequence	£149,862	1.361	£3,729	0.052	Extendedly dominated	£17,383
1F: UST90 sequence	£150,244	1.364	£4,111	0.056	Extendedly dominated	£14,687
1A: IXE sequence	£152,036	1.486	£5,903	0.178	£33,246	-
1D: INF sequence	£152,193	1.368	£6,060	0.060	Dominated	Dominated
1E: SEC sequence	£180,093	1.463	£33,959	0.154	Dominated	Dominated
4. Increasing BSC costs by 20%						
1C: ETN sequence	£158,360	1.308			-	£24,630
1B: ADA sequence	£161,558	1.361	£3,198	0.052	Extendedly dominated	£10,603
1E: UST45 sequence	£161,569	1.346	£3,209	0.038	Dominated	£9,499
1F: UST90 sequence	£161,940	1.364	£3,580	0.056	Extendedly dominated	£7,971
1A: IXE sequence	£162,998	1.497	£4,638	0.188	£24,630	-
1D: INF sequence	£163,889	1.368	£5,529	0.060	Dominated	Dominated
1E: SEC sequence	£191,112	1.463	£32,752	0.154	Dominated	Dominated
4. Decreasing BSC costs by 20%						
1C: ETN sequence	£133,428	1.302	-	-	-	£40,274
1E: UST45 sequence	£137,415	1.340	£3,987	0.037	Extendedly dominated	£23,703
1B: ADA sequence	£137,698	1.355	£4,270	0.053	Extendedly dominated	£24,286
1G: UST90 sequence	£138,075	1.358	£4,647	0.056	Extendedly dominated	£21,989
1D: INF sequence	£139,979	1.362	£6,550	0.060	Extendedly dominated	£7,807
1A: IXE sequence	£140,973	1.490	£7,544	0.187	£40,274	-

Sequence	Total costs	Total QALY gain	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER (£): IXE sequence vs. comparator
1E: SEC sequence	£168,166	1.455	£34,738	0.152	Dominated	Dominated
5. Alternative treatment sequence (secukinumab as second-line therapy (sequence 1I))						
1C: ETN sequence	£145,464	1.292			-	£32,766
1E: UST45 sequence	£149,136	1.332	£3,671	0.040	Extendedly dominated	£16,749
1B: ADA sequence	£149,240	1.346	£3,776	0.054	Extendedly dominated	£17,741
1G: UST90 sequence	£149,618	1.349	£4,154	0.057	Extendedly dominated	£15,257
1D: INF sequence	£151,498	1.353	£6,034	0.061	Extendedly dominated	£932
1A: IXE sequence	£151,616	1.480	£6,152	0.188	£32,766	-
1I:ADA-SEC sequence	£172,679	1.373	£27,215	0.081	Dominated	Dominated
1E: SEC sequence	£178,942	1.446	£33,478	0.153	Dominated	Dominated

[*] For this sensitivity analysis, all variables were made probabilistic except the PASI response rates of ixekizumab

ADA = adalimumab; ERG = Evidence Review Group; ETN = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; NR = not reported; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

7. END OF LIFE

The CS does not discuss issues regarding end of life criteria and the ERG considers this intervention does not meet the end of life criteria.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

The evidence regarding clinical effectiveness was based on three randomised controlled trials comparing the efficacy and safety of ixekizumab to placebo in patients with moderate to severe plaque psoriasis. In addition, the UNCOVER-2 and UNCOVER-3 studies included an active comparator (etanercept) arm. The data available indicate that ixekizumab is more efficacious in the treatment of moderate to severe plaque psoriasis in adults than placebo and etanercept. There were statistically significant increases in sPGA (0,1) and PASI 75 response rates for patients treated with ixekizumab compared with placebo at week 12 ($p<0.001$ for all comparisons). Furthermore, the improvements in PASI response rate appeared to be maintained for up to 60 weeks during of the long-term extension period. Health-related quality of life improved compared to baseline in significantly more patients with ixekizumab than with placebo and etanercept. The relative performance of ixekizumab in difficult-to-treat areas, including nails, scalp and palmoplantar areas is broadly more efficacious than placebo and etanercept. However, the improvement of psoriasis symptoms of the face which is included in the final scope has not been reported in any of the UNCOVER studies. Ixekizumab was generally well-tolerated in the UNCOVER trials.

It should be noted that the populations in the UNCOVER trials and the other studies used to inform the NMA were not fully in line with the final scope. In the CS, *moderate to severe* psoriasis was defined as a total PASI score of 10 or more and a DLQI score of more than 10. However, the patients recruited in the UNCOVER trails were those with PASI score of more than 12 and no restriction related to DLQI. The patients recruited in the NMA trials were not always those with PASI score of 10 or more and their baseline DLQI scores were not clear.

The economic model described by the company is considered by the ERG to meet the NICE reference case for most part. The model structure is similar to models that were submitted in previous assessments and models described in the literature. Although common in this field, the ERG questions the use of relative PASI response to model the cost effectiveness as it may not reflect true differences in costs and health-related quality of life between treatments and treatment sequences. The model uses a treatment sequencing approach, which the ERG regards as superior to comparing single treatments. Although the ERG acknowledges that the submission could not possibly include all possible treatment sequences, the ERG thinks it is especially important to also consider a treatment sequence in which ixekizumab is a second line treatment instead of a first line treatment. In the base-case analysis, it is assumed that treatment response does not depend on the position in the treatment sequence. Although evidence suggests this may be the case for treatment with different mechanisms of action, or when patients discontinue due to intolerance, this remains an area of uncertainty.

The population in the base-case analysis was labelled by the company as biologic naïve patients with prior systemic failure and moderate to severe psoriasis (PASI≥10 and DLQI>10). This is not fully in line with the scope, nor is it fully in line with the populations used to estimate values for input parameters, most importantly the PASI response. The PASI responses were based on the NMA, and study population included could not be restricted to PASI≥10 *and* DLQI>10. Apart from the population in the NMA, it is important to note that all usual caveats apply to the validity of comparative effectiveness estimates derived with this methodology. In addition, the ERG considered the estimates of utility gain per PASI response and BSC costs uncertain.

In the company's base-case analysis the ICER for the ixekizumab sequence versus the etanercept sequence was £33,858 (deterministic results). Other treatment sequences were dominated (secukinumab sequence) or extendedly dominated by the ixekizumab sequence. In the ERG base case, the sequence with ixekizumab as a second line treatment after adalimumab (ADA-IXE) has an ICER of £25,532 versus the etanercept sequence, and the ixekizumab in the first line sequence has an ICER of £39,129 compared to ADA-IXE (probabilistic results). Explorative analyses showed that alternative assumptions regarding the population to derive utility estimates and costs of BSC were most influential.

8.2 Strengths and limitations of the assessment

The CS report was generally well written. The treatment sequencing approach adopted by the company is superior to comparing single treatments. An NMA was used to inform treatment response instead of naïve comparison of study arms. Given the company's later clarification that non-RCT evidence was not actively sought, the ERG conducted a small independent clinical effectiveness search combining the condition and drugs facets with a validated RCT filter. Screening a sample of 600 titles and abstracts of identified references, the ERG did not identify any further relevant papers.

Insufficient details were reported on how the inclusion screening, data extraction and quality assessment was done. This could be a limitation of the review, e.g. if relevant studies were missed or incorrect study details were extracted by a single reviewer only, i.e. not by at least two independent reviewers as it is best practice.

The ERG notes that there is no agreed consensus on diagnostic criteria or tests available to set a threshold between moderate and severe in current clinical guideline. However, it should be noted again that the populations in the UNCOVER trials and the other studies used to inform the NMA were not fully in line with the final scope. In addition, results for one outcome defined in the final scope, psoriasis symptoms of the face, have not been reported.

Not all relevant treatment sequences were included, especially omitting a sequence with ixekizumab as second line treatment was not realistic. The population in the base-case analysis did not reflect the scope and was not always consistent with the sources used to inform input parameters. The Excel model was overly complicated and not transparent. The population in the studies included in the NMA does not exactly reflect the population in the scope.

9. REFERENCES

[1] Eli Lilly and Company Limited. *Ixekizumab for the treatment of moderate to severe plaque psoriasis [ID:904]: Company submission to National Institute of Health and Clinical Excellence (version 1.0). Single technology appraisal (STA)*: Eli Lilly and Company Limited, July 2016 [accessed 11.7.16]. 333p.

[2] Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* 2015;386(9993):541-51.

[3] Eli Lilly and Company Limited. UNCOVER-1 (RHAZ): Clinical Study Report (CSR). 2016 [Data on file provided by the company].

[4] Eli Lilly and Company Limited. UNCOVER-2 (RHBA): Clinical Study Report (CSR). 2016 [Data on file provided by the company].

[5] Heidenreich R, Rocken M, Ghoreschi K. Angiogenesis drives psoriasis pathogenesis. *Int J Exp Pathol* 2009;90(3):232-48.

[6] Bergboer JG, Zeeuwen PL, Schalkwijk J. Genetics of psoriasis: evidence for epistatic interaction between skin barrier abnormalities and immune deviation. *J Invest Dermatol* 2012;132(10):2320-31.

[7] National Clinical Guideline Centre. *Psoriasis: assessment and management of psoriasis. Clinical Guideline: methods, evidence and recommendations. October 2012. Commissioned by the National Institute for Health and Clinical Excellence [Internet]*. London: National Clinical Guideline Centre, 2012 [accessed 22.7.16] Available from: https://www.nice.org.uk/guidance/cg153/evidence/full-guideline-188351533

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

[9] Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol* 2010;146(8):891-5.

[10] Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. *J Am Heart Assoc* 2013;2(2):e000062.

[11] Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. *Am J Med* 2011;124(8):775 e1-6.

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

[13] Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol* 2014;70(5):871-81 e1-30.

[14] Korman NJ, Zhao Y, Li Y, Liao M, Tran MH. Clinical symptoms and self-reported disease severity among patients with psoriasis: implications for psoriasis management. *J Dermatolog Treat* 2015;26(6):514-9.

[15] Globe D, Bayliss MS, Harrison DJ. The impact of itch symptoms in psoriasis: results from physician interviews and patient focus groups. *Health Qual Life Outcomes* 2009;7:62.

[16] Amatya B, Nordlind K. Focus groups in Swedish psoriatic patients with pruritus. *J Dermatol* 2008;35(1):1-5.

[17] Stinco G, Trevisan G, Piccirillo F, Pezzetta S, Errichetti E, di Meo N, et al. Pruritus in chronic plaque psoriasis: a questionnaire-based study of 230 Italian patients. *Acta Dermatovenerol Croat* 2014;22(2):122-8.

[18] Baker CS, Foley PA, Braue A. Psoriasis uncovered: measuring burden of disease impact in a survey of Australians with psoriasis. *Australas J Dermatol* 2013;54 Suppl 1:1-6.

[19] Lynde CW, Poulin Y, Guenther L, Jackson C. The burden of psoriasis in Canada: insights from the pSoriasis Knowledge IN Canada (SKIN) survey. *J Cutan Med Surg* 2009;13(5):235-52.

[20] Bundy C, Borthwick M, McAteer H, Cordingley L, Howells L, Bristow P, et al. Psoriasis: snapshots of the unspoken: using novel methods to explore patients' personal models of psoriasis and the impact on well-being. *Br J Dermatol* 2014;171(4):825-31.

[21] National Institute for Health and Care Excellence. *Secukinumab for treating moderate to severe plaque psoriasis: NICE technology appraisal guidance 350 [Internet]*. London: NICE, 2015 [accessed 15.3.16] Available from: https://www.nice.org.uk/guidance/ta350

[22] Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. *Arch Dermatol* 2007;143(12):1493-9.

[23] Office for National Statistics. Deaths Registered in England and Wales 2014 [Internet]. ONS, 2015 [accessed 9.8.16]. Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables

[24] Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009;161(5):987-1019.

[25] Salonen S. *The EUROPSO psoriasis patient study: treatment history and satisfaction reported by 17,990 members of european psoriasis patient associations*. Helsinki, Finland: EUROPSO, 2003 [accessed 9.8.16] Available from: http://www.europso.eu/media/archive2/europso_survey_en.pdf

[26] Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, Burden AD, et al. Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol* 2015;135(11):2632-40.

[27] Young Park J, Hyun Rim J, Beom Choe Y, Il Youn J. Facial psoriasis: comparison of patients with and without facial involvement. *J Am Acad Dermatol* 2004;50(4):582-4.

[28] Crowley J. Scalp psoriasis: an overview of the disease and available therapies. *J Drugs Dermatol* 2010;9(8):912-8.

[29] Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. *Br J Dermatol* 2014;170(2):398-407.

[30] Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology* 2005;210(3):194-9.

[31] National Institute for Health and Clinical Excellence. *Single Technology Appraisal. Ixekizumab for treating moderate to severe plaque psoriasis: Final scope [Internet]*. London: NICE, May 2016 [accessed 6.6.16]. 5p. Available from: https://www.nice.org.uk/guidance/GID-TA10063/documents/final-scope

[32] European Medicines Agency (EMA). *Summary of product characteristics (SmPC): Taltz, INN-ixekizumab [Internet]*. London: EMA, 2016 [accessed 9.8.16] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003943/WC500205804.pdf

[33] Eli Lilly and Company Limited. *Ixekizumab for the treatment of moderate to severe plaque psoriasis [ID:904]: response to request for clarification from the ERG*: Eli Lilly and Company Limited, 2016. 43p.

[34] Canadian Agency for Drugs and Technologies in Health. *CADTH peer review checklist for search strategies [Internet]*. Ottawa: CADTH, 2013 [accessed 17.7.13]. 3p. Available from: http://www.cadth.ca/en/resources/finding-evidence-is

[35] National Institute for Health and Care Excellence. *Single Technology Appraisal: specification for manufacturer/sponsor submission of evidence [Internet]*. London: NICE, 2012 [accessed 6.9.16]. 76p. Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Specification-for-manufacturer-sponsor-submission-of-evidence-June-2012.doc

[36] Eli Lilly and Company Limited. *Ixekizumab for the treatment of moderate to severe plaque psoriasis [ID:904]: Appendices to accompany company submission to National Institute of Health and Clinical Excellence (version 1.0). Single technology appraisal (STA)*: Eli Lilly and Company Limited, July 2016 [accessed 11.7.16]. 157p.

[37] National Institute for Health and Care Excellence. *Ixekizumab for the treatment of moderate to severe plaque psoriasis [ID:904]: Clarification letter*. London: NICE, 2016

[38] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

[39] Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials [Internet]*, 2016 [accessed 6.9.16] Available from: http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%202Sep2016v2.pdf

[40] Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med* 2016: Epub 2016 Jun 8.

[41] Eli Lilly and Company Limited. UNCOVER-3 (RHBC): Clinical Study Report (CSR). 2016 [Data on file provided by the company].

[42] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). *Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02) [Internet]*. London: EMEA, 2004 [accessed March 2016] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf

[43] Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. *Dermatologica* 1978;157(4):238-44.

[44] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19(3):210-6.

[45] Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008;159(5):997-1035.

[46] Cardiff University, Department of Dermatology. *Quality of life questionnaires: frequently asked questions (FAQs) [Internet]*, 2016 [accessed 9.8.16] Available from: http://sites.cardiff.ac.uk/dermatology/quality-of-life/frequently-asked-questions-faqs/#44.

[47] Khilji F, Gonzalez M, Finlay A. Clinical meaning of change in Dermatology Life Quality Index scores [Abstr P59]. Presented at British Association of Dermatologists Annual Meeting 2002; 9-11 July 2002; Edinburgh. *Br J Dermatol* 2002;147(Suppl. 62):50.

[48] Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean? *J Invest Dermatol* 2005;125(4):659-64.

[49] Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006;55(4):598-606.

[50] Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008;158(3):558-66.

[51] Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. *Circ Cardiovasc Imaging* 2013;6(1):83-90.

[52] Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008;58(1):106-15.

[53] Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. *J Dermatol* 2010;37(4):299-310.

[54] Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 2003;139(12):1627-32.

[55] Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;349(21):2014-22.

[56] Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005;152(6):1304-12.

[57] van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *Br J Dermatol* 2008;159(5):1177-85.

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

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

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

[61] Thaci D, Blauvelt A, Reich K, Tsai TF, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol* 2015;73(3):400-9.

[62] Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;366(9494):1367-74.

[63] Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007;56(1):31 e1-15.

[64] Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001;357(9271):1842-7.

[65] Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004;51(4):534-42.

[66] Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis: a randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci* 2010;59(1):40-9.

[67] Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chin Med J (Engl)* 2012;125(11):1845-51.

[68] Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010;362(2):118-28.

[69] Igarashi A, Kato T, Kato M, Song M, Nakagawa H. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *J Dermatol* 2012;39(3):242-52.

[70] Zhu X, Zheng M, Song M, Shen YK, Chan D, Szapary PO, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *J Drugs Dermatol* 2013;12(2):166-74.

[71] Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, Shen YK, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci* 2011;63(3):154-63.

[72] Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371(9625):1665-74.

[73] Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371(9625):1675-84.

[74] Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med* 2015;373(14):1318-28.

[75] Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med* 2015;373(2):136-44.

[76] National Institute for Health and Care Excellence. *The assessment and management of psoriasis: NICE clinical guideline 153 [Internet]*. London: NICE, 2012 [accessed 15.3.16] Available from: https://www.nice.org.uk/guidance/CG153/

[77] National Institute for Health and Care Excellence. *Single Technology Appraisal: company evidence submission template [Internet]*. London: NICE, 2015 [accessed 20.7.16]. 28p. Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/specification-for-company-submission-of-evidence-2015-version.docx

[78] Colombo GL, Di Matteo S, Peris K, Fargnoli MC, Esposito M, Mazzotta A, et al. A cost-utility analysis of etanercept for the treatment of moderate-to-severe psoriasis in Italy. *Clinicoecon Outcomes Res* 2009;1:53-9.

[79] Heinen-Kammerer T, Daniel D, Stratmann L, Rychlik R, Boehncke WH. Cost-effectiveness of psoriasis therapy with etanercept in Germany. *J Dtsch Dermatol Ges* 2007;5(9):762-8.

[80] Knight C, Mauskopf J, Ekelund M, Singh A, Yang S, Boggs R. Cost-effectiveness of treatment with etanercept for psoriasis in Sweden. *Eur J Health Econ* 2012;13(2):145-56.

[81] Pan F, Brazier NC, Shear NH, Jivraj F, Schenkel B, Brown R. Cost utility analysis based on a head-to-head Phase 3 trial comparing ustekinumab and etanercept in patients with moderate-to-severe plaque psoriasis: a Canadian perspective. *Value Health* 2011;14(5):652-6.

[82] Anis AH, Bansback N, Sizto S, Gupta SR, Willian MK, Feldman SR. Economic evaluation of biologic therapies for the treatment of moderate to severe psoriasis in the United States. *J Dermatolog Treat* 2011;22(2):65-74.

[83] Sawyer LM, Wonderling D, Jackson K, Murphy R, Samarasekera EJ, Smith CH. Biological therapies for the treatment of severe psoriasis in patients with previous exposure to biological therapy: a cost-effectiveness analysis. *Pharmacoeconomics* 2015;33(2):163-77.

[84] Villacorta R, Hay JW, Messali A. Cost effectiveness of moderate to severe psoriasis therapy with etanercept and ustekinumab in the United States. *Pharmacoeconomics* 2013;31(9):823-39.

[85] Lloyd A, Reeves P, Conway P, Reynolds A, Baxter G. Economic evaluation of etanercept in the management of chronic plaque psoriasis. *Br J Dermatol* 2009;160(2):380-6.

[86] Sizto S, Bansback N, Feldman SR, Willian MK, Anis AH. Economic evaluation of systemic therapies for moderate to severe psoriasis. *Br J Dermatol* 2009;160(6):1264-72.

[87] Shikiar R, Heffernan M, Langley RG, Willian MK, Okun MM, Revicki DA. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. *J Dermatolog Treat* 2007;18(1):25-31.

[88] Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol* 2008;158(3):549-57.

[89] Reich K, Segaert S, Van de Kerkhof P, Durian C, Boussuge MP, Paolozzi L, et al. Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. *Dermatology* 2009;219(3):239-49.

[90] Puig L, Strohal R, Husni ME, Tsai TF, Noppakun N, Szumski A, et al. Cardiometabolic profile, clinical features, quality of life and treatment outcomes in patients with moderate-to-severe psoriasis and psoriatic arthritis. *J Dermatolog Treat* 2015;26(1):7-15.

[91] Pfizer. A phase 3, multi site, randomized, double blind, placebo controlled study of the efficacy and safety comparing CP- 690,550 and etanercept in subjects with moderate to severe chronic plaque psoriasis. NCT01241591. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 [accessed 3.8.16]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01241591.

[92] Novartis Pharmaceuticals. Efficacy and safety of subcutaneous secukinumab (AIN457) for moderate to severe chronic plaque-type psoriasis assessing different doses and dose regimens

(SCULPTURE). NCT01406938. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 3.8.16]. Available from: https://clinicaltrials.gov/ct2/show/NCT01406938.

[93] Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. *Br J Dermatol* 2010;163(4):807-16.

[94] Eedy DJ, Griffiths CE, Chalmers RJ, Ormerod AD, Smith CH, Barker JN, et al. Care of patients with psoriasis: an audit of U.K. services in secondary care. *Br J Dermatol* 2009;160(3):557-64.

[95] Schaefer C, Mamolo C, Cappelleri JC, Le C, Daniel S, Mallbris L, et al. Disease burden, outcomes and costs among adults admitted to hospital in the United Kingdom (UK) due to plaque or erythrodermic psoriasis. *Value Health* 2015;18(7):A425.

[96] Iskandar IY, Ashcroft DM, Warren RB, Yiu ZZ, McElhone K, Lunt M, et al. Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. *Br J Dermatol* 2015;173(2):510-8.

[97] Woods AL, Rutter KJ, Gardner LS, Lewis VJ, Saxena S, George SA, et al. Inpatient management of psoriasis: a multicentre service review to establish national admission standards. *Br J Dermatol* 2008;158(2):266-72.

[98] Agius E, Fleming C, Smith C. Clinical utility of virtual patient follow-up in a tertiary psoriasis service [Abst: P20]. Presented at British Association of Dermatologists 94th Annual Meeting; 1–3 July 2014; Glasgow, U.K. *Br J Dermatol* 2014;171(Suppl 1):27.

[99] Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess* 2006;10(46):1-233, i-iv.

[100] Mauskopf J, Samuel M, McBride D, Mallya UG, Feldman SR. Treatment sequencing after failure of the first biologic in cost-effectiveness models of psoriasis: a systematic review of published models and clinical practice guidelines. *Pharmacoeconomics* 2014;32(4):395-409.

[101] Klaassen KM, van de Kerkhof PC, Pasch MC. Nail Psoriasis, the unknown burden of disease. *J Eur Acad Dermatol Venereol* 2014;28(12):1690-5.

[102] Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol* 2015;172(1):244-52.

[103] Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011;303(1):1-10.

[104] Electronic Medicines Compendium (eMC). Summary of product characteristics: Humira 40 mg/0.8 ml vial for paediatric use [Internet]. 2016 [accessed: 23.8.16]. Available from: https://www.medicines.org.uk/emc/medicine/21201

[105] Electronic Medicines Compendium (eMC). Summary of Product Characteristics: Stelara 45 mg solution for injection [Internet]. 2016 [accessed 23.8.16]. Available from: https://www.medicines.org.uk/emc/medicine/21425

[106] Amgen. Highlights of prescribing information: Enbrel (R) (etanercept) [Internet]. 2015 [accessed: 23.8.15]. Available from: http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf

[107] Reich K, Mrowietz U, Radtke MA, Thaci D, Rustenbach SJ, Spehr C, et al. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res* 2015;307(10):875-83.

[108] Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;54(8):2368-76.

[109] Electronic Medicines Compendium (eMC). Summary of Product Characteristics: Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen [Internet]. 2016 [accessed 23.8.16]. Available from: https://www.medicines.org.uk/emc/medicine/29848

[110] Amgen. Highlights of prescribing information: Enbrel (R) (etanercept). 2015. Available from: http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf

[111] Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;54(8):2368-76.

[112] McGowan J, Sampson M, Lefebvre C. An evidence based checklist for the peer review of electronic search strategies (PRESS EBC). *Evid Based Libr Inf Pract* 2010;5(1):1-6.

[113] Electronic Medicines Compendium (eMC). Summary of Product Characteristics: Stelara 90 mg solution for injection in pre-filled syring [Internet]. 2015 [accessed 23.8.16]. Available from: https://www.medicines.org.uk/emc/medicine/31083

[114] Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D (Discussion Paper 172) [Internet]*. York: Centre for Health Economics, The University of York, 1999 [accessed 23.8.16] Available from: http://www.york.ac.uk/che/pdf/DP172.pdf

[115] Cummins E, Scott N, Cruickshank M, Fraser C, Ormerod A, Brazzelli M. *Secukinumab for treating moderate to severe plaque psoriasis: a single technology appraisal [Internet]*: Aberdeen HTA Group, 2015 [accessed 3.8.16] Available from: https://www.nice.org.uk/guidance/ta350/resources/secukinumab-for-treating-moderate-to-severe-plaque-psoriasis-committee-papers2

[116] Monthly Index of Medical Specialities (MIMS) [Internet]. 2016 [accessed 3.8.16]. Available from: http://www.mims.co.uk/

[117] National Institute for Health and Care Excellence. *Ustekinumab for the treatment of adults with moderate to severe psoriasis: NICE technology appraisal guidance 180 [Internet]*. London: NICE, 2009 [accessed 15.3.16] Available from: https://www.nice.org.uk/guidance/ta180

[118] Department of Health. *NHS reference costs 2014-2015 [Internet]*. London: Department of Health, 2015 [accessed 3.8.16] Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.

[119] Personal Social Services Research Unit. Unit Costs of Health and Social Care 2015. Canterbury: University of Kent, 2015 [accessed 3.8.16]. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/

[120] Wade R, Hinde S, Yang H, Harden M, Palmer S, Woolacott N, et al. *Apremilast for treating moderate to severe plaque psoriasis: a single technology appraisal [Internet]* CRD and CHE Technology Assessment Group, 2015 [accessed 25.8.16] Available from: https://www.nice.org.uk/guidance/TA368/documents/psoriasis-plaque-moderate-to-severe-apremilast-id679-committee-papers-4

[121] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed 14.4.16]. 93p. Available from: http://publications.nice.org.uk/pmg9

[122] Kaltenthaler E, Tappenden P, Paisley S, Squires H. *NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-*

effectiveness models[Internet]: NICE Decision Support Unit, 2011 [accessed 23.8.16] Available from: http://www.nicedsu.org.uk/TSD%2013%20model%20parameters.pdf.

[123] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

[124] Pharmaceutical Benefits Advisory Committee. *Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3) [Internet]*. Canberra: Department of Health and Aging (Australian Government), 2008 [accessed 6.9.16] Available from: https://pbac.pbs.gov.au/content/information/archived-versions/pbac-guidelines-v4.3-2008.pdf

Appendix 1: Additional search conducted by the ERG

In order to test whether the approach reported in the Ovid strategy in Table 1 Appendix 2[1] may have led to loss of potentially relevant records, the ERG ran a test search using just the Embase database. The ERG reran the first 6 lines of the company's clinical effectiveness search as reported in the response to clarification. The ERG then combined the condition and drugs facets reported in lines #1 and #2 and with a recognised trials filter. The ERG then 'not'ed' the original set of results retrieved by the Company search against this new set of results to identify those records missed within Embase.

Embase (OvidSP): 1974-2016/08/23

Searched: 24.8.16

1 Psoriasis.ti,ab. (45567)

2 (Ixekizumab or acitretin or apremilast or adalimumab or brodalumab or c#closporin* or etanercept or fumaric acid esters or guselkumab or infliximab or methotrexate or namilumab or ponesimod or PUVA or secukinumab or tildrakizumab or tofacitinib or ustekinumab).mp. (309494)

3 (PASI or PGA or sPGA or IGA or SF-36 or DLQI or patient global assessment or skin pain VAS or QIDS or EQ-5D or HADS or depression or WPAI or work productivity or productivity or healthcare resource utili#ation or itch or itch VAS or itch NRS).mp. (687247)

4 (Infection* or adverse event* or death or malignancy or immunogenicity or injection site reaction* or infusion reaction* or withdrawal* or severe adverse effect* or serious adverse effect* or Treatment-emergent adverse events or cardiovascular event*).mp. (3420723)

5 3 or 4 (4016793)

6 1 and 2 and 5 (5695) *Lines 1-6 of original CS strategy*

7 Random$.tw. or clinical trial$.mp. or exp health care quality/ (3918282)

8 animal/ (1794358)

9 animal experiment/ (1956628)

10 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6322901)

11 or/8-10 (6322901)

12 exp human/ (17537708)

13 human experiment/ (357321)

14 or/12-13 (17539158)

15 11 not (11 and 14) (4956477)

16 7 not 15 (3730998)

17 1 and 2 and 16 (5335) *CS condition and drugs facet combined with an RCT filter*

18 17 not 6 (2189) *Records missed in Embase by the CS approach.*

Trial filter: Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc 2006;94(1):41-7.

Appendix 2: Disaggregated results of QALYs and costs by health state and cost category

Table A.1: Summary of QALY gain by health state

Health state	QALY intervention (1A)	QALY comparator (1B-G)	Increment	Absolute increment	% absolute increment
	1A: IXE sequence	*1B: ADA sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.36	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.28	[redacted]	[redacted]	[redacted]
Total	1.45	1.32	0.13	0.28	100%
	1A: IXE sequence	*1C: ETN sequence*			
PASI<50	[redacted]	0.27	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.35	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.36	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.25	[redacted]	[redacted]	[redacted]
Total	1.45	1.27	0.18	0.33	100%
	1A: IXE sequence	*1D: INF sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.35	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.29	[redacted]	[redacted]	[redacted]
Total	1.45	1.33	0.13	0.25	100%
	1A: IXE sequence	*1E: SEC sequence*			
PASI<50	[redacted]	0.25	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.34	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.43	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.37	[redacted]	[redacted]	[redacted]
Total	1.45	1.42	0.03	0.10	100%
	1A: IXE sequence	*1F: UST45 mg sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.36	[redacted]	[redacted]	[redacted]

Health state	QALY intervention (1A)	QALY comparator (1B-G)	Increment	Absolute increment	% absolute increment
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.26	[redacted]	[redacted]	[redacted]
Total	1.45	1.30	0.15	0.30	100%
	1A: IXE sequence	*1G: UST90 mg sequence*			
PASI<50	[redacted]	0.26	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	0.03	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	0.36	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	0.39	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	0.28	[redacted]	[redacted]	[redacted]
Total	1.45	1.32	0.13	0.27	100%

Source: based on Table 93 of the CS[1]
ADA = adalimumab; CS = company submission; ETN = etanercept; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; SEC = secukinumab; UST = ustekinumab

Table A.2: Summary of costs by health state

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
	1A: IXE sequence	*1B: ADA sequence*			
PASI<50	[redacted]	£53,685	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,471	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£30,952	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£32,793	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£23,449	[redacted]	[redacted]	[redacted]
Total	£150,889	£148,350	£2,539	£22,672	100.00%
	1A: IXE sequence	*1C: ETN sequence*			
PASI<50	[redacted]	£55,976	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,492	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£29,442	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£30,026	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£21,700	[redacted]	[redacted]	[redacted]
Total	£150,889	£144,635	£6,254	£27,991	100.00%
	1A: IXE sequence	*1D: INF sequence*			
PASI<50	[redacted]	£53,697	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,494	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£30,602	[redacted]	[redacted]	[redacted]

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
PASI 90-100	[redacted]	£33,539	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£25,018	[redacted]	[redacted]	[redacted]
Total	£150,889	£150,350	£539	£20,043	100.00%
	1A: IXE sequence	*1E: SEC sequence*			
PASI<50	[redacted]	£50,588	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,342	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£35,437	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£44,944	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£38,790	[redacted]	[redacted]	[redacted]
Total	£150,889	£177,101	-£26,212	£26,212	100.00%
	1A: IXE sequence	*1F: UST 45 mg sequence*			
PASI<50	[redacted]	£54,421	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,672	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£31,280	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£32,429	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£22,417	[redacted]	[redacted]	[redacted]
Total	£150,889	£148,218	£2,671	£25,335	100.00%
	1A: IXE sequence	*1G: UST 90 mg sequence*			
PASI<50	[redacted]	£53,770	[redacted]	[redacted]	[redacted]
PASI 50-75	[redacted]	£7,531	[redacted]	[redacted]	[redacted]
PASI 75-90	[redacted]	£30,761	[redacted]	[redacted]	[redacted]
PASI 90-100	[redacted]	£32,903	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	£23,754	[redacted]	[redacted]	[redacted]
Total	£150,889	£148,719	£2,170	£22,213	100.00%

Source: based on Table 94 of the CS[1]
ADA = adalimumab; CS = company submission; ETN = etanercept; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; SEC = secukinumab; UST = ustekinumab. Adapted from PBAC guidelines[124]

Table A.3: Summary of predicted resource use by category of cost

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
	1A: IXE sequence	*1B: ADA sequence*			
Treatment costs	[redacted]	£82,185	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£1,958	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,377	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£187	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,373	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,270	[redacted]	[redacted]	[redacted]
Total	£150,889	£148,350	£2,539	£11,648	100.00%
	1A: IXE sequence	*1C: ETN sequence*			
Treatment costs	[redacted]	£75,935	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£2,015	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,169	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£178	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,411	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£62,928	[redacted]	[redacted]	[redacted]
Total	£150,889	£144,635	£6,254	£20,867	100.00%
	1A: IXE sequence	*1D: INF sequence*			
Treatment costs	[redacted]	£83,873	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£2,389	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,100	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£188	[redacted]	[redacted]	[redacted]

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,530	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,270	[redacted]	[redacted]	[redacted]
Total	£150,889	£150,350	£539	£10,824	100.00%
	1A: IXE sequence	*1E: SEC sequence*			
Treatment costs	[redacted]	£113,989	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£1,888	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,706	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£202	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,323	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£56,992	[redacted]	[redacted]	[redacted]
Total	£150,889	£177,101	-£26,212	£26,423	100.00%
	1A: IXE sequence	*1F: UST45 mg sequence*			
Treatment costs	[redacted]	£81,253	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£1,969	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,322	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£184	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,601	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,890	[redacted]	[redacted]	[redacted]
Total	£150,889	£148,218	£2,671	£13,496	100.00%
	1A: IXE sequence	*1G: UST90 mg sequence*			
Treatment costs	[redacted]	£82,338	[redacted]	[redacted]	[redacted]

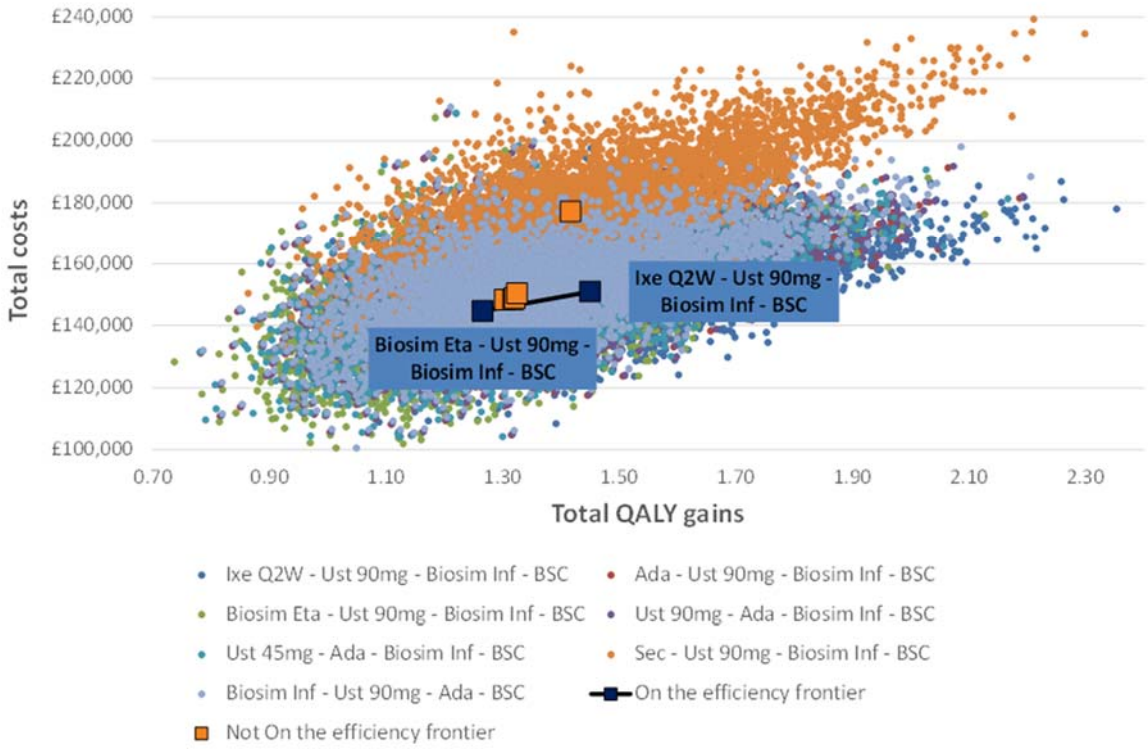
Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Administration costs	[redacted]	£1,956	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,378	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£187	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Non responders costs	[redacted]	£1,590	[redacted]	[redacted]	[redacted]
BSC	[redacted]	£60,270	[redacted]	[redacted]	[redacted]
Total	£150,889	£148,719	£2,170	£11,709	100.00%

Source: based on Table 95 of the CS[1]

ADA = adalimumab; CS = company submission; ETN = etanercept; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; SEC = secukinumab; UST = ustekinumab.

Appendix 3: Scatterplot, CEAC and CEAF of the company base-case analysis and tornado diagram of the DSAs

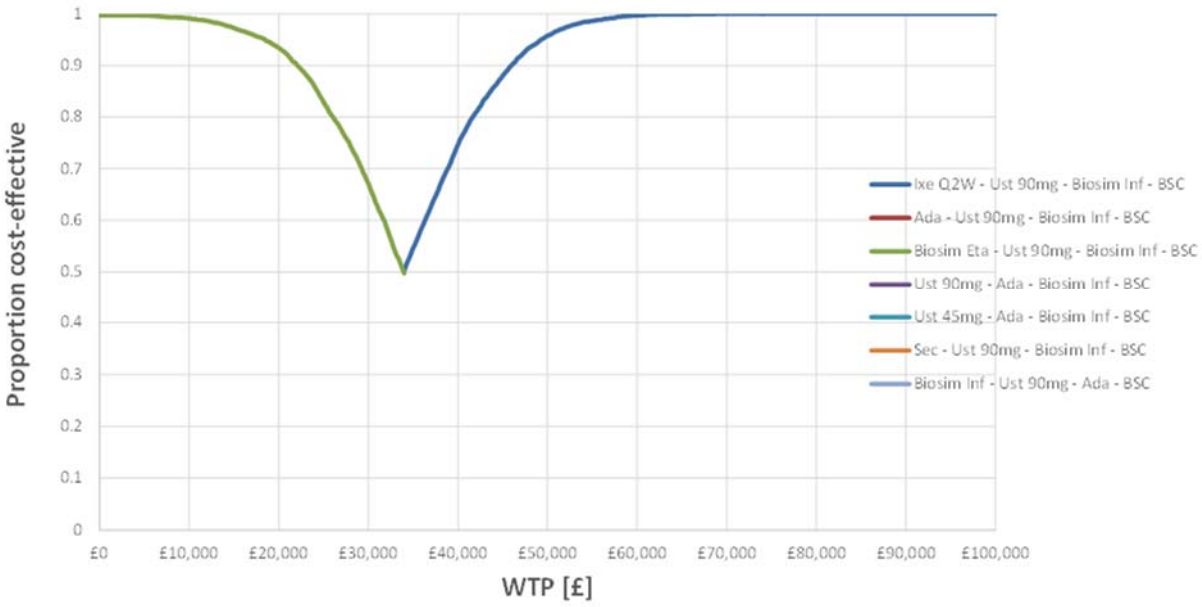
Figure A.1: CE plane



Source: Based on Figure 40 of the CS[1]

ADA = adalimumab; BSC = best supportive care; CE = cost-effectiveness; CS = company submission; ETN = etanercept; INF = infliximab; IXE = ixekizumab; QALYs = quality-adjusted life years; SEC = secukinumab; UST = ustekinumab

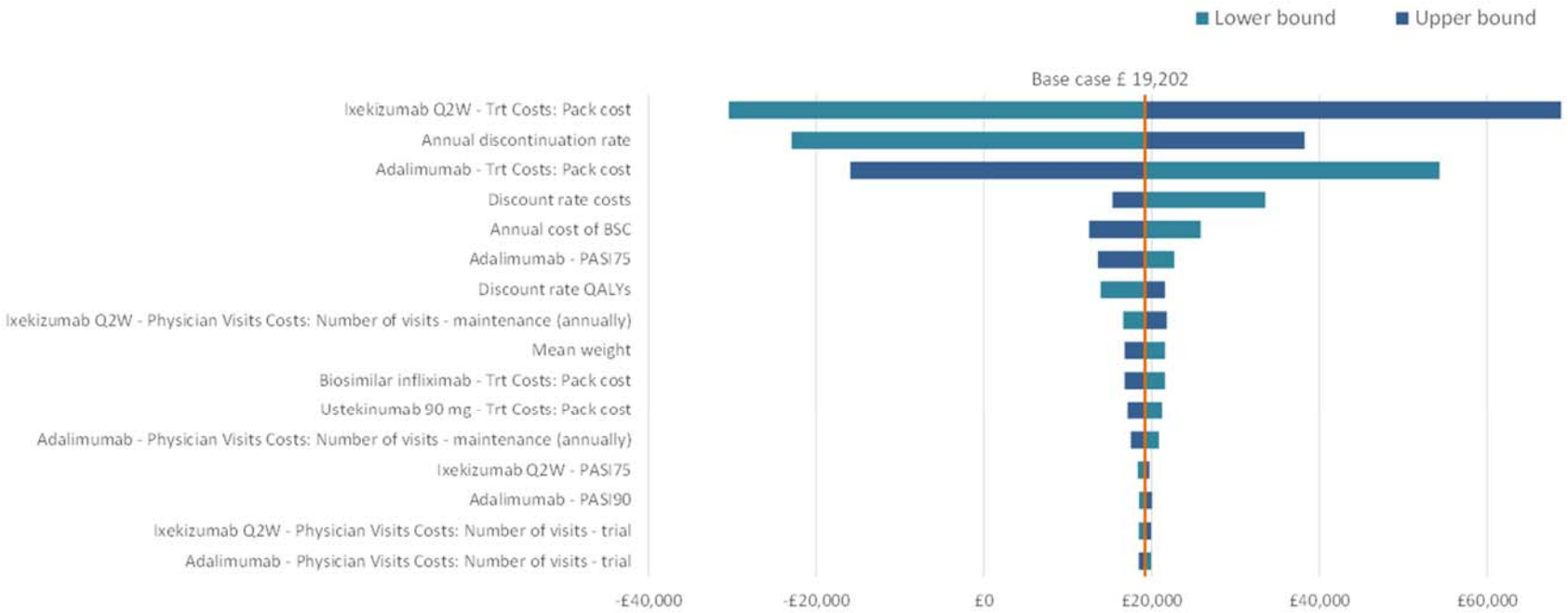
Figure A.2: CEAF



Source: Based on Figure 42 of the CS[1]

ADA = adalimumab; BSC = best supportive care; CEAF = cost-effectiveness acceptability frontier; CS = company submission; ETN = etanercept; INF = infliximab; IXE = ixekizumab; SEC = secukinumab; UST = ustekinumab; WTP = willingness to pay

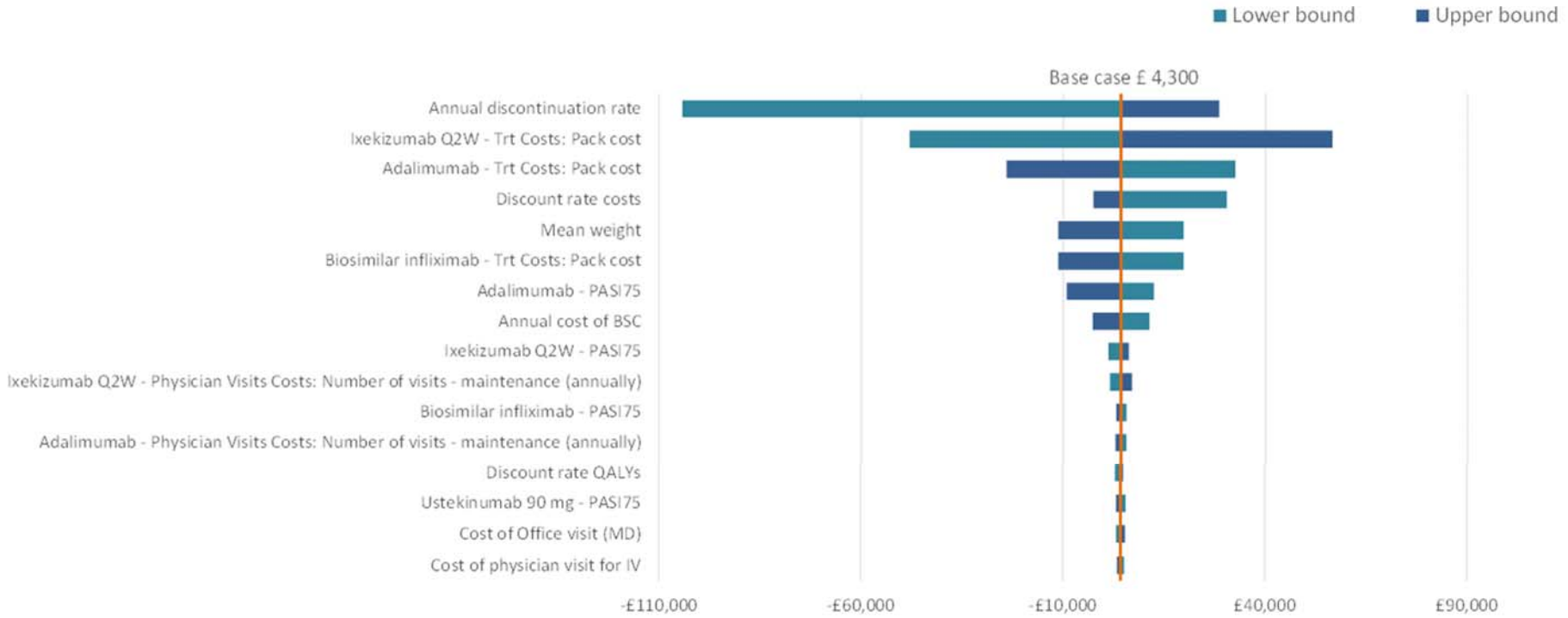
Figure A.3: Tornado diagram: ixekizumab sequence versus adalimumab sequence



Source: Based on Figure 43 of the CS[1]

ADA = adalimumab; BSC = best supportive care; CEAF = cost-effectiveness acceptability frontier; CS = company submission; ETN = etanercept; INF = infliximab; IXE = ixekizumab; SEC = secukinumab; UST = ustekinumab

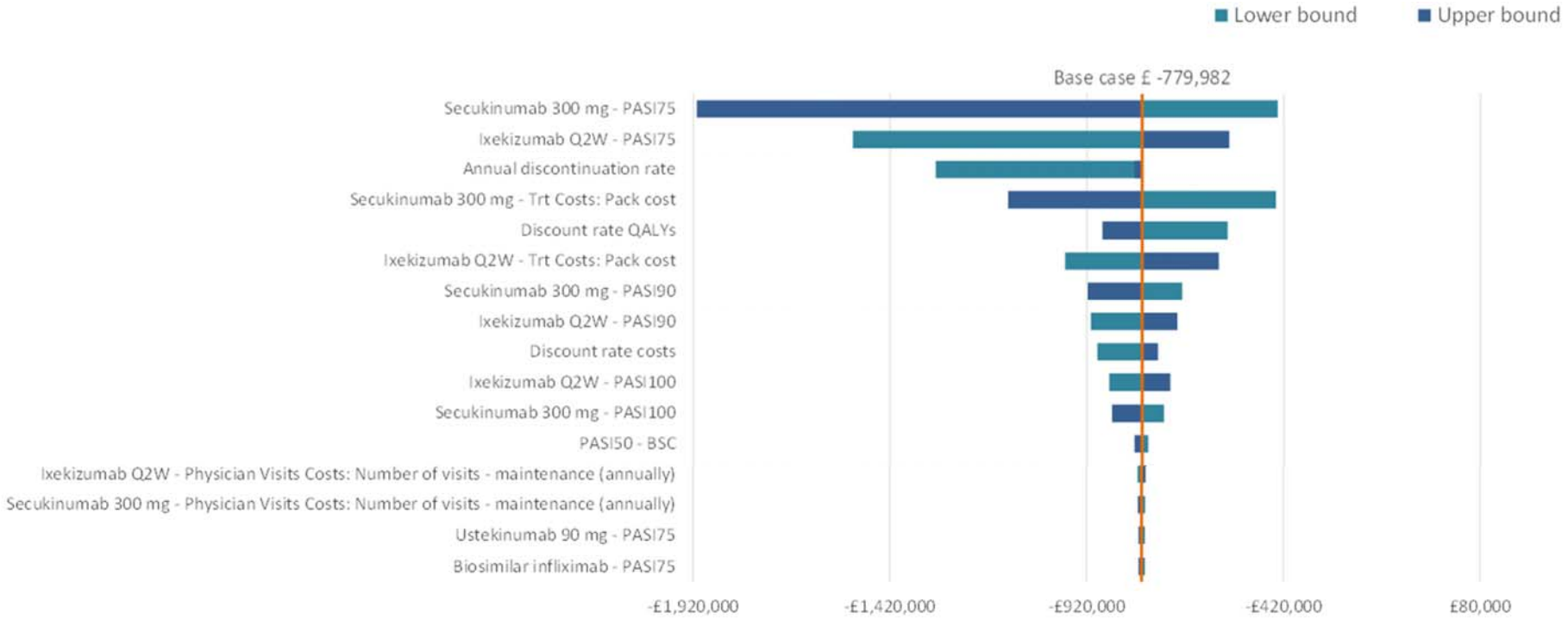
Figure A.4: Tornado diagram: ixekizumab sequence versus infliximab sequence



Source: Based on Figure 45 of the CS[1]

ADA = adalimumab; BSC = best supportive care; CS = company submission; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; Trt = treatment; UST = ustekinumab

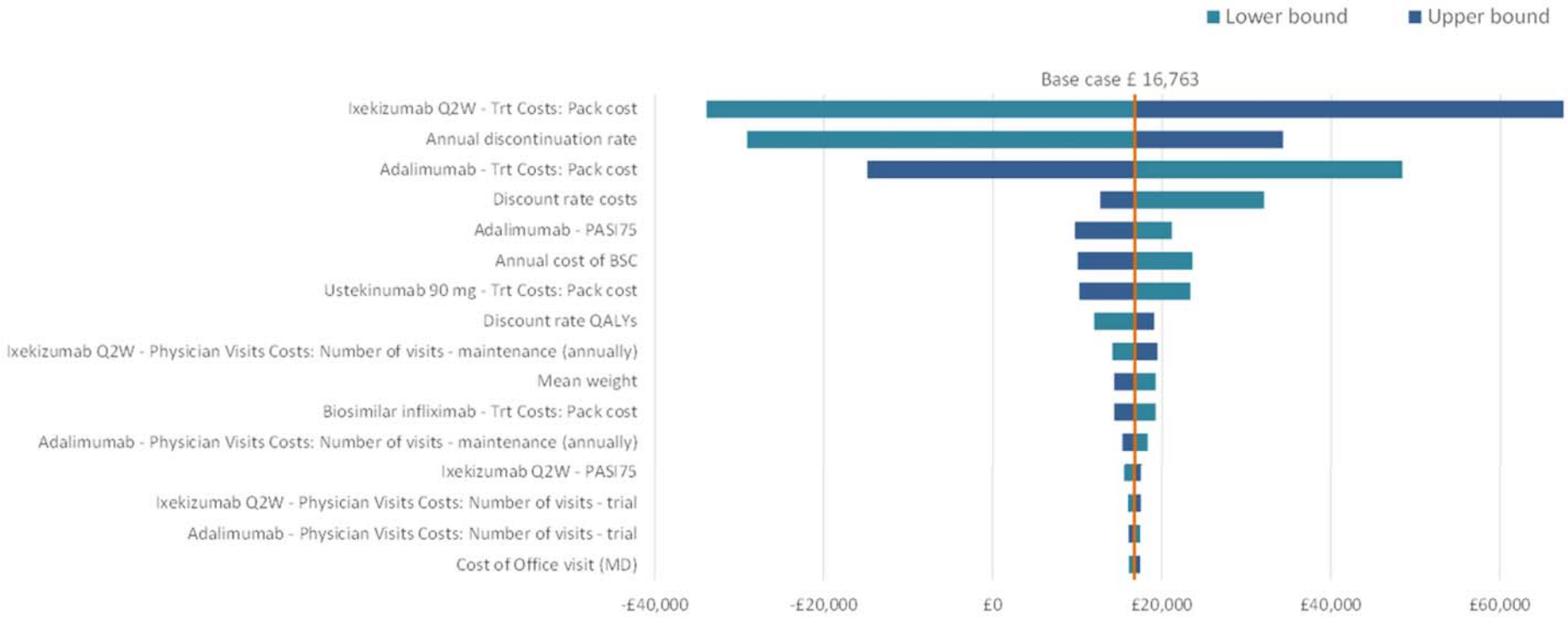
Figure A.5: Tornado diagram: ixekizumab sequence versus secukinumab sequence



Source: Based on figure 46 of the CS[1]

BSC = best supportive care; CS = company submission; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; SEC = secukinumab; Trt = treatment; UST = ustekinumab

Figure A.6: Tornado diagram: ixekizumab sequence versus ustekinumab 90 mg sequence



Source: Based on figure 47 of the CS[1]

ADA = adalimumab; BSC = best supportive care; CS = company submission; ICER = incremental cost-effectiveness ratio; INF = infliximab; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALYs = quality-adjusted life years; Q2W = every 2 weeks; Trt = treatment; UST = ustekinumab

Appendix 4: ERG modifications on the company cost effectiveness model

Adjustments in the Excel sheets

Adjustment of AEs costs, the following cells have been adjusted:

- 'AEs'!E14
- 'AEs'!E17:E22
- 'AEs'!E30
- 'AEs Default'!E14
- 'AEs Default'!E17:E22
- 'AEs Default'!E30
- See adjustments in the 'Reset' macro

Correction of SE calculation based on NHS reference costs upper and lower bounds

- 'PSA Inputs'!H26:H27
- 'PSA Inputs'!H29
- 'PSA Inputs'!H31
- 'PSA Inputs'!H33:H34

Correction of number of secukinumab administration during the maintenance period

- 'Input Data'!E72
- 'Input Data Default'!E72

Explorative sensitivity analysis

1. Use of DLQI>10 effectiveness estimate from the UNCOVER trials for ixekizumab

- 'Input Data'!D16:G16
- 'Input Data Default'!D16:G16
- 'CODA'!AH5:AH30004
- 'CODA'!AX5:AX30004
- 'CODA'!BN5:BN30004
- 'PSA Inputs'!G49:G51

2. Use of effect modification

- See adjustments in the 'Reset' macro

3. Use of ITT population for calculation of utility increments

- See adjustments in the 'Reset' macro
- See adjustments 'MainUIHealthUtilityGainDropDown' macro

4. Increase/decrease of BSC costs

- 'BSC'!J68:K68

Adjustments in the company's macros

Adjustments made in the Macro's by the ERG have been marked in red.

Adjustment of the 'Resets' – macro, which is coupled to the 'Set value' button on the 'ERG control!'-sheet:

```
'Option Explicit

Public Sub reset()

    'Dim rangeSuffix As String

    'Dim rowiter, coliter As long


    With Worksheets("Main")

        .Range("UIStartAge") = 45

        .Range("UIDiscountRateCost") = "3.5%"

        .Range("UIDiscountRateUtil") = "3.5%"

        .Range("UITimeHorizon") = "Lifetime"

        If Sheets("ERG control").Range("ERG_mod") = 0 Then

        .Range("UIEffectModYN") = "No"

        Else

        .Range("UIEffectModYN") = "Yes"

        End If

        .Range("UIEffectModApplyTo") = "Any biologic"

        .Range("UIEffectModNaiveBaseline") = "Yes"

        .Range("UIEffectModSize") = 1.24

        .Range("UIDefOfResponse") = "PASI75"

        .Range("UIIncludeMortality") = "Yes"

        .Range("UIIncreasedMortalityDueToSeverity") = "No"

        If Sheets("ERG control").Range("ERG_aes") = 0 Then

        .Range("UIIncludeAEs") = "No"

        Else

        .Range("UIIncludeAEs") = "Yes" 'ERG base-case includes AEs costs

        End If
```

```
        .Range("UIPropMale") = 0.678
        .Range("UIMeanweight") = 91.56
        .Range("MainNMA") = 2
        If Sheets("ERG control").Range("ERG_lin") = 0 Then
        .Range("MainHUCalcIter") = 2
        Else
        .Range("MainHUCalcIter") = 3 'ERG base-case uses linear gain
        End If
        If Sheets("ERG control").Range("ERG_util") = 0 Then
        .Range("MainHUDropDownIter") = 1
        Else
        .Range("MainHUDropDownIter") = 2 'ERG base-case uses utilities based on the ITT population
        End If

    End With

    Call MainUI.MainUIUpdate


End Sub
```

Adjustment in the 'RunModel' macro (to avoid jumping back to the 'CE Results'-tab after each pairwise comparison):

" Worksheets("CE Results").Select

Range("A1").Select"

Changed in:

"Worksheets("ERG control").Select

Range("P3").Select"

Adjustement in the 'MainUIHealthUtilityGainDropDown' macro:

```
Public Sub MainUIHealthUtilityGainDropDown()


    Dim oldAppScrUpd As Boolean
    Dim oldCalcMode As XlCalculation


    Dim rangeName As String
    Dim sheetName As String
    Dim counter As Long
    Dim addr As String


    oldAppScrUpd = Application.ScreenUpdating
    Application.ScreenUpdating = False
    oldCalcMode = Application.Calculation
    Application.Calculation = xlCalculationManual



    Worksheets("Main").Range("UtilityGainMainPage").Select
    With Selection.Interior
        .ThemeColor = xlThemeColorDark1
        .TintAndShade = -4.99893185216834E-02
    End With
    Worksheets("Main").Range("A4").Select
```

```
If Worksheets("Main").Range("MainHUDropDownIter").value = 1 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_Ixe_DLQIGT10_BL_Adj"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 2 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_Ixe_All_Pat"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 3 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_Ixe_DLQIGT10"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 4 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_Ixe_PSO_DLQIGT10"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 5 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_York_2"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 6 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_ADA_STA_1"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 7 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_UST_STA_1"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 8 Then
    sheetName = "Input Data"
    rangeName = "IDataHealthUtility_Secu_HU"
ElseIf Worksheets("Main").Range("MainHUDropDownIter").value = 9 Then
    Worksheets("Main").Range("UtilityGainMainPage").ClearContents
    Worksheets("Main").Range("UtilityGainMainPage").Select
    With Selection.Interior
        .ThemeColor = xlThemeColorDark1
```

```
        End With
        Worksheets("Main").Range("A4").Select
        Exit Sub
    End If

    If Sheets("ERG control").Range("ERG_util") = 0 Then 'ERG base-case: use of ITT population utilities
        For counter = 1 To 5
            addr = "='" & sheetName & "'!" & Worksheets(sheetName).Range(rangeName).Cells(counter).Address
            Worksheets("Main").Range("UtilityGainMainPage").Cells(counter) = addr
        Next counter
    Else
        For counter = 1 To 5
            addr = "='" & "Input Data" & "'!" & Worksheets("Input Data").Range("IDataHealthUtility_Ixe_All_Pat").Cells(counter).Address
            Worksheets("Main").Range("UtilityGainMainPage").Cells(counter) = addr
        Next counter

    End If
    Application.ScreenUpdating = oldAppScrUpd
    Application.Calculation = oldCalcMode

End Sub
```

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ixekizumab for treating moderate to severe plaque psoriasis [ID904]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 16 September** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg. 14 - Table I, For the outcome – Health-related quality of life (DLQI) – the change from baseline LSM (SE) value in UNCOVER 2 for the etanercept arm is incorrect	The change from baseline LSM (SE) value should be [redacted]	Transcription error from CSR	Not a factual error. Result has been correctly extracted from Griffiths 2015, referenced as #2 in the ERG report and #16 in the company submission.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg. 15 – Table 1, Title of the sub-section is incorrect- it states that psoriasis symptoms on the face, scalp and nail are reported. The section actually reports nail, skin and palmoplantar responses	Amend table section title to 'Psoriasis symptoms on nail, scalp and palmoplantar regions	To correctly title information reported in the table	Not a factual error. Heading is in line with the final scope.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg. 17 - Table II, 'Relapse Rate' The section of the table correctly reports clinical response at 60 weeks, for clarity this is not a relapse rate although relapse rates may be inferred through comparison to response rates	Re-title to 'Clinical response at 60 weeks'	To avoid confusion with the results reported in this section of table II of the report.	Not a factual error. Heading is in line with the final scope and was amended to match the company submission.

reported at an earlier timepoint			

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg. 17 - Table II sub heading Psoriasis symptoms on the scalp and nail- as per Issue 2, this section also reports palmoplantar symptoms	Amend table section title to 'Psoriasis symptoms on nail, scalp and palmoplantar regions	To correctly title information reported in the table	Not a factual error. Heading is in line with the final scope.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg. 17 - Table II, for UNCOVER-2 the week 60 NAPSI scores have been taken from the week 60 CSR. Values for the other endpoints have been sourced from the week 36 CSR	Use NAPSI score mean change from baseline LSM (SE) values from the week 36 CSR	To ensure consistency in the reporting of outcomes	The ERG has now sourced all numbers in this section of Table II from the week 60 CSR.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg. 20 - The ERG report makes the following comment: '…it seems that the UNCOVER trials failed to include patients with moderate psoriasis…and there is an issue with generalisability' To	To add the following qualifier to this sentence '…although it should be made clear that recent treatments assessed by NICE have considered a similar patient population (e.g.secukinumab, apremilast, ustekinumab etc.)	To add relevant context to this point that is considered a limitation by the ERG.	Not a factual error. The ERG correctly identified an issue with the generalisability of the UNCOVER results.

fully reflect the available evidence base, this sentence should be qualified to state that this is the case for all recent trials for biologic and other novel treatments for psoriasis			

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg. 20 - The ERG report comments that PASI has a limitation around the clinical improvement of facial psoriasis. This could potentially be misleading as the head is one of the four body components considered when scoring PASI.	The paragraph should be appended to add that 'although, it should be noted that the head is one of the four body components used to asses symptoms in the calculation of a PASI score.'	To correctly place the stated limitation in context.	Not a factual error. The outcome facial psoriasis was included in the final scope. It is correct that PASI assesses the head as one of four anatomical reasons. However, this does directly translate into facial psoriasis and has not been included in the company submission.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.21 - In the second paragraph, the report states that ixekizumab was only modelled as a first line treatment. This is not correct as the company submission presented a scenario analysis of ixekizumab used second line	This sentence should be amended to state that a second line scenario analysis was presented.	To correctly represent the analyses presented in the company submission with regard to ixekizumab as a second-line treatment.	Not a factual error. The summary paragraph refers to the fact that ixekizumab is only modelled as a first line therapy in the base case analysis. This issue is discussed in section 5.2.4 in

compared to other treatments used second line (Pg. 290 - Table 5.8.3 of the company submission)			the ERG report.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.21 - The second from last paragraph states that drug costs were based on list prices apart from ustekinumab 90mg. This creates some doubt as to what price was used for ustekinumab and why.	Additional detail to confirm that the company submission used the publically available information on the access scheme for ustekinumab that provides 45mg and 90 mg doses at the same cost.	To clearly inform what prices was used for ustekinumab 90mg.	Not a factual error. The ERG explains that the publically available information on the access scheme for ustekinumab that provides 45mg and 90 mg doses at the same cost was used.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.22 - The third paragraph in section 1.5 discusses the ERGs points on ixekizumab being used as a second line treatment. As highlighted in Issue 8, this omits to add that second line use was considered in a scenario analysis.	Amend to state that the company submission did consider second line use as a scenario analysis.	To correctly report what was included in the company submission.	Not a factual error. The paragraph refers to the fact that no analysis is presented in which ixekizumab as a first line therapy and ixekizumab as a second (or further) line are comparators. This issue is discussed in section 5.2.4.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.27 - third paragraph contains a typographical error ; the word 'systematic' is used when it should be 'systemic'	Correct 'systematic' to 'systemic'	Typographical error	Changed accordingly

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.34 - section 3.4, the ERG comment once more on psoriasis symptoms of the face. As noted in issue 7, the calculation of the PASI score does take into account symptoms on the head, which is not clear from the ERG statement	Proposed amendment should be as per the suggestion made in Issue 7	As per issue 7, to correctly communicate how PASI score does attempt to account for symptoms of the face.	Not a factual error. The outcome facial psoriasis was included in the final scope. It is correct that PASI assesses the head as one of four anatomical reasons. However, this does directly translate into facial psoriasis and has not been included in the company submission.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.49 – Table 4.5, in UNCOVER-1 patients with nail psoriasis is incorrectly shown as 284 (65.)	Amend to 284 (65.5)	Typographical error	Changed accordingly

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.51 – First paragraph, eligibility criteria for patients in the UNCOVER trials is stated as '…defined by a PASI score of more than 12'	The correct eligibility is a PASI score of greater than or equal to 12 (PASI≥12)	Incorrect definition of eligibility criteria	Changed accordingly

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.51 - Typographical error in the second paragraph in the patient characteristics section- 'systematic' instead of 'systemic'	Amend to 'systemic'	Typographical error	Changed accordingly

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.51 - the last paragraph in the ERG comment section again suggests that the UNCOVER studies have limited generalisability. As stated in issue 6, this does not accurately reflect the available evidence for other NICE appraised treatments	As per issue 6.	To accurately reflect the generalizability of the UNCOVER studies.	Not a factual error. The ERG correctly identified an issue with the generalisability of the UNCOVER results.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.60 – Table 4.8, For the outcome – Health-related quality of life (DLQI) – the change from baseline LSM (SE) value in UNCOVER 2 for the etanercept arm is incorrect	The change from baseline LSM (SE) value should be [redacted]	Transcription error from CSR	Not a factual error. Result has been correctly extracted from Griffiths 2015, referenced as #2 in the ERG report and #16 in the company submission.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.65 – Table 4.9, for UNCOVER-2 the week 60 NAPSI scores have been taken from the week 60 CSR. Values for the other endpoints have been sourced from the week 36 CSR	Use NAPSI score mean change from baseline LSM (SE) values from the week 36 CSR	To ensure consistency in the reporting of outcomes	The ERG has now sourced all numbers in this section of Table 4.9 from the week 60 CSR and amended the last sentence on page 57 accordingly.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.97 – Table 4.15, the subheading incorrectly states 'Not connect due to intervention not being licensed'. However, apremilast is licensed for the treatment of psoriasis but at the time was excluded as it was not	The subheading should be corrected to 'Not included due to intervention not being licensed or not recommended by NICE'	To correctly present the rationale for excluding interventions from the indirect comparison	Changed accordingly

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
recommended by NICE as a treatment option			

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.101 - Table 4.16. The table gives the NMA PASI responses for etanercept, to avoid confusion; this should state the dose of etanercept.	Add that this refers to etanercept 50mg weekly/25mg twice weekly	To make clear which etanercept dose this refers to.	Changed accordingly

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg108 - Table 5.3, in the row for comparators, the 4th sequence in the list is incorrectly stated as 1) Infliximab; 2) Ustekinumab; 3) Infliximab; 4) BSC	The 3rd treatment in the sequence should be adalimumab not infliximab	Incorrect treatment sequence shown	Changed accordingly

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.111 - Table 5.4, the comment on population states that the scope covers all patients under the licensed indication (including	Add a statement to confirm that conventional systemic treatments were considered in an scenario analysis	To correctly present the analyses for the manufacturer submission.	Not a factual error. The statement is on the population, not on the

conventional systemic treatments). Whilst the base case did not consider conventional treatments, a scenario analysis (Pg.291 of company submission) did consider ixekizumab in comparison with conventional systemic treatments.			comparators.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.114 - Table 5.4, the last paragraph discusses the use of relative PASI response and suggests that 'the quality of life and costs of patients with 75% PASI response on one treatment is not the same as on another treatment'. This statement could be misleading as it does not present the alternative viewpoint of why relative PASI may be appropriate.	This section should be amended to capture the following: If absolute PASI were used but if treatments are assumed to be equivalent in terms of AEs etc., then the QoL of a patient who went from baseline PASI 12 to PASI 3 (PASI75 response) would realistically be expected to have a similar QoL regardless of what treatment got them to a PASI 3 except where there is significant treatment related disutility which is likely not the case between comparators in this case.	For balance, the report should be amended to make clear that relative PASI is an equally valid approach.	Not a factual error. The potential drawback of the use of relative PASI response is explained in the ERG report (e.g. section 5.2.2).

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.115 - third paragraph (line 6) contains a typographical error ; the word 'were' is used when it	Correct 'were' to 'where'	Typographical error	Changed accordingly

should be ‘where’			

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.115 - Third paragraph ends with statement that the ERG were unable to incorporate estimates of the impact of AEs on HRQoL. This implies that the ERG were able to source appropriate data to inform this but no reference or detail on the nature of this data is provided.	The ERG need to provide information on the source, nature and quality of the data on the impact of AEs on HRQoL which they would like to incorporate into the model.	Provision of this data would allow an assessment of the appropriateness of the data and give a sense of the potential impact of this on model outputs.	Not a factual error. The ERG was unable to incorporate the impact of AEs for various reasons (time constraints, and the complexity and lack of transparency of the model).

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.115 - in the second last paragraph of Section 5.2.2, the ERG suggest that a linear gain of utility in the induction phase is the most plausible assumption. This is a potentially misleading statement as it does not take into account the available evidence- for example Figure 16 of the company submission shows the proportion of patients with a PASI75 response between weeks 0 to 12 in UNCOVER-2. There is a clear difference between	The report should acknowledge the evidence presented with respect to regard to the rate of response and therefore utility gain in the induction period in order to qualify the suggested plausible assumption. Additionally, it should be noted that there is limited available evidence to inform this assumption for all relevant comparators.	The report needs to take into account the evidence available for this assumption.	Not a factual error. As stated on page 126, “As the treatment effect will probably occur gradually over time the ERG considers the linear approach of assigning utility gain to the induction period to be most plausible.” This is applied for all comparators. This indeed biases against treatments with rapid response, but less than assuming no utility gain during induction

ixekizumab and etanercept, suggesting that utility gain over the induction period varies between interventions- therefore the linear gain assumption i.e. same rate of gain for all interventions may bias against treatments with a more rapid onset of response.			phase, as is the case in the company's base case, as rapid response seems to occur in therapy's with high response. Additionally, this is labelled as matter of judgement and should be considered as such.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.117 - Point 2 in the ERG comment section notes that non-biologic systemic treatments are not included in the treatment sequences. This does not acknowledge that: • Inclusion of these treatments in the sequences containing biologics (other than ixekizumab) would not be appropriate as all biologic interventions are approved by NICE in a population not suitable for non-biologic systemic therapy • As noted in Issue 22, the company submission presents a scenario analysis comparing to non-biologic	Report to be amended to acknowledge the scenario analysis presented with respect to this issue.	To correctly represent what was provided in the company submission	Not a factual error. This issue is discussed in section 5.2.4 of the ERG report.

systemic therapy			

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.117 - Point 3 in the ERG comment section puts forward that sequences should include the most optimal treatment sequence based on available trial evidence. This comment is subject to misinterpretation as it suggests that there is available trial evidence that considers sequences. The evidence search conducted found no trials that investigated true treatment sequences within a clinical trial.	This comment should be amended to include the fact that there is no trial evidence regarding treatment sequences of biologic interventions in psoriasis (optimal or otherwise).	To place this comment into its appropriate context.	Not a factual error. This issue is discussed in section 5.2.4 of the ERG report.

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.117 - Point 4 in the ERG comment section again discusses ixekizumab as a first line biologic treatment and requires significant clarification due to the following: • Again, a scenario analysis with ixekizumab as a second line treatment was presented (Pg.290 of the company	The comments section should be amended to acknowledge the second line scenario presented in the company submission, clarify that ixekizumab could be cost-effective as either a 1st or 2nd line treatment relative to other NICE approved options, Lastly, for factual accuracy, it needs to be made clear that ixekizumab does not currently have a license for psoriatic arthritis.	Factual accuracy and a clear representation of the information presented in the company submission.	Not a factual error. This issue is discussed in section 5.2.4 of the ERG report.

submission) • The clinical expert input that the inclination would be use ixekizumab second line is clearly valid but is a decision based on clinical factors and not cost-effectiveness. The company submission puts forward that ixekizumab is cost-effective as both a first and second line option relative to treatments already approved by NICE and this needs to be acknowledged. • The last sentence mentions co-morbid arthritis. Assuming this refers to psoriatic arthritis, it should be noted that although there are ongoing clinical studies in psoriatic arthritis, ixekizumab does not currently have a license for the treatment of psoriatic arthritis.			

Issue 30

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.118 - Table 5.6 compares the clinical outcome data in the model to the data from the clinical studies. For full transparency and to allow appropriate interpretation	Add credible intervals to the model values in the table.	To allow a better interpretation of the information provided in this table.	Not a factual error. The footnote of the table refers to table 52 and table 92 in the company submission, where

of this table, the provided credible intervals should be included for the model results.			the 95% intervals can be found.

Issue 31

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg121 - The last sentence in point 1 of the ERG comment section suggests that the treatment responses did not relate to the specific population being addressed. Whilst this is often an issue in all NMAs, this omits to acknowledge that: • Comparator trial designs were largely similar and were not specific to the population stated by the ERG, and nor was any sub-group data available • The company submission presented a number of sub-group analyses (section 4.8 and within clarification questions) that show similar responses regardless of prior treatment and DLQI.	The comment should be updated to acknowledge that it was not possible to specifically address the population stated and that ixekizumab response rates were similar in the sub-group analyses presented.	To provided relevant and appropriate detail to the comment with respect to the available evidence.	Not a factual error. The NMA is extensively discussed in chapter 4 of the ERG report.

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.123 - The final paragraph states that utility weights were derived from the EQ-5D-5L using the UK tariff. This is not correct as there is only available tariff at the time was the England tariff.	Amend to state the England tariff was used.	Factual accuracy.	Changed accordingly.

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.124 - The ERG comment expresses concern about the inconsistency of using the total ITT population to calculate PASI response. This again does not acknowledge the points highlighted in issue 31 and elsewhere regarding the available evidence for comparator treatments and the sub-group data presented for ixekizumab	The comment to be amended to acknowledge the issues behind the suggested inconsistency.	To clearly represent the evidence presented in the company submission.	Not a factual error. See response on issue 31.

Issue 34

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.126 - The ERG comment	As per Issue 26	As per Issue 26	Not a factual error.

again discussed the plausibility of linear utility gain in the induction period. The points made in Issue 26 apply again			See response on issue 26.

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.144 - Point 3 of the ERG comment section refers to table 5.20 and suggests that PASI response rates were 'slightly lower' in the DLQI>10 sub-population. This may be subject to misinterpretation as this is a post-hoc analysis on a sub-group that was not powered, and the comment does not highlight that regardless of this, there was no significant interaction between the groups as shown by the p-values presented	The comments should make clear that this is a post-hoc sub-group analysis that was not powered for, which, in addition to the non-significant interaction p-values mean it is not possible to state that PASI response is slightly lower in the DLQI >10 population.	To accurately represent the available data.	Not a factual error. The ERG report does not state that response was statistically significantly lower. Absence of evidence is not evidence of absence.

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.145 - The ERG notes the (requested) alternative discontinuation rate analysis is not informed properly. This does not	The comment should be amended to state that ixekizumab will not have the long-term 'real-life' data of older comparators.	To correctly represent the limitations of the available evidence.	Not a factual error. The ERG correctly points out the uncertainty regarding an

acknowledge the fact that due to ixekizumab (and indeed secukinumab) being newer drugs, they are by definition not going to have the long-term registry data that might inform discontinuation rates for older drugs.			input parameter in the model.

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.148 - Table 5.23 references TA305 which is for aflibercept. It is assumed that this should actually refer to TA350 (secukinumab in psoriasis)	Correct to TA350	Typographical error	Changed accordingly.

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.150 - Fixing errors point b states that the ERG found and error which was corrected in the ERG base case, but does not provide any detail on what this error was.	Provide details on the error so that it can be verified.	No information is given on the error.	Not a factual error. The text on page 150 refers to section 5.2.7, where it states: "After recalculating the AE rates of adalimumab, the ERG came up with a slightly different rate for non-melanoma skin cancer (NMSC; 0.0096 instead of 0.0097) and used this in its base-case."

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.150 - Point 3 on the error fixed states that the number of annual administrations of secukinumab was amended from 13 to 12. We do not believe this is appropriate as: • The secukinumab clinical studies were based on 4 weekly administration, and therefore the response rates of secukinumab, are accurately represented by 4 weekly administration (Pg.47, Figure 7 of the secukinumab company submission) • The ERG report for TA350 prefers 13 doses per year (Pg.88 of the ERG report) Therefore, the 13 doses is the correct option for annual maintenance dosing for secukinumab. The calculation error is mentioned throughout the submission.	This was not an error that needed fixing and should be changed back to 13 doses as per the company submission base case.	This was not an error that needed correcting.	Not a factual error. The ERG corrected the model to be consistent with the monthly dosing described for Secukinumab 300 mg in CS Table 68. Whether this is incorporated as 12 (monthly administration) or 13 (4-weekly administration) administrations annually is a matter of judgement.

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.154/155 - Point 7 introduces the exploratory analysis using DLQI>10 sub-group data that was provided in response to clarification questions. Whilst the report states that results should be interpreted with caution, this fails to highlight a number of points that mean these results rather than being treated with caution, are highly misleading and arguably should not be considered at all: • As highlighted in issue 35, this analysis was provided on request but represents an unpowered, post-hoc analysis. Regardless, there is no significant interaction which suggests that the ITT population is appropriate. • The response rates populating the model are derived from a robust NMA. Introducing naïve non-NMA data for ixekizumab whilst keeping NMA data for comparators is suspect methodologically and should not be considered unless there are strongly valid reasons to do so	Due to the significant issues highlighted with this exploratory analysis, it should not be considered at all for decisions making and should be removed from the exploratory analysis conducted.	The report gives insufficient weight to the significant issues with this exploratory analysis and does not justify its inclusion.	Not a factual error. The analysis is labelled as exploratory in the ERG report.

• Furthermore, only using DLQI>10 data for ixekizumab and ITT data for comparators is likely to significantly bias against ixekizumab with no justification			

Issue 41

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.155 - Point 8 of the ERG report discusses the use of effect modification and the 1.24 value included in the model. The report does not state the fact that this figure was derived from a registry study that did not include ixekizumab (or secukinumab) and therefore there is of course a large degree of uncertainty as to how applicable this figure is to ixekizumab and secukinumab	To add the suggested caveat so the validity of this analysis can be appropriately be considered.	Without including this, the value used in this analysis cannot properly be assessed for validity.	Not a factual error. The analysis is labelled as exploratory in the ERG report.

Issue 42

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pg.172 - The last paragraph of section 8.2 again makes comment on the apparent absence of ixekizumab as a second line treatment. This again ignores the fact that a second-line scenario	State that a second line scenario analysis was presented	To accurately reflect the analyses provided in the company submission.	Not a factual error. See responses to comment 8 and 10.

was presented (Pg.290 Section 5.8.3 of the company submission).			