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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.

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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

Table of Contents

Table of Tables

Table of Figures

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,

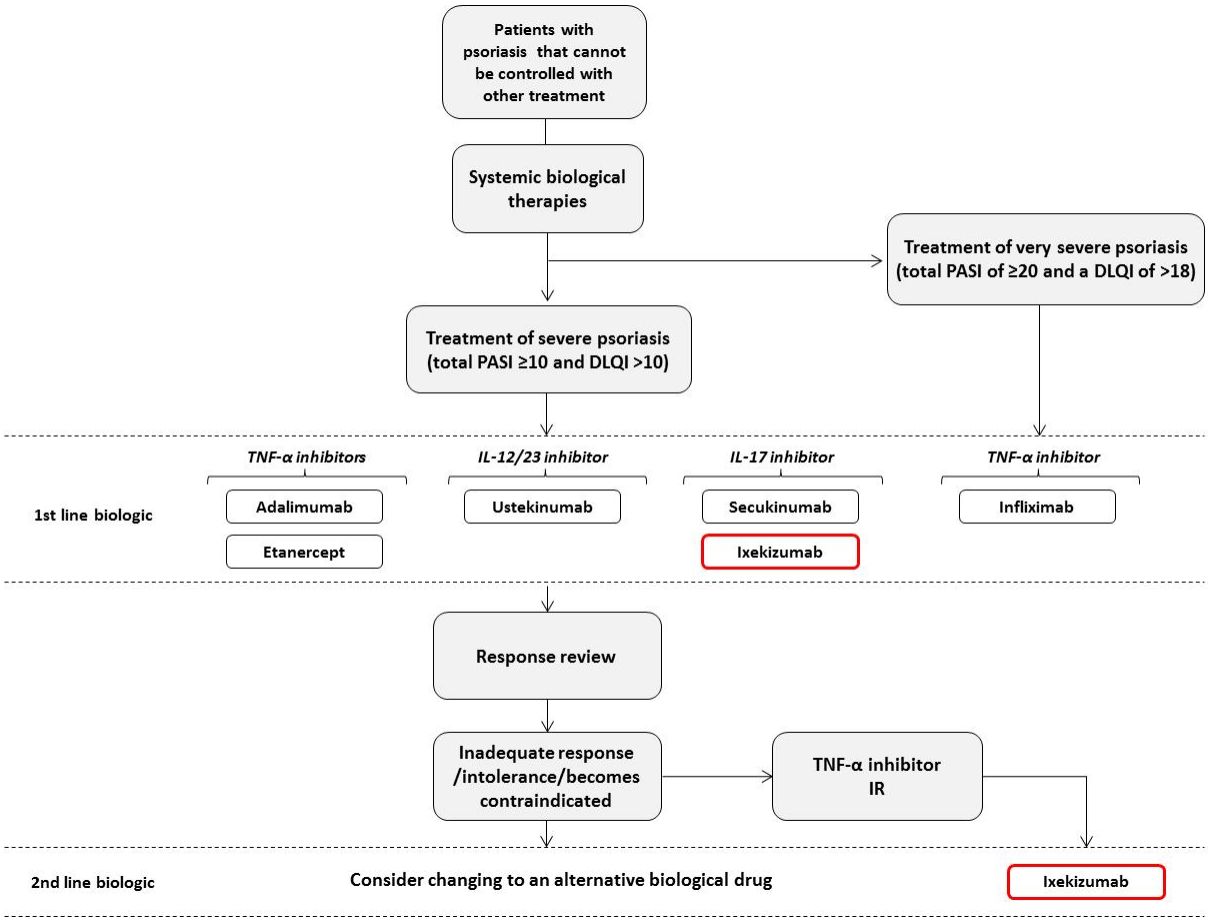
adalimumab and ustekinumab are a Psoriasis Area and Severity Index (PASI) score ≥ 10 and a Dermatology Life Quality Index (DLQI) > 10 (severe disease) and for infliximab, a PASI ≥ 20 and a DLQI > 18 (very severe disease).[7]

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	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
		comparators based on the results 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

	Inclusion	Exclusion
Outcomes	Key clinical outcomes: PASI, relative and absolute: PASI 50* PASI 75 PASI 90 PASI 100 Global assessments, relative and absolute: PGA 0, 1 sPGA 0, 1 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. EQ-5D) Depression** (e.g. HADS, QIDS) (Work) productivity** (e.g. 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
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

	Inclusion	Exclusion
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 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)	**Induction dosing period** Ixekizumab Q2W (n = 351) Ixekizumab Q4W (n= 347) Etanercept (n = 358) Placebo (n =168) **Maintenance dosing period**	**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]
	Ixekizumab Q12W (n= 227) Placebo (n = 226)	Ixekizumab Q4W (n = 187) 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		

Trial number (acronym)	**UNCOVER- 1**[3, 40]	**UNCOVER-2**[2, 4]	**UNCOVER-3**[2, 41]

	• 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 (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
			• 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

	• Superiority of ixekizumab (Q4W and Q12W) to placebo in the proportion of patients maintaining: • sPGA (0,1) from week 12 to week 60		
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		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

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]

Study outcome	Definition
Nail Psoriasis Severity Index (NAPSI)	The NAPSI was used only if the patient had fingernail psoriasis at 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 *Biologics and non-biologics*	118 (27.4) 124 (28.8)	132 (30.6) 106 (24.5)	152 (35.1) 124 (28.6)	61 (36.3) 24 (14.3)	28 (8.1) 147 (42.4) 57 (16.4)	29 (8.3) 141 (40.2) 55 (15.7)	149 (41.6) 43.(12.0)	72 (37.3) 17 (8.8)	23 (6.0) 166 (43.0) 35 (9.1)	157 (40.8) 33 (8.6)	162 (42.4) 34 (8.9)
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

Outcome	Final scope	UNCOVER-1	UNCOVER-2	UNCOVER-3	Table
sPGA (0,1) at week 60	"Relapse rate"	reported	reported	not reported	Table 4.9
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

	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)
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
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

	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)
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, 76.15) 0.008	75.44 (10.49, 542.60) <0.001	113.79 (16.20, 799.34) <0.001	-	N/A	N/A	N/A
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

	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)
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, 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
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

	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)
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
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)†

	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)	-	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; 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)

	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)	-	59.55 (13.97, 253.88) <0.001	-	31.96 (11.03, 92.55) <0.001	-	41.16 (17.52, 96.70) <0.001	-	72.00 (9.58, 541.40) <0.001	-	80.81 (18.81, 347.23) <0.001	-	73.81 (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*	-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
change from 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]

	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

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)

	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 (%)**
Pneumocystis pneumonia (PCP)	0	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
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)

	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 (%)
Cerebrocardiovascular events	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)
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	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)
				Serious adverse 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.	No	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	Secukinumab 150 mg was excluded.	Mean 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	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		Mean 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:	Secukinumab 300 mg Ustekinumab 45 mg	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)
		CLEAR, a randomised controlled trial	Ustekinumab 90 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	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)
				Serious adverse events Withdrawals							
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	PASI 75	This study met all inclusion	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	Adalimumab 40 mg QW Placebo	Adverse events Serious adverse events Withdrawals	criteria. 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

Author	Year	Title	Interventions	Outcomes	CS: Included in			Rationale for inclusion/ exclusion
					Table 48	Table A10	Tables 49-50	
								Kerkhof 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;	The model structure is similar to that of the York model which has been used in all NICE submissions	CS section 5.2.2

	Approach	Source / Justification	Signpost (location in CS)
	• Maintenance period; • 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.	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

	Approach	Source / Justification	Signpost (location in CS)
Population	Biological-naïve patients who have failed to respond to prior 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"*	The company states *"it is anticipated that ixekizumab will be used in the population currently eligible for biological therapies"*	CS section 5.2.1
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

	Approach	Source / Justification	Signpost (location in CS)
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 clinically defined subgroups was not warranted because treatment response to ixekizumab was consistent across these groups	CS section 4.8
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	

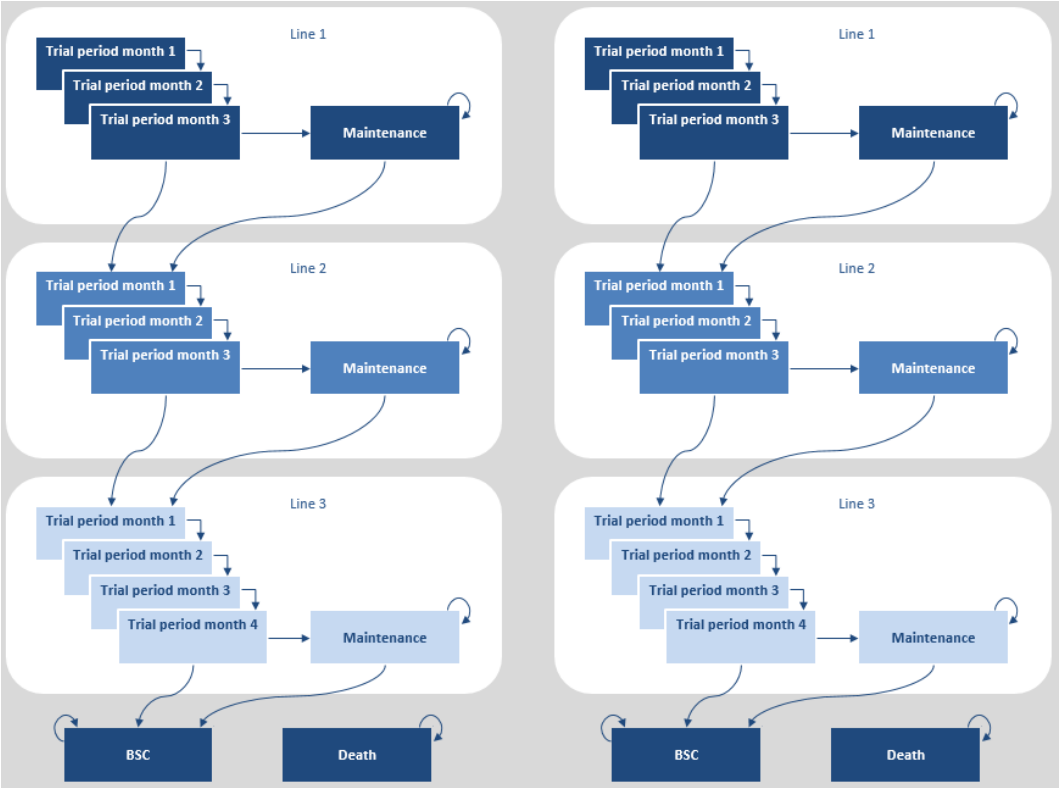
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Y	
Source of preference data for valuation of changes 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 EQ5D-5L.	All covariates except PASI 75 & 90, but including baseline PASI had [redacted]. Mean utility changes differed slightly.	Table 17+18 of RRfC

ERG request	Response and result	Source
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	1	100 mg	£377.66	£1,728.93*	£5,186.78*	£11,238.03*	MIMS,

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (induction period)	Total annual cost (maintenance period)	Source
infliximab (Remsima)							June 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

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
						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-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

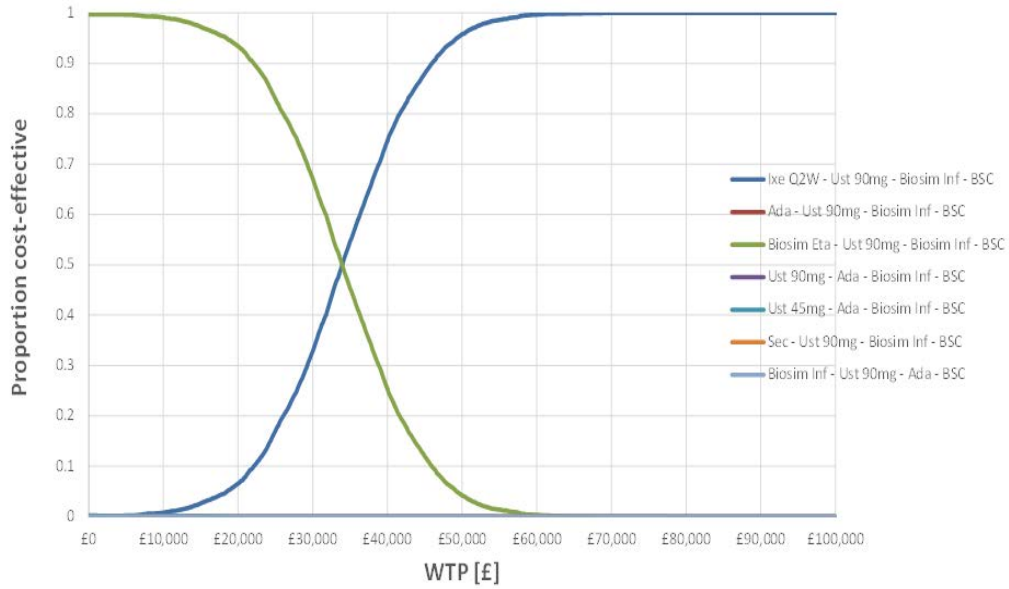
Base-case PSA results are provided (Table 5.18). PSA simulation results were used to draw the PSA scatterplot, the cost effectiveness acceptability curve (CEAC) (Figure 5.2) and the cost effectiveness acceptability frontier (CEAF) (Appendix 3). The results show that the etanercept sequence and the ixekizumab 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

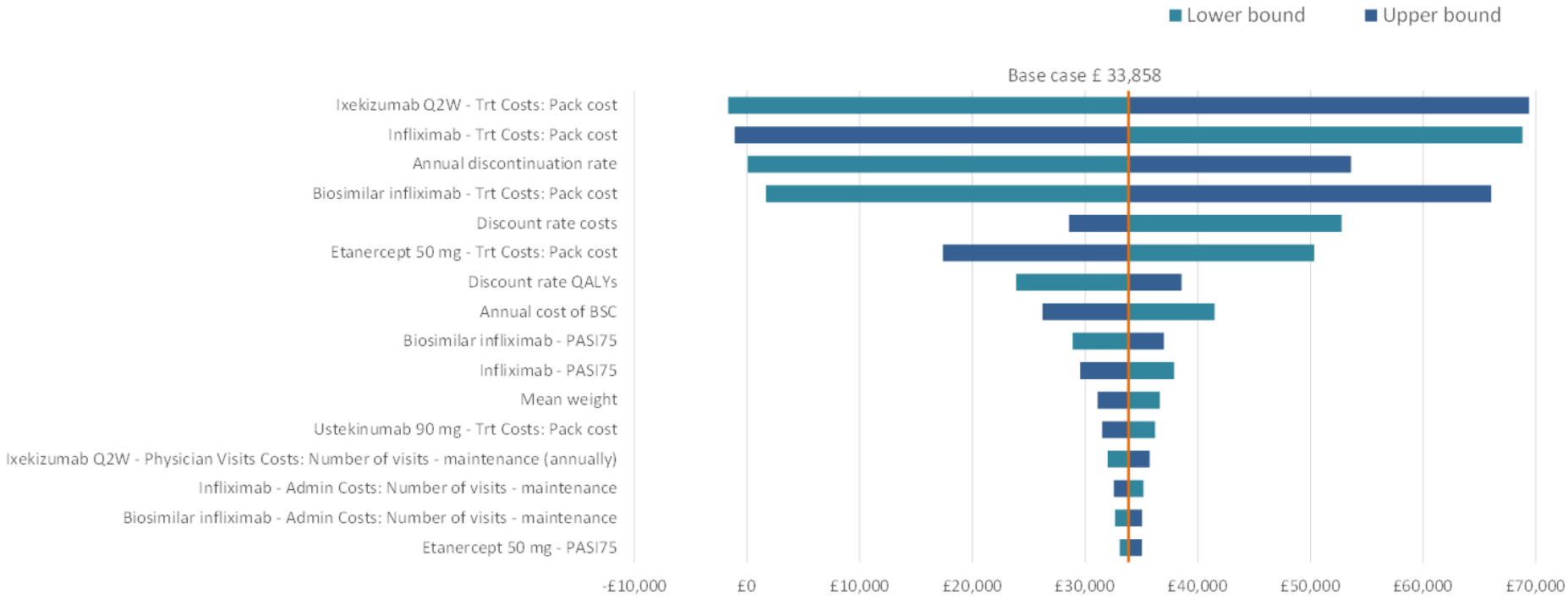
Deterministic sensitivity analyses

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	£16,109(York: 4th DLQI) to £47,235 (all patients UNCOVER)

Scenario analysis	Details scenario analysis	ICER IXE versus comparator
	from the 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

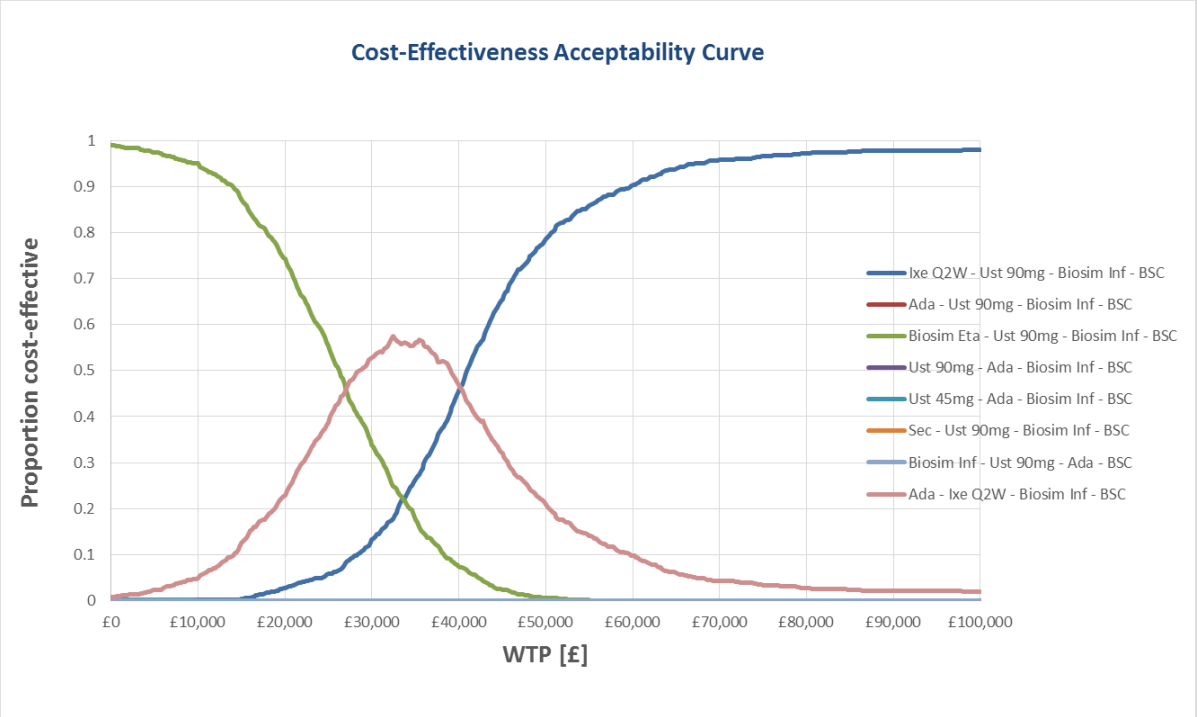
Sequence	Total costs (£)	Total QALYs gained	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE 1st line (1A) sequence vs. comparator	ICER/QALY(£): IXE 2nd line sequence (1H) vs. comparator	ICER/QALY (£) fully incremental (excluding IXE 1st line (1A) sequence)
1E: 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)

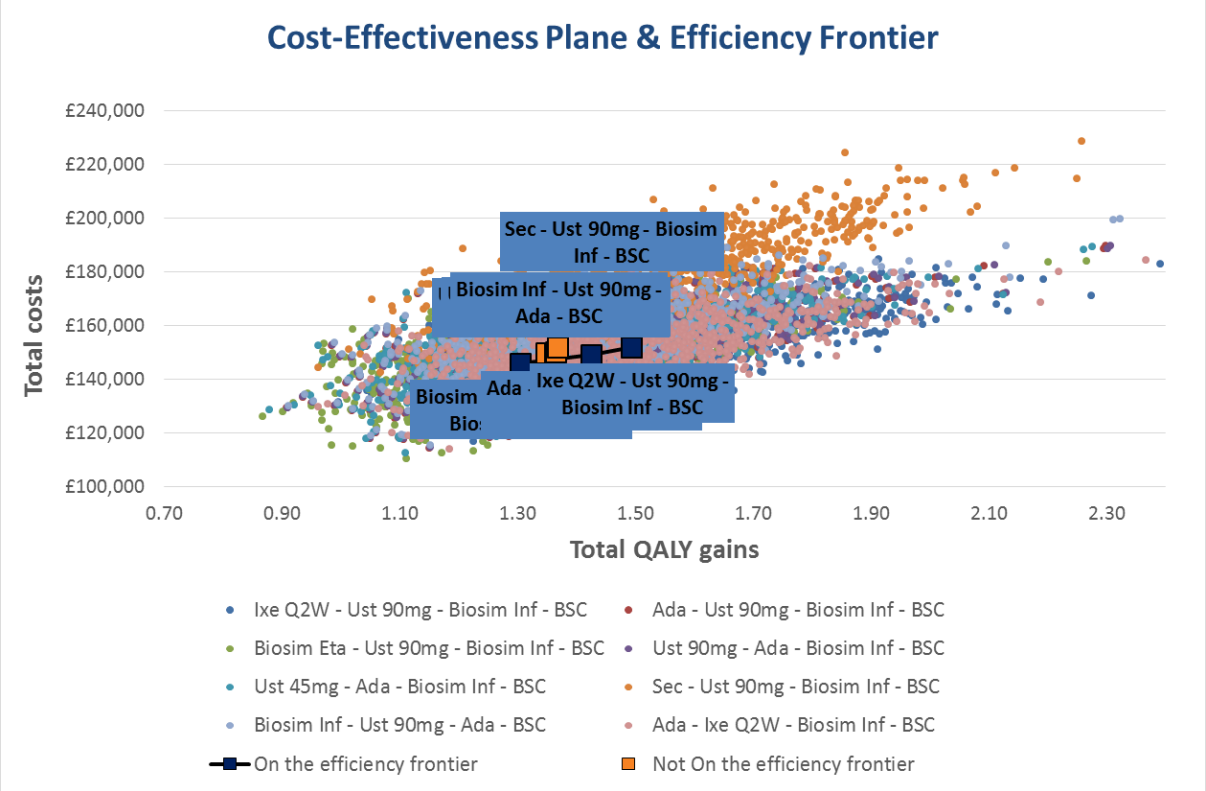
A PSA was performed to capture the parameter uncertainty in the ICER. The scatterplot and CEAC of this analysis are presented in Figures 5.4 and 5.5 respectively. Based on the ERG base-case analysis, thus also including the adalimumab>ixekizumab>infliximab>BSC (sequence 1H), ixekizumab has a probability 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

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	£139,186	1.469	£4,052	0.121	£33,352	£45,709	-	£33,352
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.

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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]

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
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	£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]

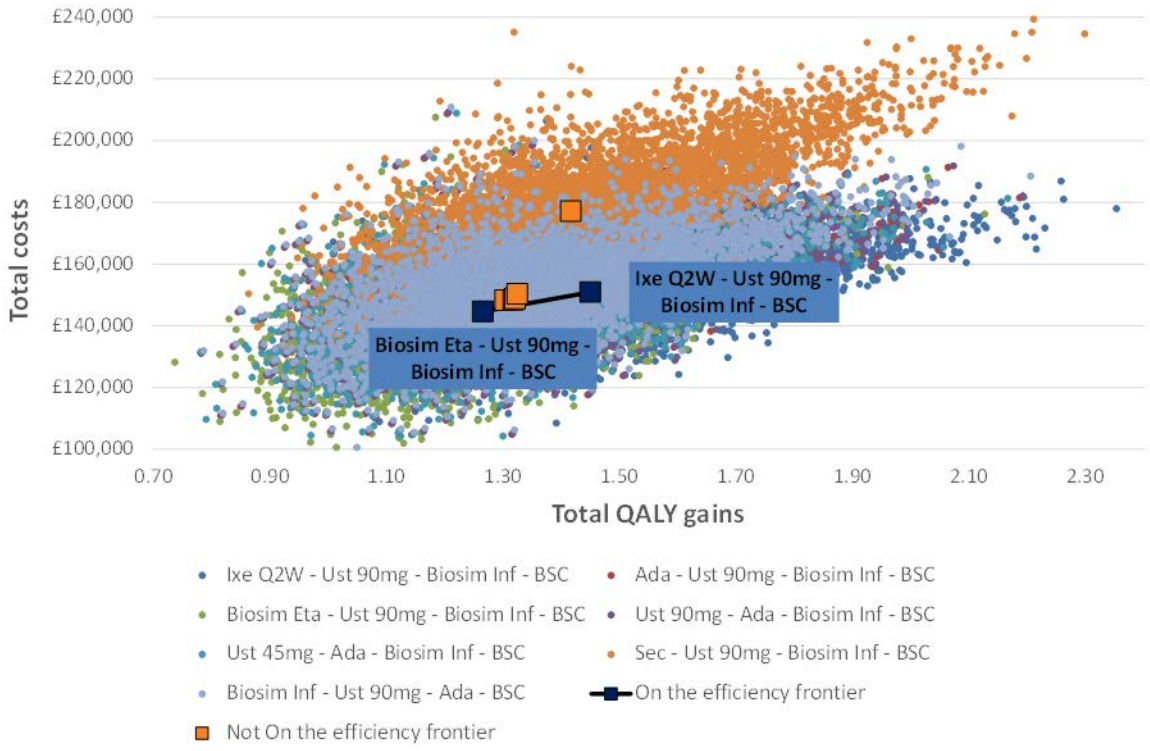
Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Administration costs	[redacted]	£1,956	[redacted]	[redacted]	[redacted]
Physician visit costs	[redacted]	£2,378	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£187	[redacted]	[redacted]	[redacted]
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

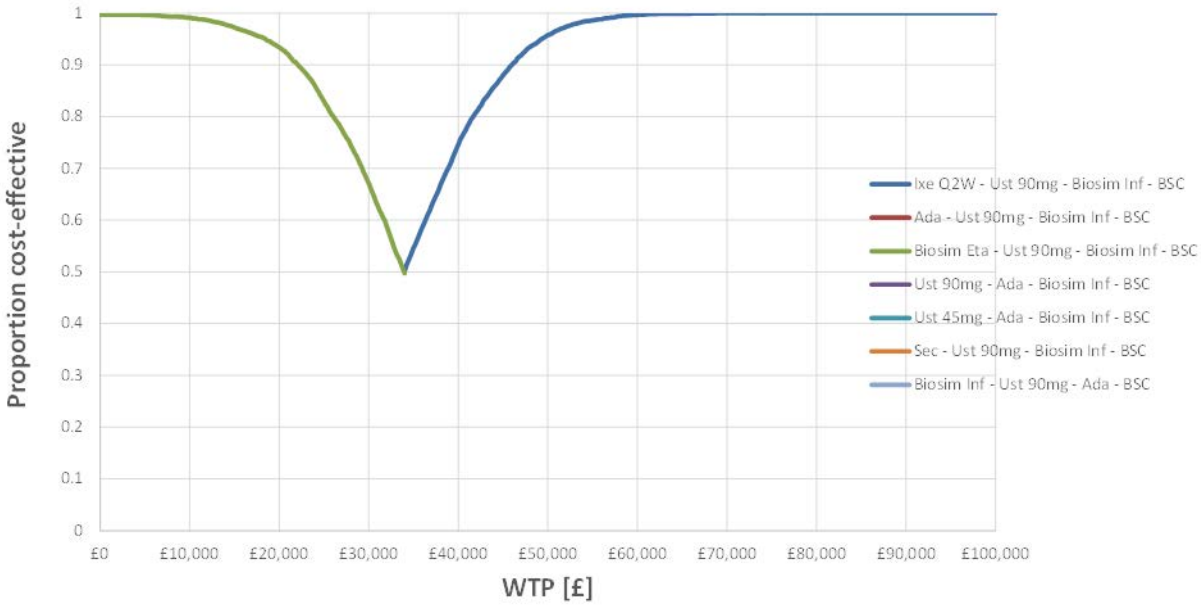
Figure A.1: CE plane



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

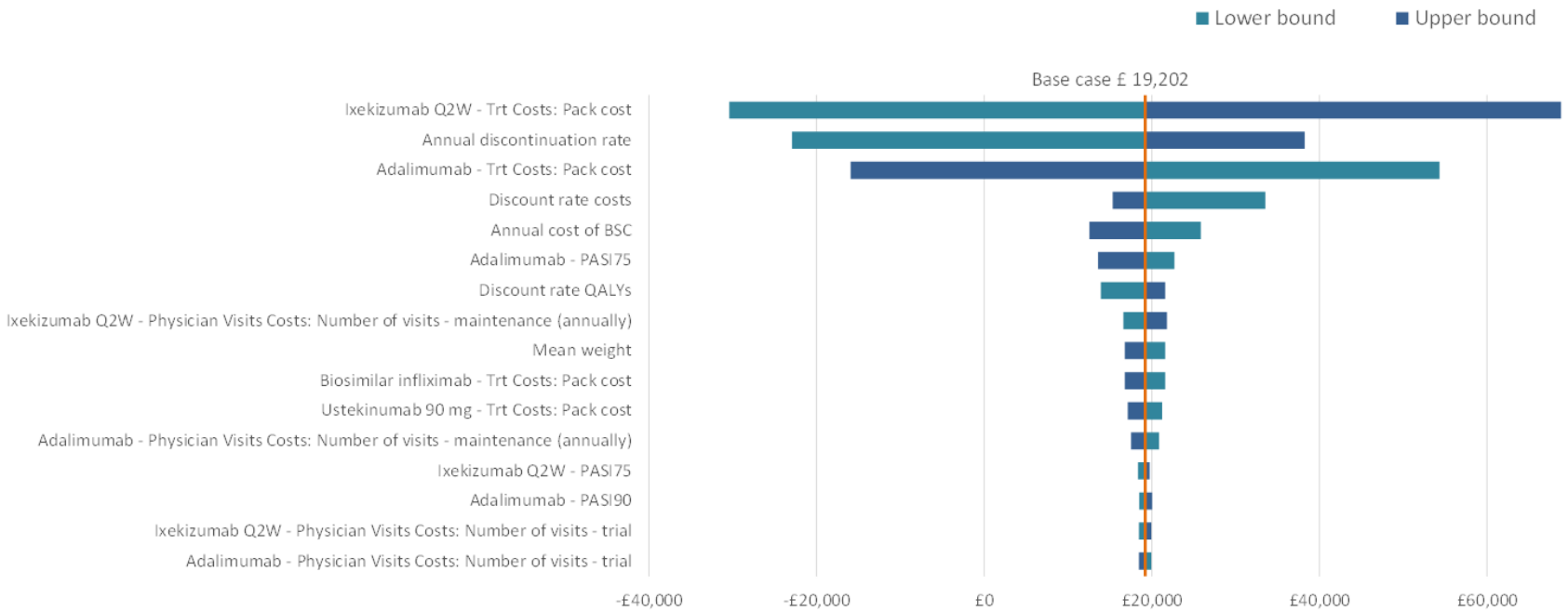
Figure A.2: CEAF



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

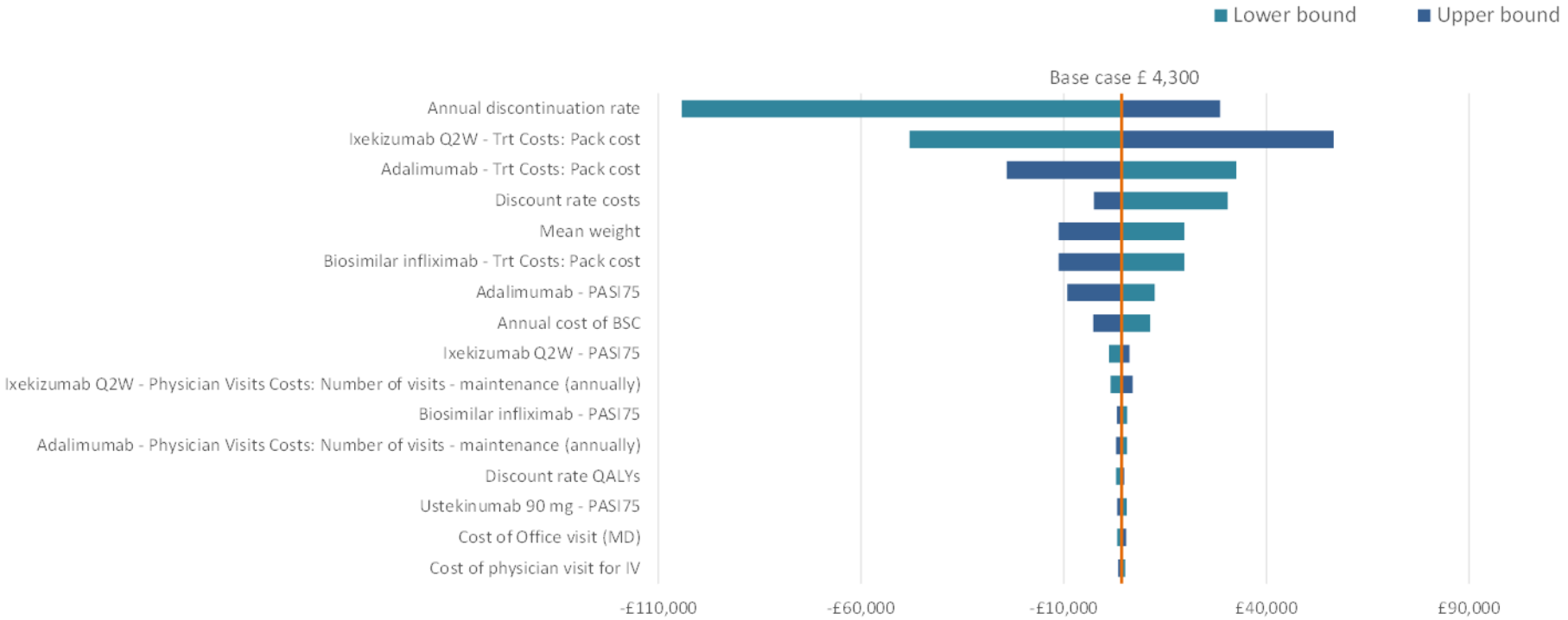
Figure A.3: Tornado diagram: ixekizumab sequence versus adalimumab sequence



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

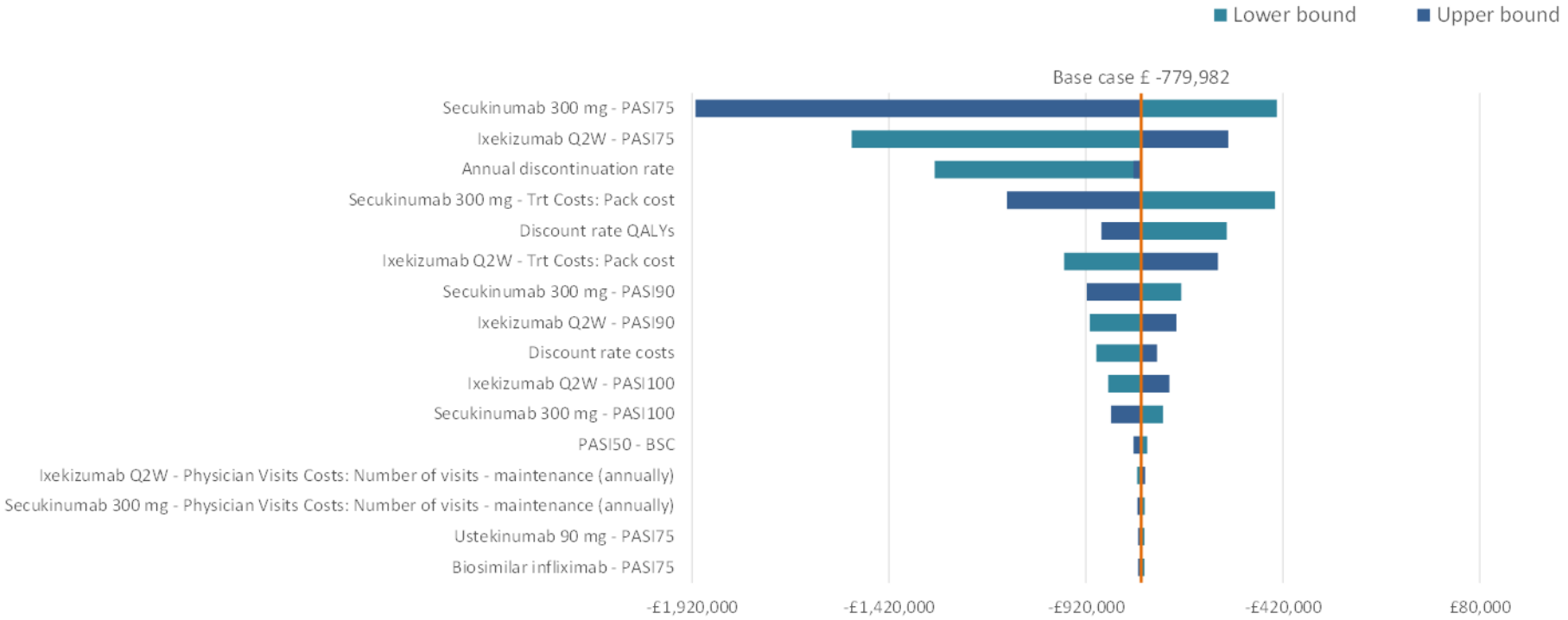
Figure A.4: Tornado diagram: ixekizumab sequence versus infliximab sequence



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

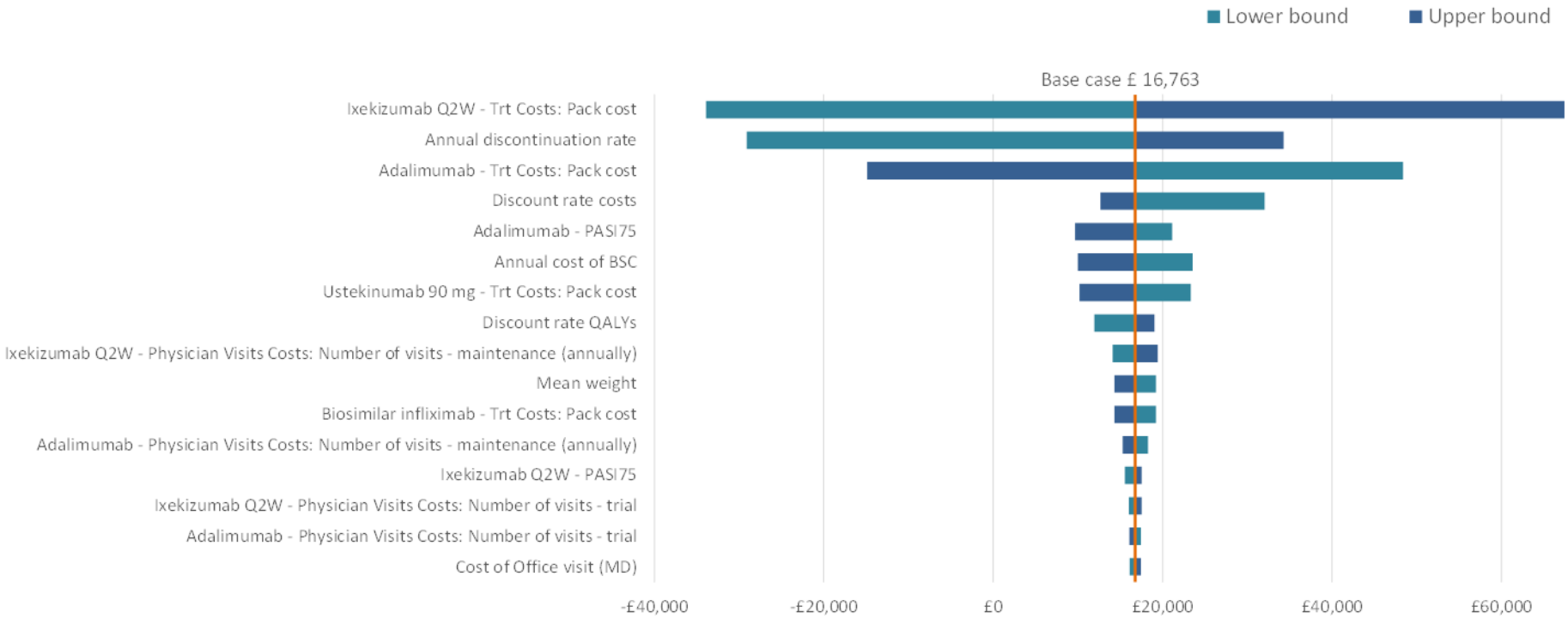
Figure A.5: Tornado diagram: ixekizumab sequence versus secukinumab sequence



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
```