Public observer slides

Lead team presentation Ixekizumab for the treatment of moderate to severe plaque psoriasis (STA)

1st Appraisal Committee meeting

Committee B, 5th October 2016

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Company: Eli Lilly

Chair: Amanda Adler

Evidence Review Group: Kleijnen Systematic Reviews Ltd

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Summary of evidence and key issues

<u>UNCOVER-1,-2,-3 results</u>
Higher PASI 75 responses at wk 12

Ixekizumab vs. placebo; etanercept (p=<0.001)

Modelled in a treatment sequence

<u>ICERs</u>
Ixekizumab sequence vs. etanercept sequence
Company base case (without comparator PAS): £33,858
(all other sequences dominated)

Ixekizumab

<u>Network meta-analysis</u>
Ixekizumab has highest probability of being ranked best for achieving PASI 75 responses at week 12

[redacted]

Biologics recommended by NICE only for severe psoriasis

Trial participants reflective of moderate to severe disease?

Ixekizumab (Taltz)
Eli Lilly

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
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 • 160mg at week 0, followed by 80mg every 2 weeks until week 12 (induction) • After week 12, 80mg every 4 weeks (maintenance)

Patient and professional feedback

- Psoriasis typically follows a relapsing and remitting course
- Can be a debilitating disease that impacts all aspects of life, physically, psychologically and socially
- 75% patients report burdensome symptoms (itching, redness, scaling, flaking)
- 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)

Decision problem - **comparators**

Acitretin, fumaric acid esters, phototherapy missing from submission

NICE scope	Company submission
1) If non-biologic systemic treatment or phototherapy 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 for analysis • Ixekizumab position in pathway aligned to biologic therapies (population 2)	

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: it did not search UVB studies in literature review; 'limited relevance' due to position in pathway. ERG: studies with UVB might be relevant for NMA estimates
Outcomes	Signs 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 signs on face

Psoriasis Area and Severity Index (PASI); Dermatology Life Quality Index (DLQI); Network Meta-analysis (NMA)

Existing NICE guidance

Moderate to severe disease, candidates for phototherapy or systemic therapy					
Phototherapy (UVB radiation)	Methotrexate	Ciclosporin	Acitretin	Fumaric acid esters*	Ixekizumab? ✪
CG153	CG153	CG153	CG153		
Severe disease (PASI ≥10 and DLQI >10) and no response, intolerance or contraindication to standard systemic therapies					
Adalimumab ★	Etanercept ★	Ustekinumab ✪	Secukinumab ✪	Ixekizumab? ✪	
TA146	TA103	TA180	TA350		
Very severe disease (PASI ≥20 and DLQI >18) and no response, intolerance or contraindication to standard systemic therapies					
Infliximab ★				Ixekizumab? ✪	
TA134					
*Not licensed but used for moderate psoriasis					

★: Tumour Necrosis Factor-alpha inhibitors ✪: Interleukin inhibitors

⊙ *Where would ixekizumab fit in the treatment pathway?*

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 then 80mg q2W or 80mg q4W*
Comparator	UNCOVER-1 placebo UNCOVER-2 placebo; etanercept 50mg twice weekly UNCOVER-3 placebo; etanercept 50mg twice weekly
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; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment

Clinical evidence – ERG critique

Generalisability of UNCOVER trials to NHS patients

Thresholds	Source	Definition
PASI ≥12 + body surface area ≥10% + sPGA ≥3	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
	NICE (previous technology appraisals)	Severe disease
PASI > 10 (or 12)	ERG's clinical experts	Moderate to severe disease for biological therapies
Ixekizumab marketing authorisation		
". . . for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"		

- *How is moderate/severe psoriasis defined in clinical practice in England?*
- *Do the patients in the UNCOVER trials represent moderate to severe psoriasis as defined in the NHS?*

PASI, Psoriasis Area and Severity Index (higher scores = more severe disease); sPGA, static Physician Global Assessment; DLQI, Dermatology Life Quality Index

Company's clinical evidence
Results – UNCOVER-1 and -2

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

UNCOVER-1		Ixekizumab q2W n=433	Ixekizumab total (q2W & q4W) n=865	Placebo n=431
PASI 75	%	89.1%	85.9%	3.9%
	Odds Ratio (95% CI)	224 (125, 401)	N/A	N/A

UNCOVER-2		Ixekizumab q2W	Ixekizumab total (q2W & q4W)	Etanercept	Placebo
		n=351	n=698	n=358	n=168
PASI75	%	89.7%	83.7%	41.6%	2.4%
	OR vs. Pbo (95% CI)	997 (173, 5745)	289 (88, 945)	30.7 (10.8, 87.2)	N/A
	OR vs. Eta (95% CI)	13.3 (8.7, 20.3)	7.6 (5.6, 10.3)	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

Results – UNCOVER-3

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

UNCOVER-3		Ixekizumab q2W	Ixekizumab total (q2W & q4W)	Etanercept	Placebo
		n=385	n=771	n=382	n=193
PASI 75	%	87.3%	85.7%	53.4%	7.3%
	OR vs. Pbo (95% CI)	72.3 (36.1, 145)	70.5 (37.8, 131)	13.7 (7.6, 24.7)	N/A
	OR vs. Eta (95% CI)	6.5 (4.4, 9.5)	5.6 (4.2, 7.5)	N/A	N/A

⊙ *Is ixekizumab more clinically effective than placebo and etanercept?*

ITT, Intention-to-Treat; Eta, Etanercept; Pbo, Placebo; q2W, every 2 weeks; q4W, every 4 weeks; PASI, Psoriasis Area and Severity Index; OR, odds ratio; CI, confidence interval

Subgroup analysis – baseline severity

Treatment effect consistent

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

IXE, Ixekizumab; PASI, Psoriasis Area and Severity Index; ITT, Intention-to-Treat; DLQI, Dermatology Life Quality Index; q4W, every 4 weeks; q2W, every 2 weeks

Subgroup analysis – previous biologic treatment

Treatment effect consistent

Proportion of patients achieving PASI 75 at week 12				
UNCOVER-2	IXE q2W	IXE q4W	Etanercept	Placebo
Biologic-naïve (n=936)	88.8%	78.6%	44.3%	3.2%
Prior biologic therapy (n=288)	92.9%	74.1%	30.3%	0%

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; ITT, Intention-to-Treat

Subgroup analysis – ERG critique Summary of results

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

⊙ *Is clinical effectiveness of ixekizumab modified by baseline disease severity and previous treatment?*

PASI, Psoriasis Area and Severity Index

Clinical evidence – network meta-analysis

Trial populations generally similar

Scenario analysis conducted for comparison with non-biologics

	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 treatment	Varied Not all patients had inadequate response or contraindicated to standard systemic therapies	Some trials had more 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

RCT, randomised controlled trial; PASI, Psoriasis Area and Severity Index

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%

⊙ *Is ixekizumab more effective than other biologics?*

q2W, every 2 weeks; q4W, every 4 weeks; EOW, every other week; BIW, twice weekly; PASI, Psoriasis Area and Severity Index; CrI, credible interval

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 (44.0 years to 99.9 years) Patients expected to spend >10 years on active treatment
Cycle length	1 month, captures induction periods when patients switch to a new treatment
Measure of health effects	Quality-Adjusted Life Year
Discounting of utilities & costs	3.5%
Perspective	NHS/PSS

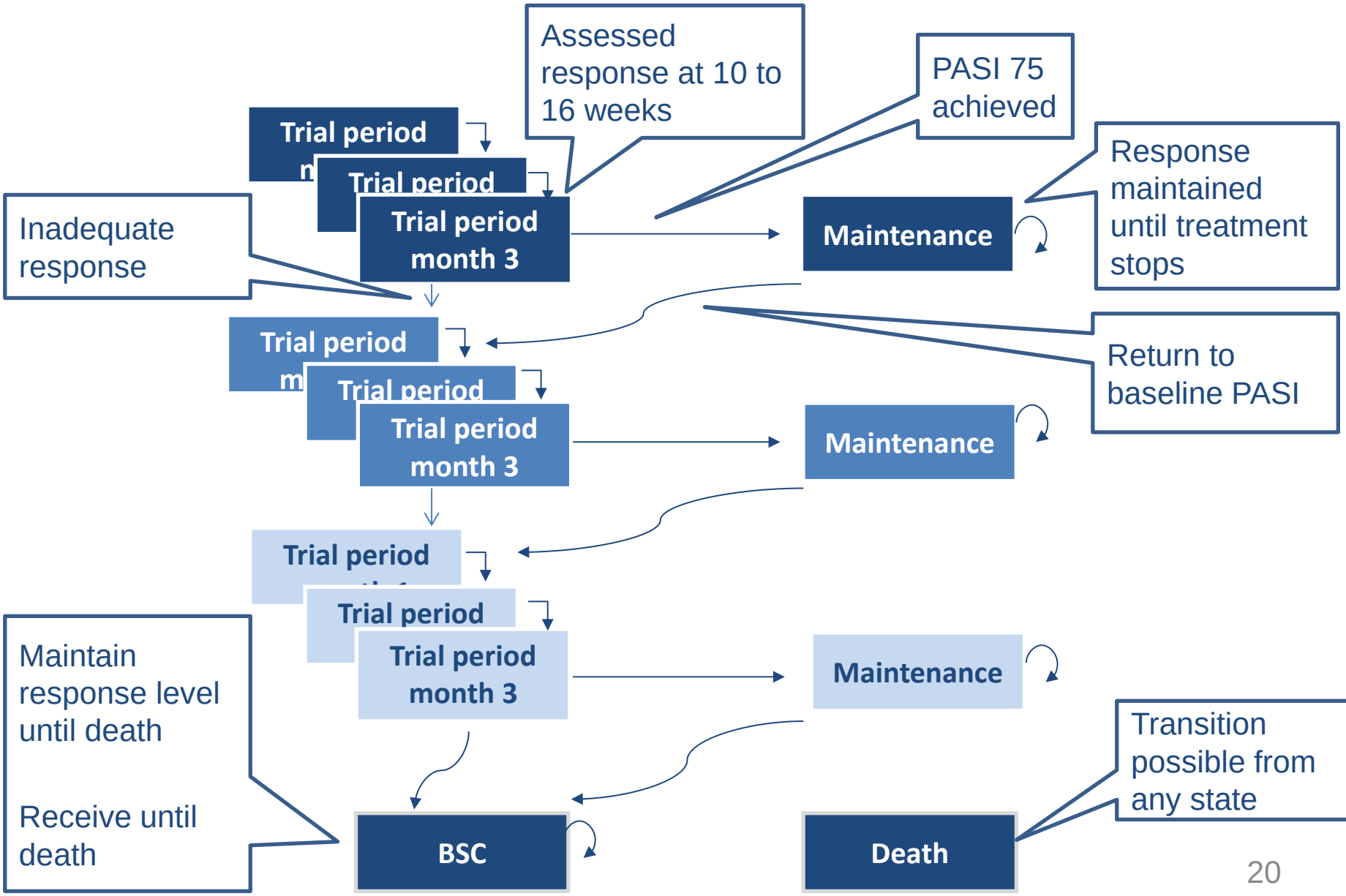
Company's model – ERG critique
Population inconsistent

- 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 it modelled ixekizumab 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'

⊙ *Can the model be used to inform decisions on all the populations in the decision problem? If not, which populations?*

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

Company's model - structure



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
- Model may not capture true impact of treatment on quality of life and resource consumption
- This may bias comparative effectiveness (QoL/resource use PASI 75 on 1 treatment may not be the same as PASI 75 on another treatment)

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

Company's model
Treatment sequences

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

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

Company's model – ERG critique
Treatment sequences

- Approach of comparing treatment sequences better than comparing single treatments
- Non-biologics not included, but this is reasonable if patients have failed these; however, phototherapy may still be an option
- Modelling should include most optimal treatment sequence not just most widely used (based on market share)
- Plausible to position ixekizumab in the sequence as a 2nd biologic treatment - clinicians suggest it will probably be used 2nd because doctors have more experience with other biologics

⊙ *Do the treatment sequences reflect NHS practice?*

⊙ *Would ixekizumab be used as 1st or 2nd line biologic?*

Company's model
Transition probabilities

Induction to maintenance	**PASI 75 response** Proportion of patients achieving PASI 75 response at 12 weeks in network meta-analysis (ITT population)
Maintenance to treatment stopping	All cause, constant annual rate of 20% (based on BADBIR, supported by previous appraisals), converted to monthly drop out rate and applied to each cycle *ERG: All cause constant annual rate not plausible or constant over time, but evidence for treatment-specific rates limited so equal rates for different treatments appropriate*
Treatment stopping to best supportive care	As above, or inadequate response to 3rd treatment after induction Level of response equal to placebo level of response in network meta-analysis
Any state to death	Probability taken from national mortality life tables (gender-weighted, age-dependent) Risk applied in all treatment states

PASI, Psoriasis Area and Severity Index; ITT, Intention-to-Treat

Company's model – ERG critique

Transition probabilities – treatment effectiveness

- Assumed treatment response did not vary with position in sequence
  - Did not include decrease in effectiveness of subsequent biologics in base case
  - Clinical expert suggests effect modification may not happen if subsequent biologics have different modes of action
- Response based on intention-to-treat populations 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
- Response to best supportive care - 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)

⊙ *Which population should be used to estimate effectiveness; intention-to-treat or DLQI >10 subgroup?*

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 collected in 3 UNCOVER trials baseline + 12 weeks
- 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
- 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
- Company did not include disutility of adverse events in model

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

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

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; • PASI response lower in DLQI >10 population: ERG agrees with using DLQI subset
⊙ *Which population should be used for utility gains; ITT or DLQI >10?*	
Estimates of utility gains – uncertain	• Regression model (with baseline EQ-5D-5L & PASI response as covariates) used to convert EQ-5D-5L to utilities. Company did not provide model diagnostics: ERG unable to assess if model appropriate • 'Last observation carried forward' used for those who stop 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

⊙ *When do people get the benefit of treatment? Should there be a utility gain in the induction period for ixekizumab?*

Company's model
Inputs: Costs – summary

- Treatment acquisition (ixekizumab PAS price, secukinumab no PAS, biosimilar list prices for infliximab and etanercept)
- Treatment administration, monitoring & best supportive care costs included
- Non-responders - applied to induction period following stopping treatment, reflecting higher disease activity and worse health after not responding, set at £274 monthly
- Company excluded adverse events (non-melanoma skin cancer, other malignancies, severe infection) - included in company sensitivity and scenario analyses and ERG's base case

⊙ *Should the cost of adverse events be included?*

Company's model and ERG critique

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
Source: Fonia et al (2010)	

- Data on hospital resource use and drug usage collected 12 months prior to and 6 months following starting biologic treatment – reflect moderate to severe psoriasis without biologic treatment
- *ERG*: Estimates do not represent best supportive care after failure of many biologic treatments; costs of systemic non-biologic treatment included, but not likely to be given
- Resource use and costs for best supportive care uncertain

⊙ *Do the estimated costs of best supportive care reflect actual cost? If not, are the costs over- or under-estimated?*

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

Treatment sequences	Total		Increments vs ETA		ICER
	Costs	QALYs	Costs	QALYs	
ETA→UST90→INF *1C*	£144,635	1.27	-	-	-
UST45→ADA→INF *1F*	£148,218	1.30	£3,583	0.04	Extendedly dominated
ADA→UST90→INF *1B*	£148,350	1.32	£3,715	0.05	Extendedly dominated
UST90→ADA→INF *1G*	£148,719	1.32	£4,083	0.06	Extendedly dominated
INF→UST90→ADA *1D*	£150,350	1.33	£5,714	0.06	Extendedly dominated
IXE→UST90→INF *1A*	**£150,889**	**1.45**	**£6,254**	**0.18**	**£33,858**
SEC→UST90→INF *1E*	£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

Company's scenario analyses results

Scenario	ICER vs. etanercept sequence unless stated
Company's base case (deterministic)	**£33,858**
1) Prior failure/contraindication to TNF-α inhibitor	ixekizumab dominant
2) Single treatment comparisons (no sequence)	**£39,563**
3) Comparison with non-biologic systemic therapy (methotrexate, ciclosporin, best supportive care)	**£65,468** vs. methotrexate
5) Effect modification of previous biologic treatment	**£38,034**
6) Branded prices for etanercept and infliximab	**£24,923**
7) Utility gain assignment in induction period	**£32,337**
8) Including costs of adverse events	**£32,932**
10) Using a range of alternative utility sources	**£16,109** to **£47,235**
11) Source of best supportive care costs	ixekizumab dominant
12) Varied best supportive care efficacy	**£30,738** to **£60,586**

Note: not all scenarios shown

ERG's exploratory analyses – ERG's base case

- 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)
- Fixed errors
  - Re-calculated adverse event unit costs, corrected error in adverse event rates
  - Re-calculated standard error for NHS reference costs (for probabilistic sensitivity analysis)
  - Corrected number of secukinumab administrations in maintenance period
- Probabilistic analysis as base case

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

Treatment sequences	Company's ICER (ERG calculated)	ERG's ICER 1st line IXE	ERG's ICER 2nd line IXE
ETA→UST90→INF *1C*	-	-	-
ADA→IXE→INF ***1H***	**Not reported**	**£25,532** vs ETA	**£25,532** vs ETA
UST45→ADA→INF *1F*	Extendedly dominated	Dominated by ADA→IXE→INF	Dominated by ADA→IXE→INF
ADA→UST90→INF *1B*	Extendedly dominated	Dominated by ADA→IXE→INF	Dominated by ADA→IXE→INF
UST90→ADA→INF *1G*	Extendedly dominated	Dominated by ADA→IXE→INF	Dominated by ADA→IXE→INF
IXE→UST90→INF ***1A***	**£32,541** vs ETA	**£39,129** vs 2nd line IXE	**Excluded**
INF→UST90→ADA *1D*	Extendedly dominated	Dominated by IXE→UST90→INF	Dominated by ADA→IXE→INF
SEC→UST90→INF *1E*	Dominated by IXE→UST90→INF	Dominated by IXE→UST90→INF	£730,630

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

Treatment sequences	Company's ICER (ERG calculated)	ERG's ICER 1st line IXE vs comparator	ERG's ICER 2nd line IXE vs comparator
ETA→UST90→INF *1C*	**£32,541**	**£30,517**	**£25,532**
ADA→IXE→INF *1H*	**Not reported**	**£39,129**	**-**
UST45→ADA→INF *1F*	**£16,550**	**£15,024**	**Dominated**
ADA→UST90→INF *1B*	**£17,460**	**£15,281**	**Dominated**
UST90→ADA→INF *1G*	**£15,027**	**£13,147**	**Dominated**
IXE→UST90→INF *1A*	**-**	**-**	**-**
INF→UST90→ADA *1D*	**£602**	**Dominated**	**Dominated**
SEC→UST90→INF *1E*	**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

ERG's scenario analyses results

Scenario	ICER: IXE 1st line vs IXE 2nd line sequence	ICER: IXE 2nd line vs etanercept sequence
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

Innovation

Company notes:

- Rapid onset of efficacy
- Improvements in difficult to treat areas
- Easy to use

British Association of Dermatologists notes:

- 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

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

Key issues for decision-making

- Where is ixekizumab in the treatment pathway? Would it be used as 1st or 2nd biologic?
- Do the patients in the UNCOVER trials represent moderate to severe psoriasis as defined in the NHS?
- Is ixekizumab more effective than placebo and etanercept?
- If so, regardless of disease severity and previous treatment?
- Can the model be used to inform decisions on all the populations in the decision problem? If not, which populations?
- Do the treatment sequences reflect NHS practice?
- Which population (intention-to-treat or DLQI >10 subgroup) should form the basis of estimates of effectiveness? For utility?
- When do people get the benefit of treatment? In induction period as well as in maintenance period?
- Should the model include the costs of adverse events?
- Are the estimated costs of best supportive care valid?
- Equalities, innovation and PPRS