NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194

The scope and matrix of consultees and commentators is available on the NICE webpage for this topic.

Contents:

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

Pre-meeting briefing

Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs

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

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

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

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

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

Abbreviations

AEs	Adverse events
ACR	American College of Rheumatology
bDMARD	Biological disease-modifying antirheumatic drug
cDMARD	Conventional disease-modifying antirheumatic drug
HAQ-DI	Health assessment questionnaire- disability index
Hrqol	Health-related quality of life
NMA	Network meta-analysis
PASI	Psoriasis area and severity index
PsA	Psoriatic arthritis
PsARC	Psoriatic arthritis response criteria
TNF-αi	Tumour necrosis factor alpha inhibitor

Key clinical issues

- Are the results of the SPIRIT trials generalisible to NHS clinical practice?
  - few patients had 2 prior cDMARDs whereas NICE guidance recommends bDMARDs after at least 2 cDMARDs

- How reliable are the network meta-analysis results?
  - overall population data used to include some comparators in the networks (apremilast, certolizumab pegol and secukinumab)
  - no prior DMARD network includes a mix of patients who have had 1 or 2 prior cDMARDs

- If PsARC response not achieved, should PASI response be considered in deciding treatment continuation? (As in recommendations for other bDMARDs)

- Any there any additional equalities issues?

Key cost effectiveness issues

- Prior bDMARD and TNF-α contraindicated populations are considered in the same analysis (considered separately in previous appraisals)

- Model based on TA445 (cert pegol and secukinumab), but results differ
  - likely to be due to different clinical effectiveness inputs (e.g. only overall population data available for NMAs)

- Other key differences to model used in TA445:
  - utility algorithm based on data from SPIRIT trials
    - ◊ scenario using TA445 algorithm: ICERs vs. BSC decrease
  - baseline PASI scores for psoriasis severity subgroups from SPIRIT
    - ◊ scenario with TA445 values shows small effect on ICER vs. BSC

- Are there any benefits not captured in the QALY calculations?

Psoriatic arthritis
Disease background

- Psoriatic arthritis is an inflammatory arthritis closely associated with psoriasis which affects joints and soft tissues
- It is a chronic progressive condition and its course may be erratic, with flare-ups and periods of remission
- Symptoms include joint stiffness, pain, swelling, and tenderness of the joints, surrounding ligaments and tendons
- These symptoms may range from mild inflammation to severe erosion of the joints.
- An estimated 5–7% of all people with psoriasis, and up to 40% of those with extensive skin disease, have psoriatic arthritis
- Peak age of onset is 30 to 50 years

Impact on patients and carers

- Most people with the disease develop it a few years after skin psoriasis
- Adding a painful, disabling connective tissue and joint disease to the skin symptoms can have a substantial psychological and physical impact
- Generally the disease affects hands and feet, but many people also have issues with other joints and their spine
- Symptoms make dressing and personal hygiene difficult and can affect the ability to work and perform activities such as childcare
- Onset is often between 20 and 40 years old, adding a substantial burden to carers who may be in employment
- Unmet need for additional options when the disease does not respond to treatment or the treatment loses efficacy and for treatments that improve symptoms such as fatigue and nail disease

Ixekizumab (Taltz)

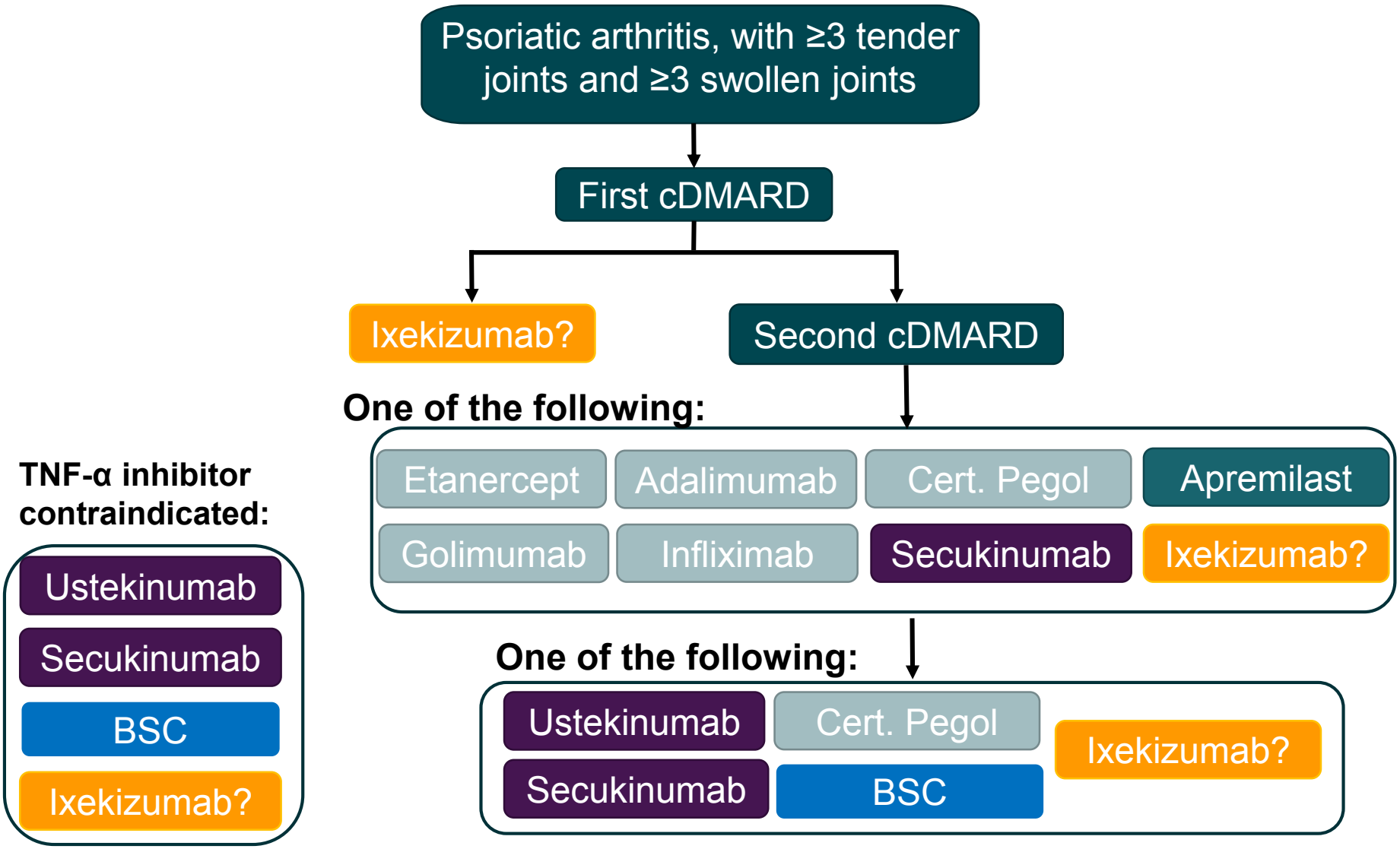
Eli Lilly

Mechanism of action	Recombinant humanised IgG4 monoclonal antibody which selectively inhibits iterleukin-17A, a pro-inflammatory cytokine.
Marketing authorisation	• For the treatment of active psoriatic arthritis in adults whose disease has inadequately responded to, or who are intolerant to 1 or more disease-modifying anti-rheumatic therapies • Alone or in combination with methotrexate
Administration and dose	• No psoriasis and mild-to-moderate psoriasis: initial 160mg subcutaneous injection followed by 80mg every 4 weeks • Moderate-to-severe psoriasis: initial 160mg subcutaneous injection followed by 80mg at weeks 2, 4, 6, 8, 10 and 12, then 80mg every 4 weeks • SmPC: consider stopping treatment if there is no response after 16 to 20 weeks of treatment
Cost	• List price: £1,125 per 80mg syringe • Average cost of a course of treatment: 1st year £16,875 - £20,250, 2nd and subsequent years £14,625 • A confidential patient access scheme is in place for ixekizumab

Clinical expert comments

- Aim of treatment is to reduce symptoms and improve quality of life
- There are 5 TNF-α inhibitors recommended in NICE guidance but there is only 1 recommended IL17 inhibitor (sekukinumab) and 1 IL12/23 inhibitor (ustekinumab)
- Advantageous to have more than 1 agent within the same class as well as different agents targeting different classes
  - for many people whose disease does not respond to 1 agent, it will respond to another agent – even within the same class
- An increasing number of people have run out of options and are left with unremitting symptoms, a very poor quality of life and disease progression
- IL17 is proven to be an important cytokine in psoriatic arthritis and has the potential to improve multiple aspects of the disease
- Ixekizumab is likely to be especially beneficial for people with significant skin psoriasis and spinal disease

Clinical pathway of care



Decision problem
Deviations from scope: comparators

NICE scope	Company submission	ERG comments
Disease not responded to 1 cDMARD: • cDMARDs	No analyses: positioning not in line with NICE Pathway/BSR guidance	Company rationale is appropriate
Disease not responded to ≥2 cDMARDs: • bDMARDs • Apremilast	• TNF-α inhibitors • Secukinumab • Apremilast • BSC	Appropriate
Disease not responded to cDMARDs and ≥1 TNF-α: • Ustekinumab, secukinumab • Certolizumab pegol • BSC	• Ustekinumab • BSC Scenario analysis only: • Certolizumab pegol • Secukinumab	Certolizumab pegol and secukinumab should be included in the base case, despite data being from mixed population (i.e. includes people who have not had a prior bDMARD)
TNF-α inhibitors contraindicated: • Ustekinumab • Secukinumab • BSC		

Clinical trial evidence

SPIRIT-P1 n=417	SPIRIT-P2 n=363
Multicentre, phase 3, randomised, double-blinded	
• Ixekizumab 80mg Q2W (n=103) • Ixekizumab 80mg Q4W (n=107) • Placebo (n=106) • Adalimumab (n=101) active reference arm, not used to test equivalence/ non-inferiority to ixekizumab	• Ixekizumab 80mg Q2W (n=123) • Ixekizumab 80mg Q4W (n=122) • Placebo (n=118)
• ≥3 tender joints, ≥3 swollen joints • Active psoriatic plaques (or history) • No prior biologic DMARD treatment	• ≥3 tender joints, ≥3 swollen joints • Active psoriatic plaques (or history) • Prior cDMARD • Inadequate response to 1 or 2 TNF-α inhibitors or intolerance to a TNF-α
• 24 week treatment period with 24 to 156 week extension period • Response assessed at 16 weeks (≥20% improvement in tender joint count and/or swollen joint count)	
• 1° outcome: ACR 20 at 24 weeks • Other outcomes used in model: PsARC, HAQ-DI, PASI 75, 90, 100, EQ-5D	

Key baseline characteristics

IXE= ixekizumab ADA= adalimumab PBO=placebo	SPIRIT-PX1				SPIRIT-P2		
	IXE Q4W	IXE Q2W	ADA	PBO	IXE Q4W	IXE Q2W	PBO
n	107	103	101	106	122	123	118
Mean age	49.1	49.8	48.6	50.6	52.6	51.7	51.5
Male, %	42.1	46.6	50.5	45.3	51.6	40.7	47.5
Years since PsA onset	10.0	10.8	9.2	10.4	13.8	11.5	11.1
No prior cDMARD, %	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
1 prior TNF-αi, %	-	-	-	-	58.2	52.8	57.6
2 prior TNF-αi,%	-	-	-	-	33.6	37.4	34.7
TNF-αi intolerant, %	-	-	-	-	8.2	9.8	7.6
Mean tender joint count	20.5	21.5	19.3	19.2	22.0	25.0	23.0
Mean swollen joint count	11.4	12.1	9.9	10.6	13.1	13.5	10.3
Mean HAQ-DI score	1.2	1.2	1.1	1.2	1.2	1.2	1.2
Mod/sev psoriasis, %	17.0	13.2	8.5	16.2	12.3	9.8	9.3

Note: [redacted] patients [redacted] across placebo/ixe arms in both trials had ≥2 cDMARDs

Outcome measures and definitions

ACR 20
American College of Rheumatology

- 7 disease activity measures
- Response: ≥20% improvement in tender joint count and swollen joint count and ≥20% improvement in at least 3 of the other measures

PASI 75
psoriasis area and severity index

- Assessment of the skin in 4 areas of the body, higher score = greater severity
- Response: 75% reduction in PASI score

PsARC: psoriatic arthritis response criteria

- 4 disease activity measures
- Response if improvement on ≥2 of the measures, 1 must be joint tenderness or swelling score, no worsening in any of the 4 measures
- NICE TA guidance for biological DMARDs specifies that PsARC should be assessed at 12 weeks to inform continued treatment decision

HAQ-DI: health assessment questionnaire- disability index

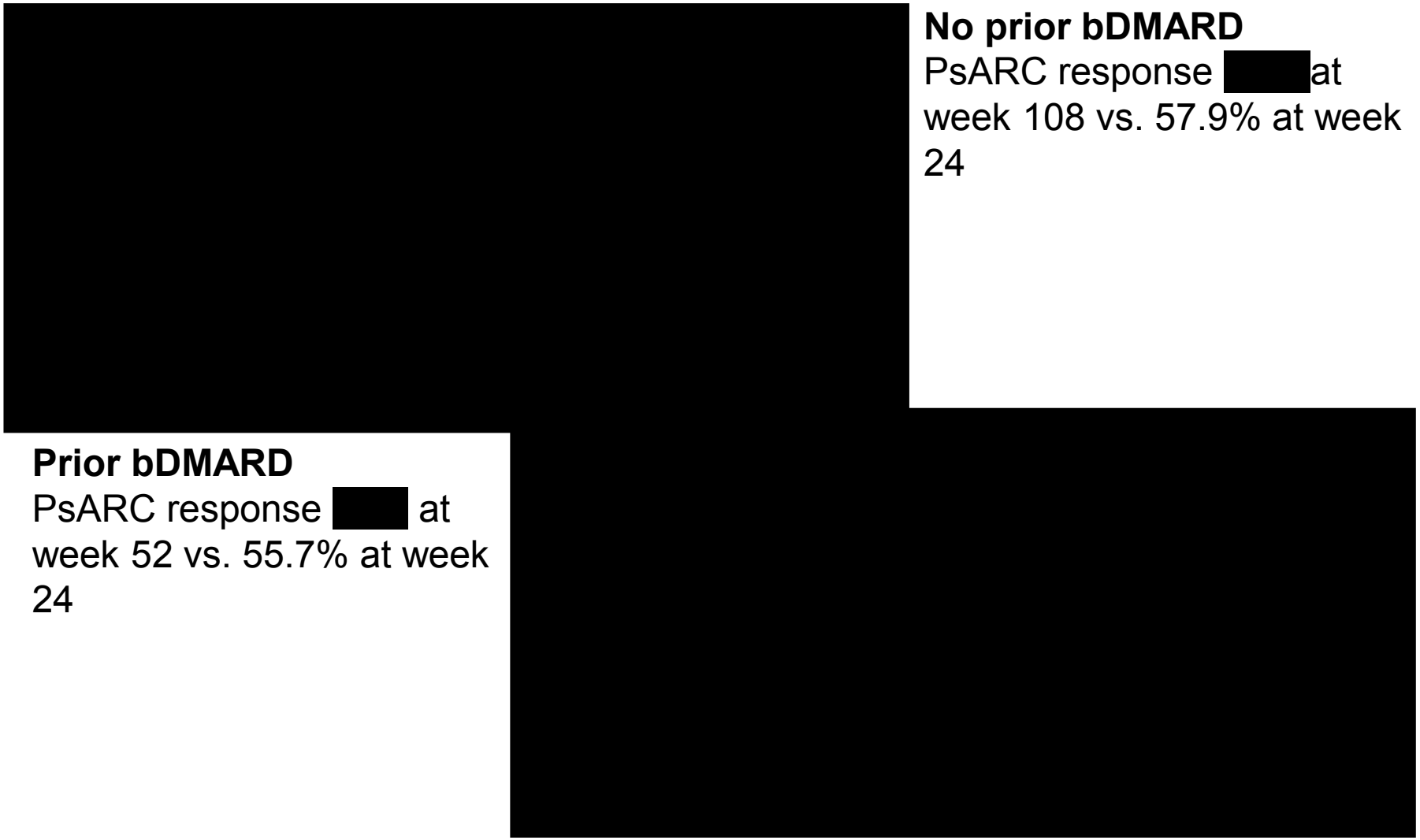
- 8 measures of daily activities, higher score indicates increased disability

Key clinical effectiveness results

	SPIRIT-P1				SPIRIT-P2		
	IXE Q4W	IXE Q2W	ADA	PBO	IXE Q4W	IXE Q2W	PBO
ACR 20 wk 12, %	**57.0**	**60.2**	**51.5**	31.1	**50.0**	**48.0**	22.0
ACR 20 wk 24, %	**57.9**	**62.1**	**57.4**	30.2	**53.3**	**48.0**	19.5
PsARC wk 12, %	**55.1**	**61.2**	**58.4**	34.0	**50.0**	**52.0**	23.7
PsARC wk 24, %	**57.9**	**66.0**	**58.4**	32.1	**55.7**	**47.2**	20.3
Change in HAQ-DI wk 12	**-0.37**	**-0.47**	**-0.35**	-0.13	**-0.40**	**-0.40**	-0.10
PASI 75 wk 12, %	**75.3**	**69.5**	**33.8**	7.5	**57.4**	**61.8**	10.4
PASI 90 wk 12, %	**52.1**	**57.6**	**22.1**	1.5	**38.2**	**42.6**	6.0
PASI 100 wk 12, %	**31.5**	**40.7**	**14.7**	1.5	**19.1**	**23.5**	6.0
Bold = significant at 95% level compared with placebo							

ACR 20 at week 24 in the analysis of patients across both trials that have had ≥2 prior cDMARDs: IXE Q4W, [redacted]; IXE Q2W, [redacted] and placebo, [redacted]

Results of open-label extension



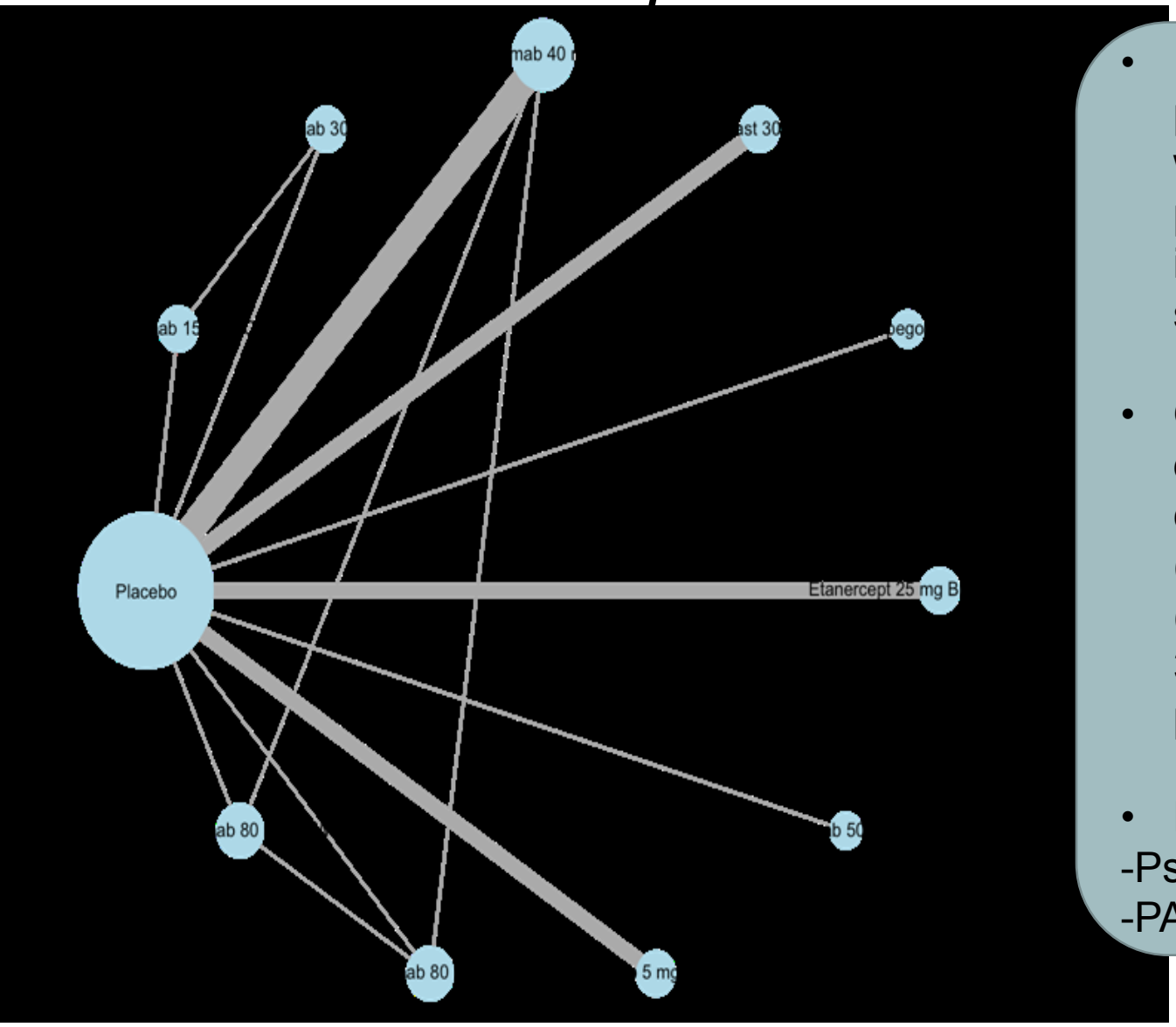
No prior bDMARD
PsARC response [redacted] at week 108 vs. 57.9% at week 24

Prior bDMARD
PsARC response [redacted] at week 52 vs. 55.7% at week 24

ERG comments: SPIRIT trials

- Both trials are well conducted randomised, blinded trials
- Trial results may not be generalisable to NHS
  - NICE Technology Appraisal guidance recommends bDMARDs only after 2 cDMARDs
  - 15% of patients in SPIRIT-1 had no prior cDMARD
  - only [redacted] patients across the two SPIRIT trials had 2 prior cDMARDs
- At week 16, patients were permitted rescue therapy if the response criteria were not met: results up to 16 weeks are more reliable

Network meta-analysis
no prior bDMARD



- Includes a mixed population of patients who have had 1 or 2 prior cDMARDs, as insufficient data for separate networks
- Overall population data used for some comparators: ~20% (cert. peg) ~35% (secukinumab) 14-30% (apremilast) had prior bDMARDs
- Network used for:

-PsARC response
-PASI 50/75/90/100

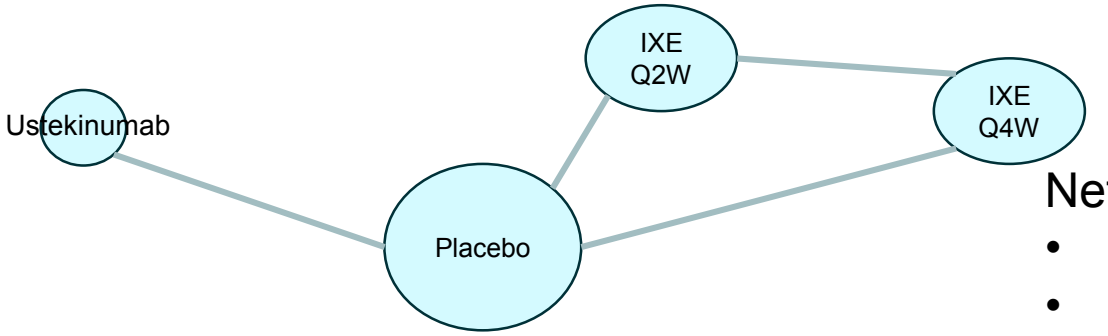
Key network meta-analysis results
no prior bDMARD

	PsARC	PsARC odds ratio vs. Ixe		PASI 75
		Ixe Q2W	Ixe Q4W	
Ixekizumab Q2W	[redacted]	-	-	[redacted]
Ixekizumab Q4W	[redacted]	-	-	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]

Odds ratio>1 favours ixekizumab

Bold = 95% credible interval does not overlap with ixe/does not embrace 1

Network meta-analysis - key results
prior bDMARD – base case



Network used for:
- PsARC response
- PASI 75/90/100

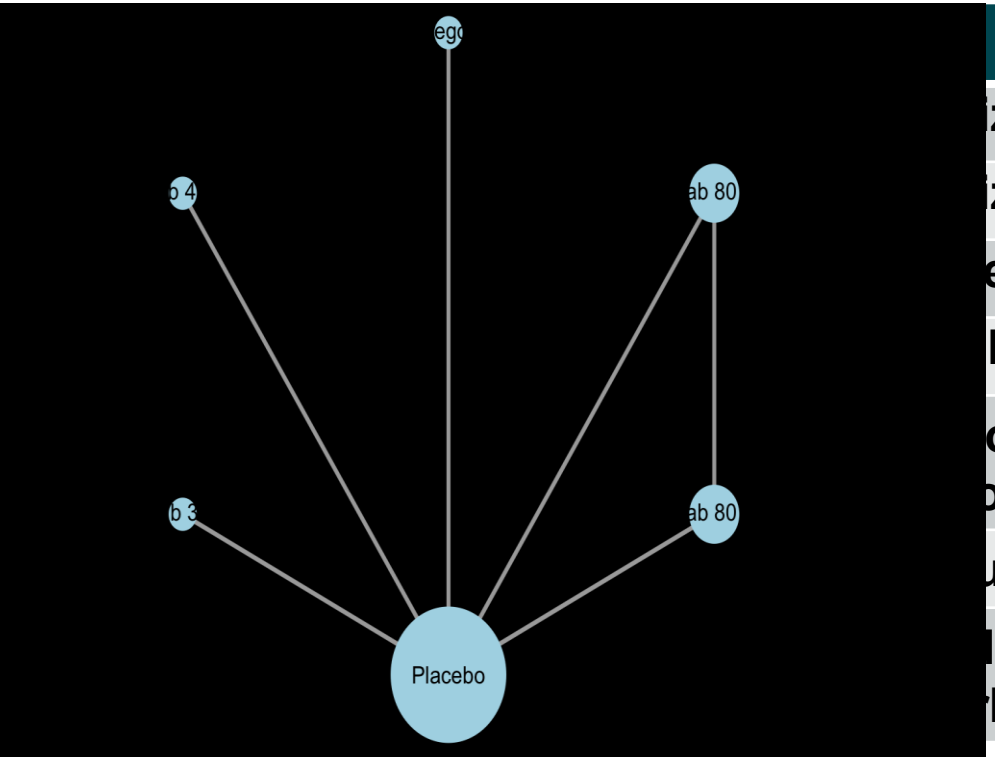
	PsARC	PsARC odds ratio vs. Ixe		PASI 75
		Ixe Q2W	Ixe Q4W	
Ixekizumab Q2W	[redacted]	-	-	[redacted]
Ixekizumab Q4W	[redacted]	-	-	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

Odds ratio>1 favours ixekizumab

Bold = 95% credible interval does not overlap with ixe/does not embrace 1

Network meta-analysis – scenario analysis

prior bDMARD: including overall population data for cert peg and secukinumab



	PsARC	PASI 75
izumab Q2W	[redacted]	[redacted]
izumab Q4W	[redacted]	[redacted]
ebo	[redacted]	[redacted]
kinumab	[redacted]	[redacted]
olizumab ol	[redacted]	[redacted]
ukinumab	[redacted]	[redacted]

= 95% credible interval does not lap with ixekizumab

Network used for:

- PsARC response
- PASI 50/75/90/100

Network meta-analysis results
mean change in HAQ-DI – overall population

	PsARC response	No PsARC response
Placebo	[redacted]	[redacted]
Ixekizumab Q2W	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Certolizumab pegol	NR	NR
Etanercept	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]

Bold = 95% credible interval does not overlap with ixekizumab

Adverse events NMA
overall population

	Treatment emergent	Serious AEs	AE discontinuation
Placebo	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Apremilast	NR	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]
Etanercept	NR	[redacted]	NR
Golimumab	NR	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Ixekizumab Q2W	[redacted]	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]	[redacted]
Ustekinumab 45mg	NR	[redacted]	[redacted]
Ustekinumab 90mg	NR	[redacted]	[redacted]
Secukinumab 150	NR	[redacted]	NR
Secukinumab 300	NR	[redacted]	NR

ERG comments: indirect treatment comparison

- Fixed effects NMAs appropriate given the small size of the networks and little difference in fit between fixed and random effects models
- To include some comparators (apremilast, secukinumab and certolizumab pegol), trial data for the full population used
  - ~20% patients (cert. peg), ~35% patients (secukinumab) and 14-30% patients (apremilast) had prior bDMARDs
  - if prior biologic exposure is an effect modifier the NMA results will not be representative of the treatment effect in each population
- Could not reproduce change in HAQ-DI results for ixekizumab from NMA
  - ERG uses results from the ixekizumab trial in its preferred base case

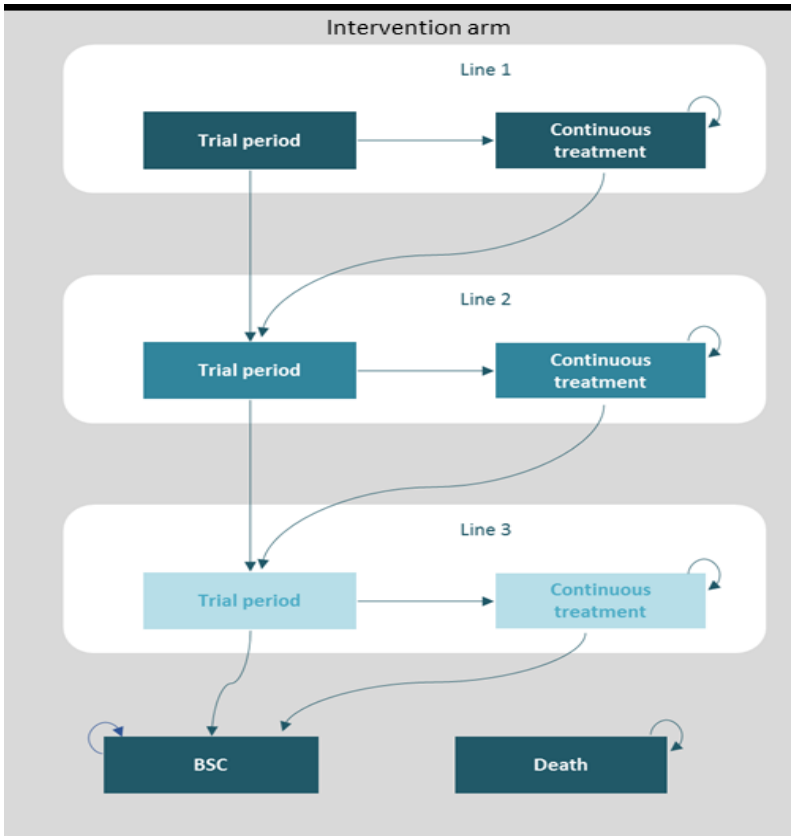
Company conclusions on the clinical effectiveness evidence

	No prior bDMARD	Prior bDMARD
PsARC	• [redacted] to ixekizumab • Ixekizumab [redacted] from other therapies	• Ixekizumab [redacted] from other therapies
PASI 75	• [redacted] best performing, but not superior to ixekizumab	• Ixekizumab [redacted] from other therapies
HAQ-DI	• [redacted] largest absolute change	

- Long-term data demonstrate sustained responses with ixekizumab
- Most biologic treatments do not effectively address extra-articular symptoms
  - ixekizumab resolved nail involvement for 30% of patients and dactylitis for over 75% of patients at week 24
- Except secukinumab, biologics do not achieve high levels of PASI 90/100
  - ixekizumab: 44-67% achieved PASI 90, 28-52% achieved PASI 100
- Ixekizumab well tolerated with a safety profile comparable to other biologics

Economic model

- Model based on AG model used in TA445



Populations based on psoriasis severity

		No prior bDMARD	Prior bDMARD	TA445
None	PASI	0	0	0
	HAQ-DI	1.17	1.39	1.22
Mild - mod	PASI	3.9	3.7	7.3
	HAQ-DI	1.17	1.20	1.22
Mod - severe	PASI	20.4	23.4	12.5
	HAQ-DI	1.19	1.16	1.22

- Cycle length: 1 month (TA445: 3 months)
- Time horizon: 40 years
- NHS/PSS perspective
- Subsequent treatment in no prior bDMARD population: ustekinumab

Health states in model

Trial period

- Trial period length depends on the therapy and lasts from 10 to 24 weeks
  - 12 weeks for ixekizumab to align with when outcome assessment in SPIRIT
- In final temporary state, PsARC and PASI response assessed
- Change in HAQ-DI score is conditional on PsARC response

Continued treatment period

- Only PsARC response used to determine continued treatment, and response is maintained while treatment continues
- Constant risk of discontinuation (16.5% as in TA445) due to any cause
- On discontinuation, PsARC response lost and HAQ-DI and PASI scores revert to baseline
- Patients move to trial period of ustekinumab (no prior bDMARD pop) or BSC

BSC

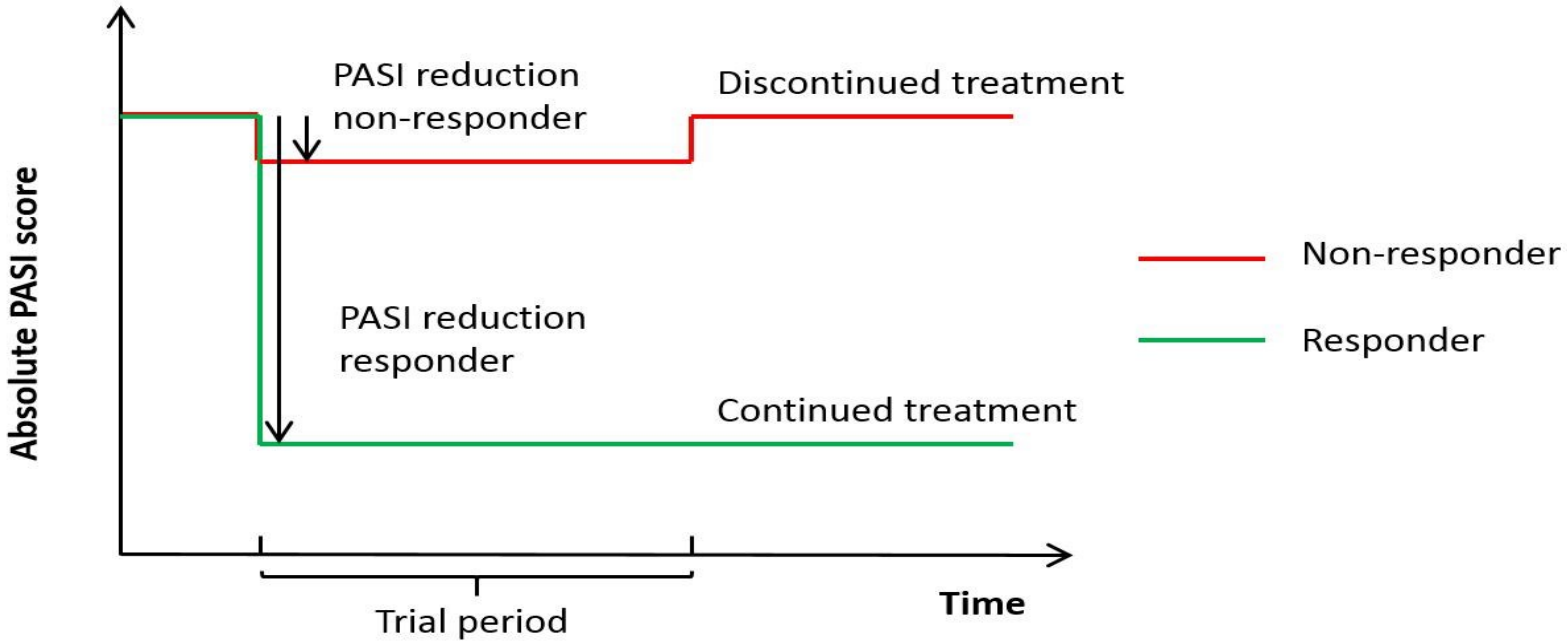
- Assumed to be a mix of cDMARDs and palliative care
- Placebo rates from the NMAs used as a proxy for BSC
- Corresponding BSC PsARC and PASI response maintained until death but HAQ-DI progresses according to natural history

Clinical data in the model

- Base case:
  - NMA results for PsARC and PASI (stratified by prior bDMARD use)
  - NMA results for HAQ-DI (not stratified by prior bDMARD use)
  - no results stratified for psoriasis severity- treatments assumed to be similarly effective (in relative terms) for each psoriasis subgroup within the prior/no prior bDMARD populations
    - ◊ differences in cost-effectiveness driven by the different baseline PASI and HAQ-DI scores (slide 24) and the subsequent impact on costs and outcomes of these differences
  - UK general population mortality data adjusted to represent the excess mortality associated with PsA using a standardised mortality ratio of 1.36 (as used in TA445)
- Scenario analysis: efficacy estimates from meta-regression with baseline risk as the covariate – to account for observed increase in placebo response over time (only for no prior bDMARD population)

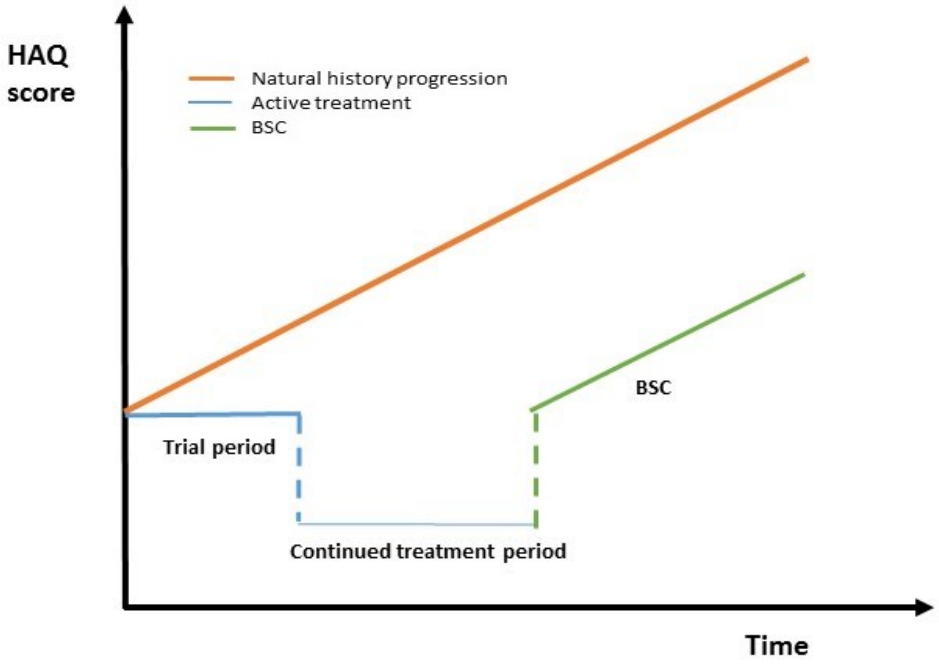
PASI response

- Instantaneous improvement in PASI in trial period
  - lower for PsARC non-responders
- PASI 75 response may be achieved with or without a PsARC response
  - correlation coefficient of 0.4 from TA445 used to model relationship
- PsARC responders maintain PASI improvement while continuing treatment
- On discontinuing treatment PASI score reverts to baseline



Change in HAQ-DI

- Instantaneous improvement in baseline HAQ-DI at start of trial period (specific to each treatment), maintained for duration of trial period
  - lower if no PsARC response
- PsARC response: improvement maintained as long as treatment continues
- For patients without a PsARC response or who stop treatment during the continued treatment period, HAQ-DI assumed to rebound to baseline and then progress in line with the natural history of the disease



ERG comments on model structure

- PsARC response is a relative measure so patients in continued treatment state may be heterogeneous in terms of resource use/hrqol
  - however, modelling is consistent with that in TA445
- Baseline PASI for psoriasis subgroups differ from TA445 (see slide 24)
  - ERG uses values from TA445 in a scenario analysis
- Only ustekinumab considered as a 2nd line treatment, but secukinumab and certolizumab pegol are also recommended
  - ERG scenario analysis explores alternative sequences
- More appropriate to include certolizumab pegol and secukinumab in base-case analysis for the prior bDMARD subgroup
- Standardised mortality ratio used by company to adjust background mortality for excess mortality associated with PsA (1.36) based on old data and may be too high, as excess mortality seems to have declined
  - ERG prefers more recent cut of the same data (1996-2004 rather than 1978-2004) which produces a value of 1.05

Utility values

- EQ-5D-5L collected in SPIRIT trials and mapped to the EQ-5D-3L using the indirect mapping approach recommended in NICE position statement
- EQ-5D-3L values used in base case, 5L used in a scenario analysis
- Data from SPIRIT trials analysed separately, to reflect differences between prior/no prior bDMARD populations
- Utility values depend on PASI score and HAQ-DI score (and therefore PsARC response) and are treatment specific

Utility algorithm	Intercept	HAQ-DI	PASI
bDMARD naive	[redacted]	[redacted]	[redacted]
bDMARD experienced	[redacted]	[redacted]	[redacted]
TA445: all populations	0.897	-0.298	-0.004

- Impact of adverse events on health-related quality of life not modelled
  - company: differences may be adequately captured in impact on initial response and long-term withdrawal rates

Costs and health care resource use

Psoriasis management costs (used in TA445 – inflated to 2017 prices)			
	No psoriasis	**Mild-moderate**	**Moderate-severe**
Uncontrolled psoriasis	£0	£892	£2,552
Controlled psoriasis (PASI 75 response)	£0	£72	£72

- Disease management costs: £1,867.56 + £565.64 x HAQ
  - Kobelt et al. algorithm (as in TA445), Poole et al. scenario analysis
- Costs of adverse events not modelled
- Drug acquisition costs:
  - certolizumab pegol recommended only if manufacturer provide first 12 weeks of treatment free – this is incorporated in model
  - secukinumab and apremilast have confidential discounts
  - common evidence base assumed for ustekinumab, no further adjustment needed to account for complex PAS
  - prices of biosimilar infliximab and etancercept used in model

ERG comments: utilities and costs

- Company base case does not adjust utilities to account for age
  - ERG base case caps utilities at the population norm
- HRQoL and costs of adverse events not included in model
  - treatment-specific adverse events could have an impact on treatment discontinuation (assumed equal), utility and costs
  - not reflecting this in the model could lead to biased outcomes, but direction of bias difficult to determine
  - company's approach is consistent with TA445
- Source for resource use data Kobelt et al. (2002) is dated
  - no better alternative source identified
  - Poole et al (2010) used in scenario analysis

Cost effectiveness results

- Several of the comparator technologies have confidential discounts
- All results including intervention and comparator discounts are confidential and are presented in a confidential appendix for committee members
- List price analyses (incl. non-confidential patient access schemes) presented for information

Company deterministic base case
no prior biological DMARD

No psoriasis: x - ustekinumab – BSC sequence						
	Total costs £	Total QALYs	Pairwise: ixe vs. comparator			ICER: fully inc. £
			Δ costs £	Δ QALYs	ICER £	
BSC	54,046	8.09	61,964	1.60	**38,750**	**-**
Apremilast	93,347	9.49	22,663	0.20	**109,534**	**Ext. Dom**
Cert pegol	99,866	9.67	16,144	0.02	**636,928**	**Ext. Dom**
Secukinumab	100,241	9.78	15,769	-0.09	***Dominated**	**Ext. Dom**
Adalimumab	101,322	9.71	14,688	-0.02	***Dominated**	**Dominated**
Etanercept	103,692	10.02	12,318	-0.33	***Dominated**	**25,810**
Golimumab	108,195	9.90	7,815	-0.21	***Dominated**	**Dominated**
Ixekizumab	116,010	9.69	-	-	**-**	**Dominated**
Infliximab	127,297	10.12	-11,287	-0.43	**26,593**	**236,122**

* Ixekizumab is dominated in the pairwise analysis

Company deterministic base case
no prior biological DMARD

Mild-to-moderate psoriasis: x - ustekinumab – BSC sequence						
	Total costs £	Total QALYs	Pairwise: ixe vs. comparator			ICER: fully inc. £
			Δ costs £	Δ QALYs	ICER £	
BSC	70,006	7.74	57,771	1.64	**35,316**	**-**
Apremilast	105,446	9.16	22,331	0.22	**99,733**	**Ext. Dom**
Cert pegol	111,375	9.34	16,402	0.04	**431,727**	**Ext. Dom**
Secukinumab	111,743	9.47	16,034	-0.09	***Dominated**	**Ext. Dom**
Adalimumab	112,849	9.39	14,928	-0.01	***Dominated**	**Dominated**
Etanercept	114,657	9.69	13,120	-0.31	***Dominated**	**22,947**
Golimumab	118,987	9.59	8,790	-0.21	***Dominated**	**Dominated**
Ixekizumab	127,777	9.38	-	-	**-**	**Dominated**
Infliximab	138,072	9.82	-10,295	-0.44	**23,230**	**175,864**

* Ixekizumab is dominated in the pairwise analysis

Company deterministic base case
no prior biological DMARD

Moderate-to-severe psoriasis: x - ustekinumab – BSC sequence						
	Total costs £	Total QALYs	Pairwise: ixe vs. comparator			ICER: fully inc. £
			Δ costs £	Δ QALYs	ICER £	
BSC	99,884	6.21	55,575	1.90	**29,170**	**-**
Apremilast	127,576	7.70	27,883	0.41	**67,096**	**Ext. Dom**
Cert pegol	132,373	7.90	23,086	0.21	**109,062**	**Ext. Dom**
Adalimumab	133,882	7.97	21,577	0.14	**155,110**	**Ext. Dom**
Etanercept	134,567	8.24	20,892	-0.13	***Dominated**	**17,055**
Golimumab	138,550	8.23	16,909	-0.12	***Dominated**	**Dominated**
Ixekizumab	155,459	8.11	-	-	**-**	**Dominated**
Secukinumab	155,532	7.97	-73	0.14	**Dominant**	**Dominated**
Infliximab	157,603	8.51	-2,144	-0.40	**5,335**	**84,228**

* Ixekizumab is dominated in the pairwise analysis

Company deterministic base case
prior biological DMARD

	Total costs £	Total QALYs	Pairwise: ixe vs. comparator			ICER: fully inc. £
			Δcosts £	ΔQALYs	ICER £	
No psoriasis: x – BSC sequence						
BSC	55,942	7.38	37,427	0.83	**45,092**	**-**
Ustekinumab	82,143	8.24	11,226	-0.03	***Dominated**	**30,311**
Ixekizumab	93,369	8.21	-	-	**-**	**Dominated**
Mild-to-moderate psoriasis: x – BSC sequence						
BSC	70,271	7.06	35,291	0.87	**40,344**	**-**
Ustekinumab	94,133	7.97	11,429	-0.04	***Dominated**	**26,231**
Ixekizumab	105,562	7.93	-	-	**-**	**Dominated**
Moderate-to-severe psoriasis: x – BSC sequence						
BSC	99,618	2.26	35,445	0.98	**36,197**	**-**
Ustekinumab	118,915	3.21	16,148	0.03	**557,092**	**20,307**
Ixekizumab	135,063	3.24	-	-	**-**	**557,092**

* Ixekizumab is dominated in the pairwise analysis

Company scenario analysis inc. cert p/secuk		Total costs £	Total QALYs	Pairwise: ixe vs. comparator			ICER: fully inc. £
				Δcosts £	ΔQALYs	ICER £	
No psoriasis x – BSC sequence	BSC	55,942	7.38	43,638	0.99	**44,182**	-
	Cert p	80,329	8.27	19,251	0.10	**211,521**	**27,197**
	Ustek	85,799	8.38	13,781	-0.01	***Dominated**	**50,168**
	Ixek	99,580	8.37	-	-	-	**Dominated**
	Secuk	103,621	8.29	-4,041	0.08	**Dominant**	**Dominated**
Mild-to-moderate x – BSC sequence	BSC	70,271	7.06	41,092	1.12	**36,508**	-
	Cert p	91,990	8.10	19,373	0.08	**241,378**	**20,778**
	Ustek	97,374	8.23	13,989	-0.05	***Dominated**	**43,069**
	Ixek	111,363	8.18	-	-	-	**Dominated**
	Secuk	115,570	8.11	-4,207	0.07	**Dominant**	**Dominated**
Moderate-to-severe x – BSC sequence	BSC	99,618	2.26	40,435	1.73	**23,258**	-
	Cert p	116,121	3.88	23,932	0.11	**199,670**	**10,195**
	Ustek	121,338	4.08	18,715	-0.09	***Dominated**	**26,082**
	Ixek	140,053	3.99	-	-	-	**Dominated**
	Secuk	140,265	3.87	-212	0.12	**Dominant**	**Dominated**

* Ixekizumab is dominated in the pairwise analysis

Key company scenario analyses

Scenario	Effect: ixekizumab ICERs vs. BSC (list price)
No prior bDMARD: no subsequent ustekinumab	up to 17% higher
No prior bDMARD: placebo-adjusted response rates	up to 17% higher
Ixekizumab response assessment at 16 weeks (SmPC: consider stopping if response not seen 16-20 weeks but measured at 12 weeks in trial)	up to 3% higher
Poole et al. algorithm for resource use costs	no/mild psoriasis: up to 10% lower severe psoriasis: up to 14% higher
Assume HAQ-DI rebounds to natural history in BSC	up to 83% higher
Assume HAQ-DI rebounds to 50% of initial gain	18-39% lower
Alternative utility algorithm (TA445 coefficients)	26-34% lower
EQ-5D-5L utility values	up to 8% higher
Treatment continuation: PsARC and PASI 75	up to 27% lower

ERG comments cost effectiveness results

- BSC may not be representative of the NHS
  - unable to assess if the effectiveness and the costs associated with BSC are valid
- Compared with the TA445 model results:
  - estimated costs of comparators lower for no prior bDMARD population, higher for prior bDMARD population
  - estimated QALYs of comparators higher for no prior bDMARD population, lower for the prior bDMARD population
- Differences could be explained by:
  - PsARC response: generally lower in current model
  - HAQ-DI for PsARC responders: generally larger reduction
  - differences in PASI response probabilities and baseline scores

ERG's preferred base case

1. Correction of error in NMA results for HAQ-DI scores for ixekizumab
   - ERG uses ixekizumab trial data instead of the NMA results
2. Calculations for PASI change based on PsARC response in the model inconsistent with methodology reported in company submission
   - ERG adjusts calculations to match those detailed in the submission
3. NMA including certolizumab pegol and secukinumab used for prior bDMARD population
4. Utilities adjusted to cap at general population values
5. Standardised Mortality Ratio derived from more recent data

ERG preferred base case results:

- Ixekizumab ICERs vs. BSC similar to company base case for no psoriasis subgroups (for prior/no prior bDMARD populations)
- Ixekizumab ICERs vs. BSC lower than company base case for moderate and severe subgroups (for prior/no prior bDMARD pops)

ERG scenario analyses

- Poole et al. for HAQ-DI related costs instead of Kobelt et al.
- Baseline PASI scores from TA445
- Alternative subsequent treatments for no prior bDMARD population
- PASI 75 in addition to PsARC to assess treatment continuation

Results of scenario analyses:

- ICERs vs. BSC robust in all ERG scenario analyses

Equality and innovation

- During scoping a potential equality issue was identified:
  - there might be difficulties for some people to self-administer this technology, if they lack hand dexterity due to the effects of arthritis
- Initial view on equality issue:
  - this issue relates to additional resources for administering the treatment, not an equality issue within the equality legislation
  - there are already processes in place in clinical practice for people who are unable to self-administer subcutaneous treatments
- Company's view on innovation:
  - 1st monoclonal antibody to block both active forms of IL-17A
  - 2nd anti-IL-17 to offer an alternative mechanism of action to TNF-alpha inhibitors and IL12/23
  - ixekizumab is effective in treating extra-articular symptoms such as skin psoriasis, nail psoriasis, dactylitis and structural progression
  - symptoms such as nail psoriasis can add an additional burden but improvements may not be captured by the EQ-5D and therefore in the QALY

Key clinical issues

- Are the results of the SPIRIT trials generalisible to NHS clinical practice?
  - few patients had 2 prior cDMARDs whereas NICE guidance recommends bDMARDs after at least 2 cDMARDs

- How reliable are the network meta-analysis results?
  - overall population data used to include some comparators in the networks (apremilast, certolizumab pegol and secukinumab)
  - no prior DMARD network includes a mix of patients who have had 1 or 2 prior cDMARDs

- If PsARC response not achieved, should PASI response be considered in deciding treatment continuation? (As in recommendations for other bDMARDs)

- Any there any additional equalities issues?

Key cost effectiveness issues

- Prior bDMARD and TNF-α contraindicated populations are considered in the same analysis (considered separately in previous appraisals)

- Model based on TA445 (cert pegol and secukinumab), but results differ
  - likely to be due to different clinical effectiveness inputs (e.g. only overall population data available for NMAs)

- Other key differences to model used in TA445:
  - utility algorithm based on data from SPIRIT trials
    - ◊ scenario using TA445 algorithm: ICERs vs. BSC decrease
  - baseline PASI scores for psoriasis severity subgroups from SPIRIT
    - ◊ scenario with TA445 values shows small effect on ICER vs. BSC

- Are there any benefits not captured in the QALY calculations?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194]

Document B

Eli Lilly and Company Limited

Please note academic in confidence (AIC) information are underlined and highlighted in yellow

Commercial in confidence (CIC) information are underlined and highlighted in turquoise

File name	Version	Contains confidential information	Date
Ixe PsA_NICE STA Document B	Final	Yes	2 February 2018

Contents

Tables and Figures

Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Adalimumab
AESI	Adverse event of special interest
AIC	Academic in Confidence
ANA	Antinuclear antibody
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APR	Apremilast
ATTC	Antithrombotic Trialists' Collaboration
AWMSG	All Wales Medicines Strategy Group
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BHPR	British Health Professionals in Rheumatology
BI	Budget impact
BID	Twice daily
BIM	Budget impact model
BIW	Twice weekly
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Registry
CADTH	Canadian Agency for Drugs and Technologies in Health
CASPAR	Classification Criteria for Psoriatic Arthritis
CCG	Clinical Commissioning Group CHMP
CE	Cost-effectiveness
CEA	Cost-effectiveness acceptability curve
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CFB	Change from Baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIC	Commercial in confidence

Abbreviation	Definition
CICLO	Ciclosporin
CMH	Cochran Mantel Haenszel
CODA	Convergence Diagnostic and Output Analysis
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
CVZ	College Voor Zorgverzekeringen
CZP	Certolizumab pegol
DARE	Database of abstracts of reviews of effects
DAS	Disease Activity Score
DCE	Discrete choice experiment
DEF	Data extraction form
DIC	Deviance information criteria
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drug
DSA	Deterministic sensitivity analyses
DSR	Database of Systematic Reviews
DSU	Decision Support Unit
EADV	European Academy of Dermatology and Venerology
EDF	European Dermatology Forum
EED	Economic Evaluation Database
EFA	Efalizumab
EMA	European Medicines Agency
ERB	Ethics Review Board
ERG	Evidence Review Group
ESR	Erythrocyte sedimentation rate
ETAN	Etanercept
ETN	Etanercept
ETV	Early termination visit
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAD	Final appraisal determination
FBC	Full blood count

Abbreviation	Definition
FDA	Food and Drug Administration
FPV	First Patient Visit
GOL	Golimumab
GPRD	General Practice Research Database
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HADS	Hospital Anxiety and Depression Scale
HAM	Hamilton Rating Scale
HAQ-DI	Health Assessment Questionnaire-Disability Index
HAS	Haute Autorité de Santé
HCRU	Health Care Resource Utilisation
HEOR	Health economics and outcomes research
HRQOL	Health-related quality of life
HTA	Health technology assessment
IBD	Inflammatory Bowel Disease
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive care unit
ICUR	Incremental cost-utility ratio
IGA	Investigator's Global Assessment
INF	Infliximab
IPC	International Psoriasis Council
IQR	Interquartile range
IRB	Institutional review board
ISE	Injection-site reaction
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
IXE	Ixekizumab
LCI	Lower Confidence Interval
LDI-B	Leeds Dactylitis Index-Basic
LEF	Leflunomide
LEI	Leeds Enthesitis Index

Abbreviation	Definition
LFT	Liver Function Test
LOCF	Last observation carried forward
LOS	Length of Stay
LPV	Last Patient Visit
LSM	Least squares mean
LTE	Long-term extension
MACE	Major adverse cardiovascular events
MAPP	Multinational Assessment of Psoriasis and Psoriatic Arthritis
MCS	Mental component summary
MDA	Minimal Disease Activity
MIMS	Monthly Index of Medical Specialities
MMRM	Mixed-effects model repeated measures
MOS	Medical Outcomes Study
MTA	Multiple technology assesment
MTC	Mixed treatment comparison
MTX	Methotrexate
NA	Not applicable
NAPSI	Nail Psoriasis Severity Index
NBST	Non-biologic systemic therapy
NBUVB	Narrow band ultraviolet B
NCPE	National Centre for Pharmacoeconomics
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NMSC	Non-melanoma skin cancer
NNT	Number needed to treat
NOAR	Norfolk Arthritis Register
NOKC	Nasjonalt kunnskapssenter for helsetjenesten
NR	Not reported
NRI	Non-responder imputation
NRS	Numerical rating scale
NSAIDS	Nonsteroidal anti-inflammatory drugs
OPAL	Oral Psoriatic Arthritis Trial
OR	Odds ratio
OWSA	One-way sensitivity analysis

Abbreviation	Definition
OXIS	Oxford Medical Information System
PAS	Patient Access Scheme
PASI	Psoriasis Area and Severity Index
PASLU	Patient Access Scheme Liaison Unit
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PCP	Pneumocystis pneumonia
PGA	Physician's Global Assessment
PICOS	Patient, Intervention, Comparators, Outcome, Study design
PIIINP	Amino-terminal propeptide of type III procollagen
PPASI	Palmoplantar Psoriasis Severity Index
PQOL	Psoriasis Quality of Life 12
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
PRPA	Psoriasis-Related Pruritus Assessment
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analysis
PSI	Psoriasis symptom inventory
PSO	Psoriasis
PSOLAR	Psoriasis Longitudinal Assessment Registry
PSS	Personal Social Services
PSSI	Psoriasis Scalp Severity Index
PSSRU	Personal Social Services Research Unit
QALY	Quality of life
QALYS	Quality-adjusted life year
QIDS	Quick inventory of depressive symptomatology
QIW	Four times per week
QOL	Quality of Life
RCT	Randomised controlled trial
RHAP	SPIRIT-P1 (NCT01695239)
RHBC	UNCOVER-3 (NCT01646177)
RHBE	SPIRIT-P2 (NCT02349295)
RHBL	UNCOVER-A (NCT01777191)
RHCF	SPIRIT-H2H
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEC	Secukinumab

Abbreviation	Definition
SJC	Swollen Joint Count
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision-Making
SPARCC	Spondyloarthritis Research Consortium of Canada Enthesitis Index
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TA	Technology appraisal
TEAE	Treatment-related adverse event
THIN	Health Improvement Network
TJC	Tender Joint Count
TLV	Tandvårds- och läkemedelsförmånsverket
TNF	Tumour Necrosis Factor
TSD	Technical Support Document
TTO	Time Trade-Off
UST	Ustekinumab
UVB	Ultraviolet B
VAS	Visual Analogue Scale
VB	Visual Basic
WHO	World Health Organisation
WPAI	Work and Activity Impairment Questionnaire
WTP	Willingness to Pay

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

1.1 Decision problem

Ixekizumab, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic (DMARD) therapies. (1)

The submission presents the clinical- and cost-effectiveness data of Ixekizumab for treating active psoriatic arthritis in adults whose disease has not responded adequately to trials of at least 2 conventional DMARDs given either alone or in combination, or have not been able to tolerate or have a contraindication to previous DMARD therapy.

Therefore, this submission covers only part of the technology marketing authorisation for this indication.

The decision problem can be seen in Table 1 below.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active psoriatic arthritis whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug therapy.	Adults with active psoriatic arthritis whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug (DMARD) therapy, or have not been able to tolerate or have a contraindication to previous DMARD therapy. Subgroups that should be considered separately are: • Patients whose disease has not responded adequately to at least two previous conventional DMARD (cDMARD) therapies either alone or in combination • Patients whose disease has not responded adequately to one or more biologic DMARDs (bMARD) • Patients with concomitant moderate to severe psoriasis for whom the anticipated dosing schedule for ixekizumab would include a Q2W induction dosing period and Q4W maintenance dosing.	NA
Intervention	Ixekizumab (Taltz®)	Ixekizumab 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks for patients without concomitant moderate-to-severe psoriasis and Ixekizumab 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 for patients with concomitant moderate-to-severe psoriasis.	NA
Comparator(s)	For people who have only received 1 prior non-biological disease modifying anti-rheumatic drug (DMARD) • Non-biological DMARDs	For people who have failed on two or more prior standard DMARDs (biologic naïve): • TNF-alpha inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol)	The positioning of biologic therapy in patients with only one prior standard DMARD is not in line with current NICE pathways or BSR guidance (except in the case of adverse prognostic factors). As noted in the Final Appraisal

	For people whose disease has not responded adequately to at least 2 non-biological DMARDs: • Biological DMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol [subject to ongoing NICE appraisal], secukinumab [subject to ongoing NICE appraisal]) • Apremilast For people whose disease has not responded adequately to non-biological and biological DMARDs, or biological DMARDs are contraindicated: • Ustekinumab • Certolizumab pegol and secukinumab (subject to ongoing NICE appraisal) • Best supportive care.	• Secukinumab • Apremilast For people whose disease has not responded adequately to non-biological and biological DMARDs, or biological DMARDs are contraindicated: • Ustekinumab • Certolizumab pegol • Secukinumab • Best supportive care.	Determination document for the multiple technology appraisal of secukinumab and certolizumab pegol, the committee questioned whether biologic therapy is established clinical practice in the NHS after failure on only one prior DMARD and which specific group of patients would use a biologic at this stage in the pathway. (2)
Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • periarticular disease (for example enthesitis, dactylitis) • mortality • adverse effects of treatment • health-related quality of life	This submission includes a range of outcome measures to assess the clinical benefit of ixekizumab, including: • Disease activity (ACR 20/ 50/ 70, PsARC, MDA) • Functional capacity (HAQ-DI) • Effect on concomitant skin condition (Psoriasis Area and Severity Index (PASI)) – including PASI 75/90/100 • Other complications of psoriatic arthritis including LEI- enthesitis, NAPSI- nail psoriasis (modified version), LDI-dactylitis, structural progression (mTSS) • Health related quality of life (EQ-5D) • Adverse events will be reported for ixekizumab and comparators based on the results from the clinical studies	Skin involvement (e.g. PASI response) is a relevant outcome to include in the scope. The following outcomes will be modelled in the economic analysis: • Disease activity, assessed by the PsARC • Functional capacity, measured by the HAQ-DI score • Health-related quality of life, measured by EQ-5D and mapped using PASI and HAQ-DI scores Data on the impact of ixekizumab on periarticular disease and disease progression, and the adverse effects of treatment are presented in the submission but not included in the economic analysis due to insufficient comparative data. No biologic treatment for psoriatic arthritis has demonstrated an effect on mortality outcomes in the context of a clinical trial, therefore mortality in the model has been modelled as the application

			of excess mortality risk associated with PsA to the mortality risk in the general population.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. For the comparators the availability and cost of biosimilars should be taken into consideration.	Cost-effectiveness results are expressed as incremental cost per quality-adjusted life year, with a lifetime model horizon, considering costs from an NHS and PSS perspective. The cost of biosimilar etanercept and biosimilar infliximab are taken into consideration in the base case analysis. Results are presented using the list price for treatments in the base case due to the confidentiality of the patient access schemes (PAS) for apremilast and secukinumab. The PAS for certolizumab pegol is taken into account.	NA
Subgroups to be considered	If evidence allows the following subgroups will be considered: • the reason for treatment failure (for example due to lack of efficacy, intolerance or adverse events). • Presence or severity of concomitant psoriasis (no psoriasis, mild to moderate psoriasis, moderate to severe psoriasis)	The subgroups of interest in the economic analysis are: Comorbid psoriasis severity (no psoriasis, mild to moderate psoriasis, moderate to severe psoriasis) and Previous bDMARD experience (bDMARD-naïve, bDMARD-experienced).	•
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No equity or equality issues identified.	As per the reference case

Abbreviations: DMARD = disease-modifying antirheumatic drugs; bDMARD = biologic disease-modifying antirheumatic drugs; ACR = American College of Rheumatology; ACR 20 = at least 20% improvement in both tender and swollen joint counts; ACR 50 = at least 50% improvement in both tender and swollen joint counts; ACR 70 = at least 70% improvement in both tender and swollen joint counts; PsARC = Psoriasis Area and Severity Index; MDA =Minimum Disease Activity; HAQ-DI = Health Assessment Questionnaire-Disability Index; LEI = Leeds Enthesitis Index; LDI-B = Leeds Dactylitis Index-Basic; NAPSI = Nail Psoriasis Severity Index; mTSS = modified Total Sharp Score; HRQoL = Health-related quality of life; NHS = National Health Service; NMA = network meta-analysis; PAS = patient access scheme; PSS = Personal Social Services; QALY = quality adjusted life year; SLR = systematic literature review; SmPC = summary of product characteristics;αα = tumour necrosis factor alpha

1.2 Description of the technology being appraised

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

Details of the technology being assessed are presented in Table 2 below.

Table 2 Technology being appraised

UK approved name and brand name	Approved name: Ixekizumab Brand name: Taltz®
Mechanism of action	Ixekizumab is a recombinant humanised IgG4 monoclonal antibody (mAb) designed and engineered to selectively inhibit interleukin-17A (IL-17A), a pro-inflammatory cytokine.(1)
Marketing authorisation/CE mark status	Date (mm/yyyy) of regulatory submission: [redacted] Date (mm/yyyy) of CHMP positive opinion: 12/2017 Date (mm/yyyy) of regulatory approval: 01/2018
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ixekizumab, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic (DMARD) therapies.
Method of administration and dosage	Ixekizumab is administered by subcutaneous injection (SC). Dosage The recommended dose of ixekizumab is dependent on the concomitant psoriasis severity: PsA patients without co-morbid moderate-to-severe psoriasis should receive an initial dose of 160 mg by SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks. PsA patients with concomitant moderate-to-severe psoriasis should receive an initial dose of 160 mg by SC injection(two 80 mg injections) at week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.
Additional tests or investigations	None.
List price and average cost of a course of treatment	**List price** Taltz® 80mg solution for injection in prefilled pen x 2 = £2,250 Taltz® 80 mg solution for injection in prefilled syringe = £1,125 Average cost of a course treatment Per annum cost for PsA patients with concomitant mild to-moderate psoriasis: First year: 15 injections – £16,875 Second year: 13 injections – £14,625 Per annum cost for PsA patients with co-morbid moderate to severe psoriasis:

	First year: 18 injections – £20,250 Second year: 13 injections – £14,625 **PAS price** Taltz® 80mg solution for injection in prefilled pen x 2 = [redacted] Taltz® 80 mg solution for injection in prefilled syringe = [redacted] Average cost of a course treatment Per annum cost for PsA patients with concomitant mild to-moderate psoriasis: First year: 15 injections – [redacted] Second year: 13 injections – [redacted] Per annum cost for PsA patients with co-morbid moderate to severe psoriasis: First year: 18 injections – [redacted] Second year: 13 injections – [redacted]
Patient access scheme (if applicable)	A simple discount PAS has been agreed with the Department of Health.

cDMARD = conventional disease-modifying antirheumatic drug; igG4 = immunoglobulin 4; IL = interleukin; mAb = monocloncal antibody; PAS = patient access scheme; PsA = psoriatic arthritis SC = subcutaneous

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

1.3.1 Health condition

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory arthropathy associated with psoriasis. (3) PsA is characterized by pain, stiffness, and swelling of joints, which can affect the whole body and, if untreated, cause permanent joint and tissue damage (4-6) and ultimately disability. (7)

PsA is a heterogeneous disease with a considerably varied clinical presentation, as joint and skin symptoms range from mild to very severe and do not always correlate with each other. (8) PsA can affect the skin, nails, peripheral joints, entheses, and spine. (9-11) Asymmetric peripheral small joint disease is present in most patients and is characterized by pain and reddish discoloration of joints along with swelling. Presentation of inflammatory arthritis can affect any joint but often affects the distal interphalangeal joints. (5, 12) Dactylitis is found in approximately 50% of patients with PsA and is characterized by swelling of an entire digit (sausage-like digits). (12) Enthesitis, characterized by inflammation at attachment sites for tendons or ligaments, is observed in 30% to 50% of patients with PsA in clinical practice, with the Achilles tendon being the most frequently affected joint. (12) Nail psoriasis is present in up to 90% of patients with PsA and can present as discoloration of the nails, pitting, subungual hyperkeratosis, and pustules; in some cases, patients can lose the nail.

(5, 12) As patients with PsA usually have psoriasis, erythematous and flaky skin is a frequent symptom. (13)

Psoriatic arthritis is a progressive disease. At an early stage, x-ray images of the hands and feet can show joint erosion, joint space narrowing, bony proliferation, osteolysis, ankylosis, and new bone formation. (13) If the joint damage experienced early in PsA is not treated promptly, it can lead to crippling damage as time and the disease progress. (14) Six months from PsA symptom onset, peripheral joint erosions develop because of active inflammation leading to poor long-term physical function. By 2 years, radiological damage is present in 47% of patients, and up to 50% of patients may have developed erosive disease. (8, 15, 16)

Psoriatic arthritis affects men and women equally, and the peak age of onset is between 30 and 50 years of age. (9-11) It is estimated that around 0.19% of the adult population in the UK is affected by PsA. (17) PsA prevalence is estimated to be higher among people with psoriasis (between one and two people in every five people with psoriasis), (4) particularly among those with severe psoriasis. (17) In around 70% of people psoriasis precedes psoriatic arthritis, (17) although, joint involvement can appear before, at the same time or after the skin symptoms. (18) On average, the onset of arthritis tends to occur from 7 to 10 years after the onset of skin symptoms, leading to an increasing cumulative incidence of PsA with longer duration of psoriatic disease. (19) Some patients only present with the typical clinical manifestations in the joints (including inflammatory arthritis, enthesitis, dactylitis, and spondylitis), no skin disease but a family history of skin disease. (18)

More than half of patients with PsA have at least one comorbidity. (20) Incidence of common PsA comorbidities can be seen in Table 3 below.

Table 3 Incidence of PsA comorbidities

Incidence of PsA comorbidities					
Comorbidity	**Husted et al, 2013 (n= 631), n (%)[a]**	**Kraishi et al, 2014 (n= 196), n (%)**	**Edson-Heredia et al, 2015 (n= 1952), n (%)**	**Feldman et al, 2015 (n=1230), n (%)[b]**	**Ogdie et al, 2015 (n= 8706), n (%)**
Obesity	204 (32.3)	117 (59.7)	—	—	—
Hypertension	221 (35.0)	64 (32.7)	376 (19.3)	440 (35.8)	—
Infection	216 (34.2)	—	—	—	—
Depression/anxiety	130 (20.6)	27 (13.8)	530 (27.2)	185 (15.0)	—
Hyperlipidemia	124 (19.7)	98 (61.6)[c]	157 (8.0)	425 (34.6)	—
Diabetes	72 (11.4)	27 (13.8)	98 (5.0)	196 (15.9)	—
Cancer	56 (8.9)	—	—	80 (6.5)	—
CVD	48 (7.6)	17 (8.7)	64 (3.3)	118 (9.6)	338 (3.9)

Gastrointestinal disease	37 (5.9)	—	—	16 (1.3)	—
Liver disease	15 (2.4)	—	—	—	—

Source: table reproduced from Husni 2015 (20)

[a] Based on a list of 15 comorbidities: CVD, hypertension, hyperlipidemia, type II diabetes, obesity, respiratory disease, gastrointestinal disease, neurologic disease, autoimmune disease, liver disease, depression/anxiety, cancer, other musculoskeletal conditions, infection, and fibromyalgia.

[b] Comorbidities in patients with PsA with moderate to severe PsO.

[c] Includes patients on dyslipidemia medications.

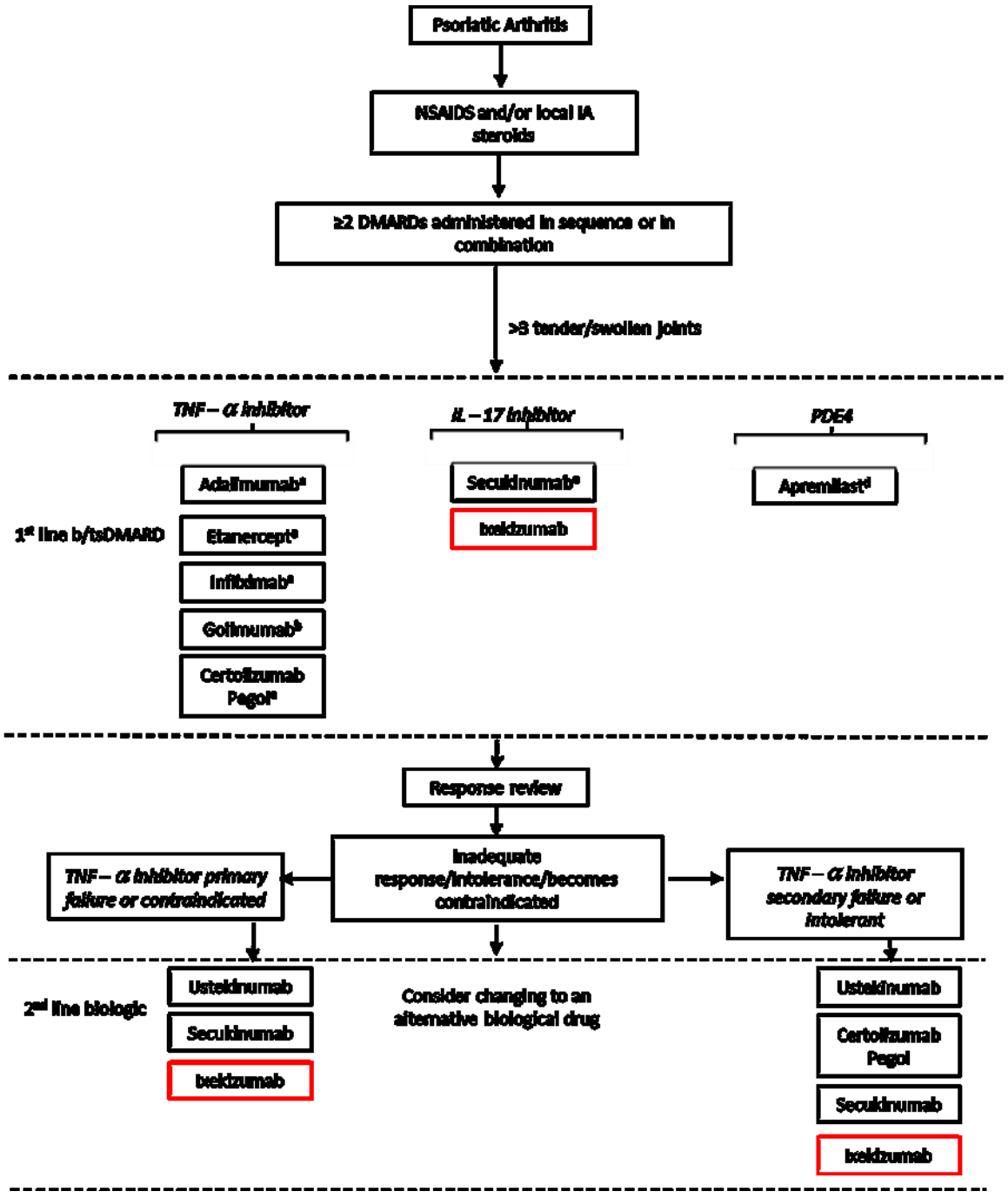
Cardiovascular disease was the leading cause of death among PsA patients. (21) Although PsA mortality risk seemed to have improved over time, (21) PsA patients still have an increased risk of death compared to the general population, with more recent studies presenting standardised mortality ratios (SMR) varying between 0.82 to 1.59. (21-24) It is estimated that PsA patients have a reduced life expectancy of approximately 3 years compared to the general population. (21)

In addition to having a detrimental effect on survival, PsA also has a substantial and negative impact on many areas of a patient's HRQoL. A cross-sectional survey of PsA patients and their treating physicians from 16 countries reported that 33-42% of participants with severe PsA experienced "a lot" of limitation in doing vigorous daily activities, such as climbing stairs or lifting heavy objects, while 23-29% could not perform daily activities such as bending, kneeling, or dressing themselves. (25) The percentage of patients who reported experiencing "a lot" of limitation in the daily activities increased with disease severity. (25) The HRQoL of PsA patients is lower than that of the general population as well as that of patients with other forms of inflammatory arthritis. (3)

1.3.2 Position of the technology in the treatment pathway

Treatment options for PsA include the use of NSAIDs, and/or intra-articular corticosteroid injections, conventional DMARDS as well as biologic DMARDS and targeted synthetic DMARDS. In the UK, the current clinical pathway of care for PsA patients according to published NICE clinical guidelines and technology appraisals can be seen in Figure 1 below.

Figure 1 Proposed position of ixekizumab within the treatment pathway for patients with PsA in accordance with NICE recommendations



NSAIDS= nonsteroidal anti-inflammatory drugs; IA= Intra-articular; DMARD= Disease-modifying antirheumatic drugs; bDAMRD= biologic Disease-modifying antirheumatic drugs; tsDMARD= targeted synthetic Disease-modifying antirheumatic drugs; TNF-alpha = tumour necrosis actor alpha; IL-17= interleukin - 17; PDE4= phosphodiesterase type 4; a=NICE TA199 (26); b=NICE TA220 (27); c=NICE TA340 (28); d=NICE TA433 (29); e=NICE TA445 (2).

Treatment guidelines have been published by multidisciplinary consortium of clinical societies, namely the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). (30, 31) While there are some differences as to how both consortiums approach the recommendations, in

general, there is alignment between the recommendations issued by both organisations. These recommendations largely correspond with technology appraisals published by NICE.

The British Society for Rheumatology and the British Health Professionals in Rheumatology have also published NICE accredited treatment guidelines for the treatment of psoriatic arthritis with biologics in 2013. (32) However, as a result of the rapidly evolving treatment paradigm in psoriasis, not all currently available treatment options are included in these guidelines (e.g. newer biologic therapies).

Symptomatic therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids, although widely used to address the symptoms of PsA, (30, 31) have limited efficacy against peripheral arthritis symptoms, may exacerbate the skin symptoms of PsA, and long-term use is associated with harmful side-effects. (33, 34)

Despite the variety of treatment options shown in Figure 1, currently available systemic therapies (including conventional disease-modifying antirheumatic drugs [cDMARD], targeted disease-modifying antirheumatic drugs [tDMARD] and biologic disease-modifying antirheumatic drugs [bDMARD]) are associated with a number of limitations, such as lack of efficacy, inability to sustain efficacy, side-effects or poor tolerability, and inconvenience or lifestyle compromise. These limitations have led to widespread dissatisfaction with treatments. Over a quarter of rheumatologists in the MAPP survey (27.7%) reported feeling as though patients were leaving their clinic due to dissatisfaction or frustration with treatments, whilst 13.3% of rheumatologists stated that PsA treatments can be worse than the condition itself. (35) Furthermore, 64% of patients in the MAPP survey expressed concern about the health risks of long-term therapy, and 90% of patients with PsA felt there was a need for better therapies. (36)

Patients receiving cDMARDs may fail to achieve adequate improvements or find them burdensome, due to side-effects or inconvenience. (36) Evidence from RCTs show that only 26–44% of patients receiving leflunomide, cyclosporine, and methotrexate (MTX) achieve an ACR 20 response within 24 weeks, whilst observational studies have found limited impact of MTX and sulfasalazine on potentially irreversible structural joint damage. (37-42) cDMARDs also have limited efficacy against skin symptoms.

While biologics are effective in some patients, (43, 44) RCT data indicate that they may not achieve adequate control across the symptom domains of PsA. Poor efficacy has been commonly reported in patients who have received currently available biologic treatments. (45-48) In a real-world study, 39–65% of patients cited lack of efficacy as their reason for discontinuation. For example, even with biologic treatments (such as adalimumab,

certolizumab pegol, golimumab, infliximab, secukinumab, and ustekinumab), American College of Rheumatology criteria ≥20% (ACR 20) response rates range from 42–65% after 24 weeks of treatment in RCTs. (49-57)(46-54) Furthermore, RCT data show these treatments do not effectively address the extra-articular symptoms. For example, only 30–49% of patients in RCTs who received these treatments achieved a PASI 90 response, whilst dactylitis and enthesitis persisted in 12–65% and 20–76% of patients after 24 weeks. (49-59)

As is the case with other biologics, anti-TNFα therapies are associated with or have demonstrated improvement in disease activity and even remission for many patients with PsA, however, their efficacy is not universal. (14, 60, 61) A substantial number of patients with PsA do not achieve or maintain satisfactory disease control with anti-TNFα therapy. (18, 60, 61) Clinical experts estimate that approximately 10% of PsA patients per year stop TNF-α inhibitor treatment. (29) Reasons for the loss of efficacy of anti-TNFα therapy are multifactorial. (60) In some, intolerability or serious adverse events may occur; in others, disease activity may change and increase despite the use of anti-TNFα therapy; and in others, gradual loss of efficacy may occur. (60) When a patient does not respond to one anti-TNFα therapy, switching to another anti-TNFα therapy is a well-established practice in the NHS. (29) However, even with switching, data from real-world studies suggest that survival/persistence on a second and subsequent agents may be lower, with discontinuation rates increasing with successive switches. (14, 47, 60) Data from the DANBIO registry showed that the proportion of patients who achieved ACR 20, 50, and 70 responses within 3–6 months of anti-TNFα treatment (adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol), decreased significantly with each consecutive treatment line. (48) For example, less than 50% of the patients who achieved an ACR 20, 50 and 70 response after treatment with a TNF-α inhibitor in first-line, achieved such a response after receiving treatment with a second-line TNF-α inhibitor. (48) Average survival/persistence of patients with PsA on anti-TNFα therapy is in the range of 2 to 4 years for the first agent and shorter for subsequent anti-TNFα therapies (60) which is not ideal given the chronic nature of PsA.

Additionally, anti-TNFs (such as infliximab, etanercept or adalimumab) may require concomitant MTX therapy to reduce immunogenicity and achieve maximal drug survival. (62) Patients contraindicated to cDMARDs may therefore not experience optimal benefits from receiving treatment with anti-TNFs alone. Furthermore, conventional non-biologic systemic therapies can prove burdensome in terms of lifestyle adaptations for patients, with some therapies requiring frequent laboratory analyses. For example, in patients receiving methotrexate therapy, NICE recommend fortnightly full blood count, liver function, and urea

and electrolytes tests, until six weeks after the last dose increase; these regular tests can prove extremely inconvenient for patients. (63)

Some patients may not be eligible for anti-TNFα therapies due to contraindications. (14) At present, the only tsDMARD approved in PsA is apremilast. Its efficacy against PsA symptoms is limited. (30, 31) For example, of the 161 patients who received the licensed 30 mg twice daily (BID) dose of apremilast in the PALACE-1 trial, only 36.6% and 19.9% attained ACR 20 and ACR 50 responses, respectively, after 24 weeks. (39) Additionally, only 21.0% of patients achieved a PASI 75 response. Furthermore, these data are not very robust as the proportion of patients in this RCT who were biologic-experienced, who are more difficult to treat, was limited to ≤10 patients. (39)

Given the limitations of apremilast as well as currently available biologic therapies for PsA, there is an important unmet need for treatments with a new mechanism of action that can obtain and sustain efficacy levels similar to those seen with TNF-α inhibitor therapies in both naïve biologic DMARDS patients as well as biologic experienced patients, while maintaining an acceptable safety profile and minimal disturbance to patients lifestyle. Additionally, treatments should be able to treat the core joint symptoms of PsA as well as the skin symptoms (psoriasis and nail psoriasis) and the extra-articular PsA symptoms (such as enthesitis and dactilytis).

Ixekizumab is the first monoclonal antibody to block both active forms of IL-17A (IL-17A is expressed in both homodimer and heterodimer forms) with high binding affinity. (64) It is the second anti IL-17 (and third biologic therapy) to offer an alternative mechanism of action to TNF-α inhibitors.

Ixekizumab could be considered to represent an important new treatment option in the management of psoriatic arthritis as it has been shown to be efficacious in the treatment of joint and other extra articular symptoms as well as skin and nail disease leading to improvements in patient reported function and quality of life. Ixekizumab has been demonstrated to be effective in patients who are either bDMARD naïve or inadequate responders to or intolerant of TNF-α inhibitors and is similarly effective in patients irrespective of the use of concomitant cDMARD therapy. Ixekizumab has also demonstrated acceptable safety and tolerability, with an AE profile consistent with currently available biologics. In addition, ixekizumab has demonstrated high levels of complete or near complete skin clearance represented by PASI 90 and 100 responses. Ixekizumab may represent a significant change in the management of psoriatic arthritis patients with concomitant moderate–to-severe psoriasis. Compared to the only other available anti IL-17

treatment, ixekizumab requires approximately half of the injections in patients with concomitant moderate to severe psoriasis or those with inadequate response to prior TNF-α inhibitor treatment.

In addition to the technology appraisals already mentioned in Figure 1, the following NICE guidance are relevant to the current submission:

- NICE National guidance. Spondyloarthritis in over 16s: diagnosis and management. [NG65]. February 2017. Last updated June 2017. (65)
- NICE quality standard. Psoriasis [QS40]. August 2013 (66)
- NICE clinical guideline. Psoriasis: The assessment and management of psoriasis [CG153]. October 2012. Last updated: April 2017(67)
- NICE Pathway. Musculoskeletal conditions. December 2013. Last updated August 2017.(68)

1.4 Equality considerations

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

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

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

2.2 List of relevant clinical effectiveness evidence

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

- I1F-MC-RHAP – SPIRIT-P1
- I1F-MC-RHBE – SPIRIT-P2

These were the only two studies identified in the systematic literature review as being relevant for the decision problem. A summary of the study designs from both ixekizumab studies is provided in Table 4.

Table 4 Summary of ixekizumab pivotal PsA RCTs

Trial name (acronym)	Trial overview	Primary trial reference
Phase III		
SPIRIT-P1 (RHAP)	Phase III, double-blind, placebo-controlled and active- controlled RCT in bDMARD naïve patients. The study consisted of a 24 weeks double-blind treatment period, followed by a 28 weeks open-label extension period and a long-term open-label extension period of up to 104 weeks.	**Mease *et al.* 2017 (69)**
SPIRIT-P2 (RHBE)	Phase III, double-blind, placebo-controlled RCT in patients with inadequate response or intolerant to TNF-α inhibitors. The study consisted of a 24 weeks double-blind treatment period followed by a 132 weeks open-label extension period.	**Nash *et al.* 2017 (70)**

bDMARD = biologic disease-modifying antirheumatic drug; RCT = randomised controlled trial;

Both SPIRIT-P1 and SPIRIT-P2 studies were phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient trials comparing the efficacy and safety of ixekizumab to placebo in two sub-groups of patients: i) biologic disease-modifying antirheumatic drug (bDMARD)-naive patients (I1F-MC-RHAP) and ii) tumour necrosis factor (TNF) inhibitor–experienced patients (I1F-MC-RHBE). In addition, SPIRIT-P1 also included an active control reference (adalimumab) arm. Long-term efficacy and safety will be evaluated for up to 3 years in the extension period for patients who participate throughout

the entire 3-year study. An overview of the SPIRIT- P1 and SPIRIT-P2 studies is provided in Table 5.

Table 5 Clinical effectiveness evidence

Study	**SPIRIT-P1 (RHAP)**		
Primary trial reference	**Mease *et al.* 2017 (69)**		
Study design	Phase III, multicentre, randomised, double-blind, placebo-controlled and active-controlled, clinical trial comparing the efficacy and safety of two regimens of ixekizumab and an active reference arm adalimumab, at the approved dose and regimen, to placebo in biologic disease-modifying antirheumatic drug (bDMARD)-naive patients. The study consisted of a 24 weeks double-blind treatment period, followed by a 28 weeks open-label extension period and a long-term open-label extension period of up to 104 weeks. Please note that the study was not to test equivalence or non-inferiority of ixekizumab versus adalimumab.		
Population	Adult patients (≥18 years of age) with active PsA who were bDMARD-naïve.		
Intervention(s)	Ixekizumab 80mg Q2W (n=103) Ixekizumab 80mg Q4W (n=107)		
Comparator(s)	Placebo (n=106) Adalimumab 40 mg Q2W (n=101) (not an active comparator)		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	NA		
Reported outcomes specified in the decision problem	• Disease activity (ACR 20/ 50/ 70, **PsARC*,** MDA) • Functional capacity (**HAQ-DI***) • effect on concomitant skin condition (Psoriasis Area and Severity Index [**PASI***]) – including PASI 75/90/100 • other complications of psoriatic arthritis (LEI- enthesitis, NAPSI-nail psoriasis [modified version], LDI-B dactylitis, structural progression [mTSS]) • Health related quality of life (**EQ-5D***) • Adverse events • Mortality		
All other reported outcomes	NA		
Study	**SPIRIT-P2 (RHBE)**		
Primary trial reference	**Nash et al. 2017 (70)**		
Study design	Phase III, multicentre, randomised, double-blind, placebo-controlled, clinical trial comparing the efficacy and safety of two regimens of ixekizumab to placebo in biologic disease-modifying antirheumatic drug (bDMARD)-experienced patients. The study consisted of a 24 weeks double-blind treatment period, followed by a 152 weeks open-label extension period.		
Population	Adult patients (≥18 years of age) with active PsA who were bDMARD-experienced.		

Intervention(s)	Ixekizumab 80mg Q2W (n=123) Ixekizumab 80mg Q4W (n=122)		
Comparator(s)	Placebo (n=118)		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	NA		
Reported outcomes specified in the decision problem	• Disease activity (ACR 20/ 50/ 70, **PsARC***, MDA) • Functional capacity (**HAQ-DI***) • Effect on concomitant skin condition (Psoriasis Area and Severity Index [**PASI***]) – including PASI 75/90/100 • Other complications of psoriatic arthritis (LEI- enthesitis, NAPSI-nail psoriasis [modified version], LDI-B dactylitis) • Health related quality of life (**EQ-5D***) • Adverse events • Mortality		
All other reported outcomes	NA		

Abbreviations: bDMARD = biologic disease-modifying antirheumatic drugs; ACR = American College of Rheumatology; ACR 20 = at least 20% improvement in both tender and swollen joint counts; ACR 50 = at least 50% improvement in both tender and swollen joint counts; ACR 70 = at least 70% improvement in both tender and swollen joint counts; PsARC = Psoriasis Area and Severity Index; MDA =Minimum Disease Activity; HAQ-DI = Health Assessment Questionnaire-Disability Index; LEI = Leeds Enthesitis Index; LDI-B = Leeds Dactylitis Index-Basic; NAPSI = Nail Psoriasis Severity Index; mTSS = modified Total Sharp Score.

*Outcomes included in the economic model.

Please note that the background mortality used in the economic modelling has been taken from UK life tables.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

The methodology and results for all the relevant SPIRIT studies for the 24 week treatment period have been published. Week 24 data for SPIRIT-P1 has been published in the Annals of the Rheumatic Diseases in August 2017 (Mease, 2017). (69) Week 24 data for the SPIRIT-P2 study have been published in Nash *et al.* 2017. (70) Where necessary, information has also been presented from the individual CSRs.

2.3.1 Trial design

Diagrammatic representations of the trial design of the relevant SPIRIT studies can be seen in Figure 2 and Figure 3. Both SPIRIT studies consisted of a 24 week double-blind 'Treatment Period'. SPIRIT-P1 is then followed by an extension period week 24 to 52, and further followed by a long-term extension period week 52 –week 156. Following the 24 week blinded period, SPIRIT-P2 has a long-term extension week 52 to week 156. During the treatment period (week 0 -24) the efficacy and safety of two dose regimens of ixekizumab

(80 mg every two weeks (Q2W) and 80 mg every four weeks (Q4W)) were compared with placebo. The adalimumab 40 mg twice weekly (Q2W) treatment arm served as an active reference for comparison with placebo in the SPIRIT-P1 trial. The SPIRIT-P1 trial was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab. (69) Patients randomised to receive ixekizumab were administered a starting dose of 160 mg given as two injections at week zero. The primary efficacy objective of the trials was evaluated at the end of the treatment period (week 24). (69, 70)

The study periods of SPIRIT-P1 and -P2 are detailed below:

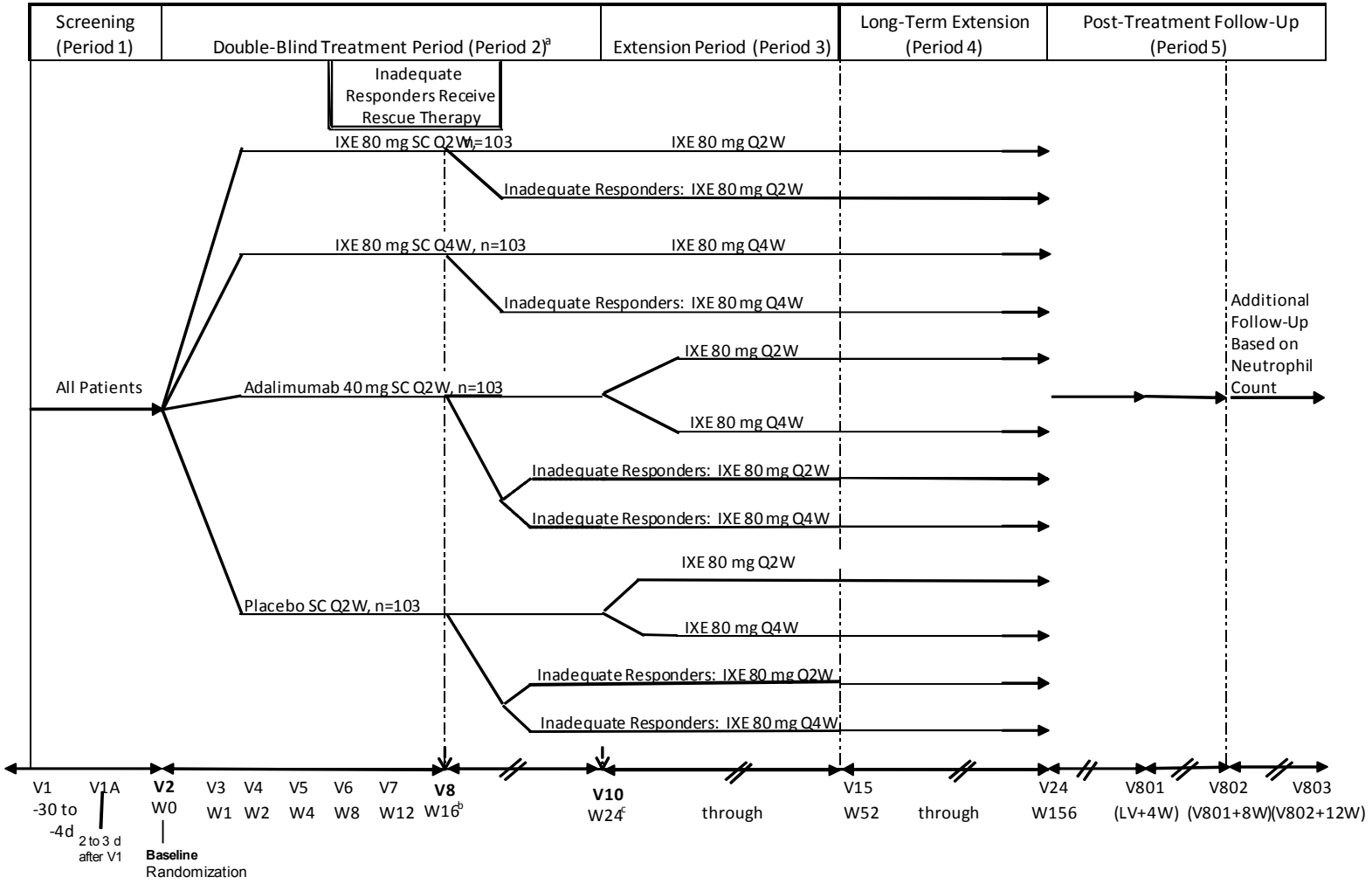
- **Period 1:** Screening period lasting from 4 to 30 days prior to Period 2
- **Period 2:** Double-blind treatment period, from week 0 (baseline) to week 24 inclusive
- **Period 3:** Extension period, after week 24 to week 52 inclusive
- **Period 4:** Long-term extension period after week 52 to week 156 inclusive (Note that in SPIRIT-P2, Period 3 and 4 were combined into one extension period (from week 24 to week 156)
- **Period 5:** Post-treatment follow-up period, from the last treatment period visit, or early termination visit, to a minimum of 12 weeks following that visit.

At week 16, patients were classified as responders or non-responders according to pre-defined blinded criteria (to investigators, study personnel and patients):

- Responders were patients who achieved ≥ 20% improvement in either tender joint count (TJC) and/or in swollen joint count (SJC) from baseline;
- Non-responders were patients who failed to meet these criteria.

All inadequate responders (i.e. patients who failed to meet defined criteria for improvement in tender and swollen joints) were administered rescue therapy (patient's background therapy) at week 16 which was maintained for the remainder of the treatment period. Patients who were receiving ixekizumab before week 16 were assigned rescue therapy while continuing with their same assigned ixekizumab dose regimen, whereas those who were receiving adalimumab or placebo were re-randomised in a 1:1 ratio to receive either ixekizumab 80 mg Q2W or Q4W (following an 8-week washout period (from week 16 to week 24, for adalimumab patients only).

Figure 2 SPIRIT-P1: Schematic of trial design



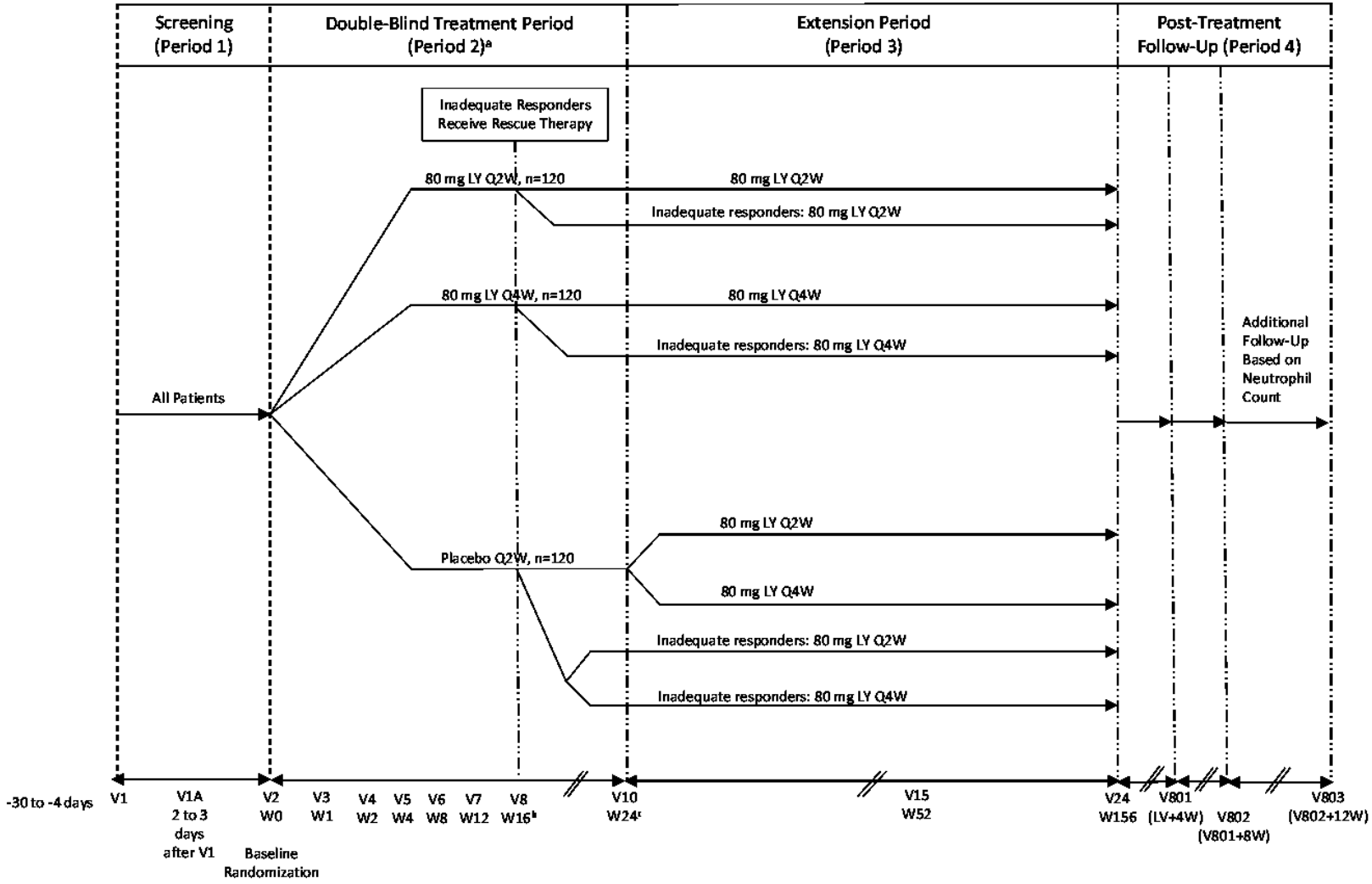
Abbreviations: d = day(s); IXE = ixekizumab; LV = date of last visit; n = number of patients; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = study visit; W = study week.

a The study remained blinded until the last patient completed Week 24 and the reporting database was locked.

b Inadequate Responders at Week 16 (as defined by blinded tender joint count and swollen joint count criteria) received rescue therapy starting at Week 16. In addition, all Inadequate Responders at Week 16 who were initially randomized to placebo were re-randomized to either ixekizumab dose regimen and receive 2 SC injections of ixekizumab (160 mg total) and, therefore, all patients received 3 SC injections of blinded investigational product at this time point to maintain the study blind. All Inadequate Responders at Week 16 who were initially randomized to adalimumab and re-randomized to either ixekizumab dose regimen received a final dose of adalimumab at Week 16 and placebo for 8 weeks (thus from after Week 16 until Week 24) as a washout procedure before beginning ixekizumab with a starting dose of 160 mg (given as 2 injections) at Week 24.

c At Week 24, all patients still receiving placebo from the placebo group were re-randomized to ixekizumab and received 2 SC injections of ixekizumab (160 mg total). All patients received 3 SC injections of blinded investigational product at this time point to maintain the study blind. Also at Week 24, all patients still receiving adalimumab received a final dose of adalimumab at Week 24 but were re-randomized to either ixekizumab dose regimen and thereafter went through a placebo washout for the following 8 weeks (Week 26 until Week 32) before beginning ixekizumab at Week 32. Patients are to be discontinued from the study if they do not meet the defined response criteria at Week 32 and any subsequent visit during the study.

Figure 3 SPIRIT-P2: Schematic of trial design



Abbreviations: LV = date of last visit; LY = LY2439821 (ixekizumab); n = number of patients; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V= study visit; W = study week.

a The study remained blinded until the last patient completed Week 24 and the clinical trial database to Week 24 (inclusive) was locked.

b Inadequate Responders (IRs) at Week 16 (as defined by blinded tender joint count and swollen joint count criteria) received rescue therapy starting at Week 16. In addition, all IRs at Week 16 who were initially randomized to placebo were re-randomized to either ixekizumab dose regimen and received 2 SC injections of ixekizumab (160 mg total); therefore, all patients received 2 SC injections of blinded study drug at this time point to maintain the study blind.

c At Week 24, all patients still receiving placebo from the placebo treatment group were re-randomized to ixekizumab and received 2 SC injections of ixekizumab (160 mg total); therefore, all patients received 2 SC injections of blinded study drug at this time point to maintain the study blind. Patients are to be discontinued from the study if they do not meet the defined response criteria at Week 32 or at any subsequent visit during the study. Patients receiving ixekizumab at Week 16 remained on the same dose through Period 3.

For both SPIRIT studies, patients who completed the double-blind treatment period entered into the open-label extension period from week 24 onwards. During this time:

- Patients who had received ixekizumab during the double-blind treatment period (up to week 24), continued with their same dose regimen.
- Patients who responded to placebo during the double-blind treatment period (up to week 24), were re-randomised (1:1) to receive ixekizumab 80 mg Q2W or Q4W beginning with a starting dose of 160 mg at week 24. Inadequate responders to placebo were treated as indicated in Figure 2 and Figure 3.
- Patients who received adalimumab during the double-blind treatment period (up to week 24), were re-randomised (1:1) to receive ixekizumab 80 mg Q2W or Q4W following an 8-week washout procedure (from week 24 until week 32). These patients did not receive an ixekizumab 160 mg starting dose. Inadequate responders to adalimumab were treated as indicated in Figure 2 and Figure 3.

Patients continued on the same dosing regimens during the whole of the extension (SPIRIT-P1 and -P2) and long-term extension periods (SPIRIT-P1).

The extension period and long-term extension period allow collection of data for the assessment of maintenance of efficacy and long-term safety data with ixekizumab. Once the extension and long-term extension periods are completed, patients stop the study drug to participate in the post-treatment follow-up period.

Finally, all patients who received at least one dose of investigational product entered the post-treatment follow-up period for a minimum of 12 weeks after their last regularly scheduled visit or the date of their Early Termination Visit (ETV) for safety monitoring.

Patients who were receiving cDMARDs at the beginning of the study (week 0), were allowed to continue with their cDMARD medication during the double-blind treatment period (Period 2), however, alteration of their cDMARD dose and/or introduction of a new cDMARD was strongly discouraged, unless required for safety reasons, or required for rescue therapy for inadequate responders at week 16. If, at any time, the investigator believed that side effects or laboratory abnormalities were attributable to the cDMARD, the cDMARD dose was lowered or the medication stopped. During the extension and long-term extension periods (Periods 3 and 4), adjustment of allowed cDMARDs (dose change, introduction, or withdrawal of DMARDs) was permitted.

2.3.2 Randomisation and blinding

Both SPIRIT trials were double-blind studies; patients and study site personnel were blinded to study treatment until after all patients completed the treatment period (week 24) or had discontinued from the study and the clinical trial database through week 24 had been locked.

Patients who met the criteria for enrolment following screening were randomised by a computer-generated random sequence using either an interactive voice response system (IVRS) (SPIRIT-P1 only) or an interactive web response system (IWRS) (SPIRIT-P2 only) to one of the double-blind treatment groups in the treatment period. Patients were stratified as follows:

- SPIRIT-P1:
    - Country
    - cDMARD experience at baseline (naive, past use, and current use)
- SPIRIT-P2:
    - Country
    - TNF inhibitor experience (inadequate responder to one TNF inhibitor, two TNF inhibitors, or intolerance to TNF inhibitors)

Inadequate responders at week 16 receiving placebo or adalimumab (SPIRIT-P1 only) were re-randomized (1:1) using IVRS/ IWRS to either ixekizumab 80 mg Q2W or 80 mg Q4W.

At week 24, patients remaining in the placebo and adalimumab (SPIRIT-P1 only) groups at the completion of the double-blind treatment period (Period 2) were re-randomized to ixekizumab 80 mg Q2W or Q4W. The re-randomization was performed by IVRS/ IWRS.

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

In order to maintain study blind, a double dummy design was used, in which the pre-filled syringes containing either ixekizumab or placebo (for ixekizumab), were visibly indistinguishable from each other. Additionally, pre-filled syringes containing either

adalimumab or placebo (for adalimumab) visibly indistinguishable from each other were also used for SPIRIT-P1.

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

2.3.3 Eligibility criteria

Key eligibility criteria for the SPIRIT studies can be seen in Table 6. A complete list of all inclusion and exclusion criteria is given in Appendix L.

Table 6 Key eligibility criteria for the SPIRIT-P1 and SPIRIT-P2 studies

Trial Code	Inclusion Criteria	Exclusion Criteria
SPIRIT-P1 (69)	• Male or female patients 18 years or older • Have an established diagnosis of PsA (of at least 6 months and currently met the Classification Criteria for Psoriatic Arthritis) • Have active PsA defined as at least 3 of 68 tender and 3 of 66 swollen joints • Have at least 1 disease-related definite joint erosion on hand or foot x-rays as determined by the central reader OR a C-reactive protein (CRP) >6 mg/L at screening • Have active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis.	• History of malignant disease (other than non-melanoma skin cancer or in situ cervical carcinoma, successfully treated and with no recurrences within the past 5 years) • Recent infection requiring hospitalization or antibiotic treatment • Positive testing for hepatitis B, hepatitis C, or human immunodeficiency virus • Liver function or haematology test results outside of predefined limits • Any history of biologic treatment for plaque psoriasis or PsA.
SPIRIT-P2 (70)	• Male or female patients 18 years or older • Have an established diagnosis of PsA (of at least 6 months and currently met the Classification Criteria for Psoriatic Arthritis) • Have active PsA defined as at least 3 of 68 tender and 3 of 66 swollen joints • Have active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis • Previously treated with tumor necrosis factor alpha inhibitor (TNFi) and had an inadequate response to one or two TNFis or were intolerant to TNFis. • Previously treated with one or more cDMARDs.	• History of malignant disease within the past 5 years (other than non-melanoma skin cancer successfully treated and with limited recurrences within 5 years before baseline) • Recent (4–24 weeks before baseline depending on infection type and severity) history of ongoing, chronic, or recurrent infections • Present ulcerative colitis or Crohn's disease (patients with a history of, but not active, Crohn's disease or ulcerative colitis were permitted to participate in this study).

2.3.4 Settings and locations where the data were collected

SPIRIT-P1 and -P2 were international, multicentre trials conducted in outpatient settings in

15 and 10 countries, respectively, across Europe, North America, Australia and Asia. Across the two studies there were a total of [redacted] based in the UK which enrolled a total of [redacted].

The summary of trial data collection locations are provided in Appendix M.

2.3.5 Study drugs

An overview of the study drugs in the SPIRIT studies can be seen in Table 7.

As the primary endpoints for the SPIRIT studies included both the Q2W and Q4W dosing regimens in the Treatment Period, the results for both these treatments groups are presented in this submission.

Table 7 Overview of study drugs in the SPIRIT-P1 and SPIRIT-P2 studies

Study drugs	SPIRIT-P1	SPIRIT-P2
Ixekizumab	*Treatment Period*	
	A single starting dose of ixekizumab 160 mg (2 x SC injections) followed by ixekizumab 80 mg given as 1 x SC injection every 2 weeks (80 mg Q2W) A single starting dose of ixekizumab 160 mg (2 x SC injections) followed by ixekizumab 80 mg given as 1 x SC injection every 4 weeks (80 mg Q4W)	
	Extension and Long-Term Extension Period	
	Ixekizumab 80 mg given as 1 x SC injection every 2 weeks (80 mg Q2W) Ixekizumab 80 mg given as 1 x SC injection every 4 weeks (80 mg Q4W)	
Placebo	*Treatment Period*	
	A single starting dose of placebo given as 2 x SC injections followed by placebo for ixekizumab Q2W Placebo for adalimumab (1 SC injection) given every two weeks (Q2W)	A single starting dose of placebo given as 2 x SC injections followed by placebo for ixekizumab Q2W
Adalimumab	*Treatment Period*	
	Adalimumab 40 mg given as a 1 x SC injection every two weeks (Q2W)	NA

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

The licensed dose of ixekizumab is 160 mg by SC injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) Q4W for patients without concomitant moderate-to-severe psoriasis and ixekizumab 160 mg by subcutaneous injection (SC) (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 for patients with concomitant moderate-to-severe psoriasis. The dosing schedule for patients with concomitant moderate-to-severe psoriasis follows the licensed dosing schedule of ixekizumab in the moderate-to-severe psoriasis indication.

2.3.6 Identity of investigational product and treatment administration

In addition to the treatment regimens outlined above in Table 7 patients were also administered placebo injections in varying regimens in order to maintain study blind.

2.3.7 Concomitant therapies

Treatment with concomitant therapies was allowed during the double-blind period of the study. Patients taking permitted medications were required to be on a chronic, stable dose at baseline (week 0) through week 24 (inclusive), unless a change was required for safety reasons or for rescue medication for Inadequate Responders at week 16.

The following concomitant therapies were permitted:

- NSAIDs (including COX-2 inhibitors) and analgesics
    - Up to the maximum recommended doses for pain
- cDMARDs
    - MTX: Up to 25 mg/week
    - Hydroxychloroquine: Up to 400 mg/day
    - Leflunomide: Up to 20 mg/day
    - Sulfasalazine: Up to 3 g/day
- Topical Steroids
    - Class 6 (mild)
    - Class 7 (least potent)
- Oral Corticosteroids
    - Up to 10 mg/day of prednisone (or its equivalent)
- Inhaled Steroids for asthma
- Other Concomitant Therapies for Ps
    - Shampoos, not containing >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues
    - Topical Products, not containing urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues
    - Bath Oils/Oatmeal Bath Preparations

- Other Concomitant Medications for Concomitant Diseases

Rescue therapy (week 16): Patients who were identified as Inadequate Responders at week 16 were required to modify their concomitant medication by adjusting the dose of existing medication(s) and/or introduction of new medication(s). Modifications made at week 16 must have remained in place and unchanged throughout the remainder of the double-blind period of the study. The following medications were eligible for modification: NSAIDs and opiate analgesics, cDMARDs, and oral corticosteroids. Additionally, one intra-articular injection of a corticosteroid was permitted for Inadequate Responders.

2.3.8 Primary and key efficacy secondary outcomes

Primary efficacy outcome

The primary efficacy measure used in the SPIRIT-P1 and –P2 trials was the American College of Rheumatology response criteria (ACR) at 24 weeks of treatment.

Using this measure, the primary objective of the trials was to assess at week 24 of treatment whether ixekizumab 80 mg Q2W or 80 mg Q4W were superior to placebo in:

i) biologic disease-modifying antirheumatic drug (bDMARD)-naive patients (SPIRIT- P1) and

ii) tumor necrosis factor (TNF) inhibitor–experienced patients (SPIRIT-P2)

measured as the proportion of patients achieving at least a 20% improvement from baseline in ACR response (ACR 20).

Definition of primary efficacy outcome

ACR 20 (American College of Rheumatology)

The American College of Rheumatology response criteria consists of 7 disease activity measurements: tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function, and an acute-phase reactant value (See Appendix N for further details).

In order to become an ACR 20 responder, a patient had to achieve the following:

- ≥20% improvement in both tender joint count (TJC) and swollen joint count (SJC), and
- ≥20% improvement in at least 3 of the following 5 ACR Core Set criteria:

1) Patient's Assessment of Pain Visual Analog Scale (VAS)

2) Patient's Global Assessment of Disease Activity (PatGA) VAS
3) Physician's Global Assessment of Disease Activity (PGA) VAS
4) Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI)
5) Acute-phase reactant as measured by high sensitivity (assay) C-reactive protein (hs-CRP)

ACR responder criteria are established, well-accepted, and the most commonly used criteria by regulators (e.g., EMA) for assessing response to therapy in PsA clinical trials. (71)

Key secondary efficacy outcomes

Key secondary efficacy measures assessed in the SPIRIT-P1 and –P2 studies included additional ACR comparisons (defining a higher degree of treatment response than ACR 20) as well as other evaluations of disease activity; evaluations of effect on concomitant skin condition, functional capacity, complications of psoriatic arthritis (dactylitis, enthesitis) and HRQoL. The key secondary efficacy outcomes discussed in this section are those endpoints that have been included in the economic analysis (ie, PsARC, HAQ-DI and PASI) as well as ACR 50 and ACR 70 (due their link to the main endpoint). Please refer to Appendix N for further details on the definition and assessment of the key secondary efficacy outcomes. Additionally, Appendix O contains an exhaustive list of the secondary efficacy endpoints included in the SPIRIT-P1 and –P2 trials, while Appendix P contains the results of other key secondary efficacy outcomes not included in the main body of the submission (ie, HAQ-DI at week 24, PASI at week 24, modified Total Sharp Score (mTSS), enthesitis, dactylitis, MDA_{PASI} and NAPSI).

The secondary efficacy outcomes assessed in the SPIRIT studies and included in the main body of the submission are: (69, 70, 72-74)

- Proportion of patients meeting the Psoriatic Arthritis Response Criteria (PsARC modified) at week 12 and 24 (used in economic model)
- Change from baseline to week 12 in HAQ-DI (used in economic model)
- Proportion of patients achieving PASI 75 response at week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA) (mayor (gated) secondary endpoint) (used in economic model)
- Proportion of patients achieving PASI 90 and PASI 100 at week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA) (used in economic model)

- Proportion of patients achieving ACR 50 and ACR 70 at week 24
- Proportion of patients achieving ACR 20, ACR 50 and ACR 70 at week 12

Additionally, the following outcomes have been presented in Appendix Q for the extension period for those patients who were randomised to ixekizumab at the start of the double-blind treatment period up to week 108 (where available):

- Proportion of patients achieving PsARC response criteria up to week 108
- Proportion of patients achieving ACR 20, ACR 50 and ACR 70 up to week 108
- Change from baseline to week 52 in HAQ-DI scores
- Proportion of patients achieving PASI 75, PASI 90 and PASI 100 up to week 108
- Change from baseline to week 52 in mTSS on hand and foot x-rays (SPIRIT-P1 only)

2.3.9 Summary of trials methodology

A comparative summary of the methodology of the SPIRIT studies is presented in Table 8.

Not all pre-specified secondary and exploratory objectives were deemed relevant for this submission (as presented in the final scope for this appraisal) and have therefore not been discussed here. A full list of all pre-specified secondary endpoints for SPIRIT-P1 and SPIRIT-P2 is presented in Appendix O.

Table 8 Comparative summary of trial methodology

Trial	SPIRIT- P1 (NCT01695239)	SPIRIT-P2 (NCT02349295)
Settings and locations where the data were collected	114 study sites in 15 countries: Belgium, Bulgaria, Canada, Czech Republic, Estonia, Japan, Spain, France, Great Britain, Mexico, Netherlands, Poland, Russia, Ukraine, United States. (Further details can be seen in Appendix M)	109 study sites in 10 countries: Australia, Czech Republic, France, Germany, Italy, Poland, Spain, Taiwan, United Kingdom, and United States (Further details can be seen in Appendix M)
Duration of trial and time trial was conducted	• Double-Blind Treatment Period (week 0-24 – primary endpoint assessment) • Extension Period (week 24-52) • Long-term Extension Period (week 52-156) • 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): 3 years	• Double-Blind Treatment Period (week 0-24 – primary endpoint assessment) • Extension Period (week 24-156) • 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): 3 years
Trial design	Randomised, double-blind, placebo-controlled, active-controlled, parallel-group study.	Randomised, double-blind, placebo-controlled, parallel-group study.
Main eligibility criteria for participants	Adult patients (≥18 years of age) with active PsA who were bDMARD-naïve.	Adult patients (≥18 years of age) with active PsA who were bDMARD-experienced.
Number of patients randomised	417	363
Trial arms (n=number randomised/not randomised; treatment period) including how and when they were administered	Treatment Period Ixekizumab 80mg Q2W (n=103) Ixekizumab 80mg Q4W (n=107) Placebo (n=106) Adalimumab 40 mg Q2W (n=101) Extension and Long-Term Extension Period Ixekizumab 80 mg Q4W (n = 191) Ixekizumab 80 mg Q2W (n= 190)	Treatment Period Ixekizumab 80mg Q2W (n=123) Ixekizumab 80mg Q4W (n=122) Placebo (n=118) Extension Period Ixekizumab 80 mg Q4W (n = 157) Ixekizumab 80 mg Q2W (n= 153)
Randomisation and masking	Computer-generated random sequence using an IVRS, including, re-randomizations at week 16 and week 24. Study site personnel, including outcomes assessor(s) and patients were blinded to study treatment until after all patients completed week 24 or had discontinued from the study and the clinical trial database through week 24 had been locked. Clinical trial material (syringes (and contents) containing either (ixekizumab or placebo for ixekizumab) and (adalimumab or placebo	Computer-generated random sequence using an IWRS, including, re-randomizations at week 16 and week 24. Study site personnel, including outcomes assessor(s) and patients were blinded to study treatment until after all patients completed week 24 or had discontinued from the study and the clinical trial database through week 24 had been locked. Clinical trial material (syringes and contents) containing either ixekizumab or placebo were visibly

Trial	SPIRIT- P1 (NCT01695239)	SPIRIT-P2 (NCT02349295)
	for adalimumab) were visibly indistinguishable from each other.	indistinguishable from each other.
Primary objective	To assess whether ixekizumab 80 mg (Q2W or Q4W) was superior to placebo at week 24 as measured by the proportions of patients achieving ACR 20.	To assess whether ixekizumab 80 mg (Q2W or Q4W) was superior to placebo at week 24 as measured by the proportions of patients achieving ACR 20.
Major secondary outcomes presented in the main body of the submission (either in main body of the submission or the Appendix)	Major secondary (gated) outcomes were assessed over 24-weeks and included: • Change from baseline to week 24 in HAQ-DI • Change from baseline to week 24 in mTSS • Proportion of patients achieving ACR 20 response at week 12 • Proportion of patients achieving PASI 75 response at week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA) • Change from baseline to Week 12 in LEI in patients with enthesitis at baseline	Major secondary (gated) outcomes were assessed over 24-weeks and included: • Change from baseline to week 24 in HAQ-DI • Proportion of patients achieving ACR 20 response at week 12 • Proportion of patients achieving PASI 75 response at week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA) • Proportion of patients achieving Coates criteria for MDA at week 24 (using LEI (6 enthesal points) to assess enthesitis) • Proportion of patients achieving complete resolution in enthesitis as assessed by the LEI at week 24 in patients with enthesitis at baseline (LEI>0).
Other secondary outcomes presented in this submission (either in main body of the submission or the Appendix)	• Proportion of patients meeting the Psoriatic Arthritis Response Criteria (PsARC modified) at week 12 and 24 • Proportion of patients achieving ACR 20, ACR 50 and ACR 70 response rates at week 12 • Proportion of patients achieving ACR 50 and ACR 70 at week 24 • Proportion of patients achieving PASI 75 at week 24 • Proportion of patients achieving PASI 90 and PASI 100 at week 12 and week 24 • Proportion of patients achieving complete resolution in enthesitis as assessed by the LEI at week 24 in patients with enthesitis at baseline	• Proportion of patients meeting the Psoriatic Arthritis Response Criteria (PsARC modified) at week 12 and 24 • Proportion of patients achieving ACR 20, ACR 50 and ACR 70 response rates at week 12 • Proportion of patients achieving ACR 50 and ACR 70 at week 24 • Proportion of patients achieving PASI 75 at week 24 • Proportion of patients achieving PASI 90 and PASI 100 at week 12 and week 24

Trial	SPIRIT- P1 (NCT01695239)	SPIRIT-P2 (NCT02349295)
	• Proportion of patients achieving Coates criteria for MDA at week 24 (using LEI (6 enthesal points) to assess enthesitis) • Proportion of patients who achieve dactylitis resolution as assessed by the LDI-B at week 24 in the subgroup of patients with dactylitis at baseline • Proportion of patients who achieve complete resolution of psoriasis fingernail involvement at week 24 measured by the Nail Psoriasis Severity Index (NAPSI) score in the subgroup of patients with fingernail involvement at baseline • Proportion of patients achieving PsARC response up to week 108 • Proportion of patients achieving ACR 20, ACR 50 and ACR 70 up to week 108 • Change from baseline (extension period) to week 52 in HAQ-DI scores • Proportion of patients achieving PASI 75, PASI 90 and PASI 100 up to week 108 • Change from baseline (extension period) to week 52 in mTSS on hand and foot x-rays	• Proportion of patients who achieve dactylitis resolution as assessed by the LDI-B at week 24 in the subgroup of patients with dactylitis at baseline • Proportion of patients who achieve complete resolution of psoriasis fingernail involvement at week 24 measured by the Nail Psoriasis Severity Index (NAPSI) score in the subgroup of patients with fingernail involvement at baseline • Proportion of patients achieving PsARC response up to week 52 • Proportion of patients achieving ACR 20, ACR 50 and ACR 70 up to week 52 • Proportion of patients achieving PASI 75, PASI 90 and PASI 100 up to week 52 • Change from baseline (extension period) to week 52 in HAQ-DI scores
Selected subgroups	• Gender • Age • Race • Ethnicity • Weight • BMI • Geographic region • cDMARD experience at baseline: naive, past use, or current use • Disease severity (hs-CRP: ≤6 or >6) • previous PsA therapy • time since PsA onset (years) • bone erosion: yes or no (for mTSS analysis only) • eligibility for biologic therapy under NICE criteria	• Gender • Age • Race • Ethnicity • Weight • BMI • Geographic region • TNFi experience (IR to 1 TNFi, IR to 2 TNFi, or intolerance to a TNFi) • DMARD concomitant medication (past use, current use) • Baseline disease severity (hs-CRP: ≤6 or >6) • time since PsA onset (years)

Trial	SPIRIT- P1 (NCT01695239)	SPIRIT-P2 (NCT02349295)
	• concomitant cDMARD use (yes/ no) (post-hoc analysis) • • A full list of all subgroup analysis performed can be found in Appendix E.	• smoking status at baseline (yes or no) • baseline psoriasis (psoriatic lesions with ≥3 BSA) • baseline moderate-to-severe psoriasis (PASI ≥12, sPGA ≥3, and BSA ≥10) • baseline enthesitis (yes or no) • baseline dactylitis (LDI-B >0): yes or no • eligibility for biologic therapy under NICE criteria • concomitant cDMARD use (yes/ no) (post-hoc analysis) • A full list of all subgroup analysis performed can be found in Appendix E.

Abbreviations: ETV = early termination visit; PsA = psoriatic arthritis; bDMARD = biologic disease-modifying antirheumatic drugs; Q2W = every 2 weeks; Q4W = every 4 weeks; IVRS = interactive voice response system; IWRS = interactive web response system; ACR = American College of Rheumatology; ACR 20 = at least 20% improvement in both tender and swollen joint counts; ACR 50 = at least 50% improvement in both tender and swollen joint counts; ACR 70 = at least 70% improvement in both tender and swollen joint counts; PASI = Psoriasis Area and Severity Index; PASI /75/90/100 = ≥75%/≥90%/100% improvement from baseline in PASI score; PsARC = Psoriasis Area and Severity Index; MDA =Minimum Disease Activity; HAQ-DI = Health Assessment Questionnaire-Disability Index; LEI = Leeds Enthesitis Index; LDI-B = Leeds Dactylitis Index-Basic; NAPSI = Nail Psoriasis Severity Index; mTSS = modified Total Sharp Score; BMI = body mass index; TNFi = tumour necrosis factor alpha inhibitor; cDMARD = conventional disease-modifying antirheumatic drugs; BSA = body surface area; sPGA = static physician's global assessment; hs-CRP = high sensitivity (assay) C-reactive protein

2.3.10 Patient demographics and baseline characteristics in the SPIRIT studies

Patient demographics, baseline characteristics, or disease severity were well balanced for all the ITT populations across the SPIRIT studies. Prior use of biologic therapy varied across studies due to the inclusion and exclusion criteria in the studies.

The mean age of patients in SPIRIT-P1 and -P2 treatment arms ranged from 48.6–50.6 years and 51.5–52.6 years, respectively. The percentage of male patients ranged from 42.1–50.5% and 40.7–51.6%, respectively. The mean disease duration (time since PsA diagnosis) ranged from 6.2–7.2 years, and 9.2–11.0 years in the SPIRIT-P1 and -P2 trials, respectively.

In SPIRIT-P1, statistically significantly greater percentage of patients had a baseline weight of ≥ 100 kg in the adalimumab group, compared to the placebo group (31.7% versus 16.0%, respectively, p=0.009); however, there were no significant differences between baseline weight categories in the ixekizumab groups (Q2W or Q4W) and the placebo group. Current methotrexate use was similar across treatment groups (ranging from 51.5–56.4%) in the SPIRIT-P1 trial. For those taking methotrexate at baseline, the mean (SD) weekly methotrexate dose was 15.8 (5.04) mg. (69)

In SPIRIT-P2, prior TNFi experience was similar between patients in the placebo, ixekizumab 80 mg Q4W, and ixekizumab 80 mg Q2W treatment groups. However, the use of methotrexate was statistically significantly different between groups, with greater proportions of patients in the ixekizumab 80 mg Q2W group using methotrexate at baseline, compared to patients in the placebo group (49.6% versus 33.9%, respectively, p=0.019). Methotrexate use was not statistically significantly different between the ixekizumab 80 mg Q4W and placebo groups. In patients who had concomitant use of methotrexate at baseline in the SPIRIT-P2 trial, the mean weekly methotrexate dose was 16.1 mg.

In addition, the baseline swollen joint count was statistically significantly different between groups in SPIRIT-P2, with the ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W groups having a higher count compared with the placebo group (13.5 and 13.1 versus 10.3, respectively, p=0.009 and p=0.023).

Full patient demographic data and baseline disease characteristics for SPIRIT-P1 and –P2 can be seen in Table 9.

Table 9 Patient demographics and baseline disease characteristics in pivotal phase 3 studies

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)
Patient demographics									
Age, mean years (SD)	50.6 (12.3)	48.6 (12.4)	49.1 (10.1)	49.8 (12.6)	49.5 (11.9)	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)	51.9 (12.0)
Male, n(%)	48 (45.3)	51 (50.5)	45 (42.1)	48 (46.6)	192 (46.0)	56 (47.5)	63 (51.6)	50 (40.7)	169 (46.6)
Race, n(%)									
White	99 (93.4)	95 (94.1)	102 (95.3)	96 (93.2)	392 (94.0)	108 (91.5)	111 (91.0)	113 (91.9)	332 (91.5)**
Asian	5 (4.7)	3 (3.0)	2 (1.9)	5 (4.9)	15 (3.6)	7 (5.9)	7 (5.7)	7 (5.7)	21 (5.8)**
Other	2 (1.9)*	3 (3.0)*	3 (2.8)*	2 (1.9)*	10 (2.6)*	3 (2.5)	4 (3.3)	2 (1.6)	9 (2.5)**
Number of patients by region, n (%)									
Europe	76 (71.7)	73 (72.3)	80 (74.8)	77 (74.8)	306 (73.4)	50 (42.4)	49 (40.2)	50 (40.7)	149 (41.0)
Rest of the world	30 (28.3)	28 (27.7)	27 (25.2)	26 (25.2)	111 (26.6)	8 (6.8)	8 (6.6)	10 (8.1)	26 (7.2)
Weight category, n (%)									
< 80 kg	44 (41.5)	33 (32.7)	43 (40.2)	54 (52.4)	174 (41.7)	38 (32.2)	45 (36.9)	55 (44.7)	138 (38.0)
≥ 80 to < 100 kg	45 (42.5)	36 (35.6)	43 (40.2)	34 (33.0)	158 (37.9)	47 (39.8)	41 (33.6)	43 (35.0)	131 (36.1)
≥ 100 kg	17 (16.0)	32 (31.7)	21 (19.6)	15 (14.6)	85 (20.4)	33 (28.0)	36 (29.5)	25 (20.3)	94 (25.9)
Mean BMI, kg/m^2 (SD)	29.2 (6.3)	32.1 (11.4)	30.2 (8.4)	28.6 (6.6)	30.0 (8.5)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)	30.9 (7.2)
Baseline characteristics									
Time since PsA diagnosis, mean years (SD)	6.3 (6.9)	6.9 (7.5)	6.2 (6.4)	7.2 (8.0)	6.7 (7.2)	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)	10.0 (8.2)
Time since PsA onset, mean years (SD)	10.4 (8.8)	9.2 (7.3)	10.0 (9.5)	10.8 (10.8)	10.1 (9.3)	11.1 (8.5)	13.8 (10.6)	11.5 (7.5)	12.2 (9.0)
Previous non-biologic systemic agent, n (%)	67 (63.2)	64 (63.4)	63 (58.9)	72 (69.9)	266 (63.8)	90 (76.3)	95 (77.9)	103 (83.7)	288 (79.3)
Previous methotrexate	45 (42.5)	43 (42.6)	37 (34.6)	45 (43.7)	170 (40.8)	69 (58.5)	69 (56.6)	72 (58.5)	210 (57.9)
Previous sulfasalazine	20 (18.9)	26 (25.7)	19 (17.8)	30 (29.1)	95 (22.8)	31 (26.3)	38 (31.1)	29 (23.6)	98 (27.0)
Previous leflunomide	13 (12.3)	15 (14.9)	19 (17.8)	10 (9.7)	57 (13.7)	25 (21.2)	26 (21.3)	29 (23.6)	80 (22.0)

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)
Patient demographics									
Previous apremilast	-	-	-	-	-	5 (4.2)	8 (6.6)	3 (2.4)	16 (4.4)
Current methotrexate use, n (%)	59 (55.7)	57 (56.4)	57 (53.3)	53 (51.5)	226 (54.2)	40 (33.9)	48 (39.3)	61 (49.6)	149 (41.0)
cDMARD use, n(%)									
Past	24 (22.6)	20 (19.8)	22 (20.6)	23 (22.3)	89 (21.3)	66 (55.9)	62 (50.8)	50 (40.7)	178 (49.0)
Current	69 (65.1)	67 (66.3)	68 (63.6)	63 (61.2)	267 (64.0)	52 (44.1)	60 (49.2)	73 (59.3)	185 (51.0)
Previous biologic agent, n (%)	-	-	-	-	-	118 (100)	122 (100)	123 (100)	363 (100)
Prior TNFi experience, n (%)									
Inadequate responder to 1 TNFi	-	-	-	-	-	68 (57.6)	71 (58.2)	65 (52.8)	204 (56.2)
Inadequate responder to 2 TNFi	-	-	-	-	-	41 (34.7)	41 (33.6)	46 (37.4)	128 (35.3)
Intolerance to a TNFi	-	-	-	-	-	9 (7.6)	10 (8.2)	12 (9.8)	31 (8.5)
DAS28-CRP, mean (SD)	4.9 (1.0)	4.9 (1.0)	5.0 (1.0)	5.0 (1.1)	4.9 (1.0)	5.0 (1.1)	5.1 (1.1)	5.1 (1.1)	5.1 (1.1)
CRP (mg/L), mean (SD)	15.1 (23.6)	(13.2 (19.1)	12.8 (16.4)	15.1 (25.9)	14.1 (21.5)	12.1 (19.6)	17.0 (27.5)	13.5 (26.1)	14.2 (24.7)
CRP category >6 mg/L, n (%)	65 (61.3)	62 (61.4)	69 (64.5)	54 (52.4)	250 (60)	57 (49.1)	60 (50.4)	53 (43.1)	170 (47.5)
Van der Heijde modified total Sharp score, mean (SD)	17.6 (28.6)	15.9 (27.4)	19.2 (32.7)	15.2 (28.9)	17.0 (29.4)	-	-	-	-
SPARCC total score, mean (SD)	NR	NR	NR	NR	NR	5.7 (4.38)	5.6 (3.98)	6.1 (4.30)	5.8 (4.21)
Patients with erosions, n (%)	93 (98.9)	91 (95.8)	93 (93.0)	94 (95.9)	371 (95.9)	NR	NR	NR	NR
Tender joint count 68 joints, mean (SD)	19.2 (13.0)	19.3 (13.0)	20.5 (13.7)	21.5 (14.1)	20.1 (13.4)	23.0 (16.2)	22.0 (14.1)	25.0 (17.3)	23.4 (15.9)
Swollen joint count 66 joints, mean (SD)	10.6 (7.3)	9.9 (6.5)	11.4 (8.2)	12.1 (7.2)	11.0 (7.4)	10.3 (7.4)	13.1 (11.2)	13.5 (11.5)	12.3 (10.3)
HAQ-DI total score, mean (SD)	1.2 (0.6)	1.1 (0.6)	1.2 (0.5)	1.2 (0.6)	1.2 (0.6)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)
Current Psoriasis, n (%)	102 (96.2)	97 (96.0)	100 (93.5)	95 (92.2)	394 (94.5)	108 (91.5)	118 (96.7)	113 (91.9)	339 (93.4)

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)
Patient demographics									
Percentage of BSA for patients who have baseline plaque psoriasis, mean (SD)	14.4 (20.2)	14.8 (19.2)	15.1 (16.3)	12.0 (15.6)	14.1 (17.9)	9.0 (12.7)	12.5 (17.4)	11.6 (18.6)	11.0 (16.4)
BSA ≥ 3%, n (%)	67 (67.7)	68 (72.3)	73 (73.0)	59 (64.8)	267 (69.5)	67 (62.6)	68 (61.8)	68 (63.0)	203 (62.5)
PASI score in patients ≥3% BSA, mean (SD)	6.2 (7.5)	5.5 (6.5)	6.9 (6.6)	6.0 (7.0)	6.1 (6.9)	7.1 (7.1)	9.3 (9.1)	8.8 (10.3)	8.4 (8.9)
Moderate to severe psoriasis as defined as PASI > 12, sPGA ≥ 3 and BSA ≥ 10, n (%)	16 (16.2)	8 (8.5)	17 (17.0)	12 (13.2)	53 (13.8)	11 (9.3)	15 (12.3)	12 (9.8)	38 (10.5)
Current enthesitis, n (%)	57 (53.8)	56 (55.4)	70 (65.4)	59 (57.3)	242 (58.0)	69 (58.5)[a]	68 (55.7)[a]	84 (68.3)[a]	221 (60.9)[a]
LEI score, mean (SD)	2.9 (1.7)	3.0 (1.6)	2.7 (1.6)	3.1 (1.8)	2.9 (1.7)	2.9 (1.7)	2.9 (1.4)	3.0 (1.7)	2.9 (1.6)
Current dactylitis, n (%)	39 (36.8)	23 (22.8)	54 (50.5)	41 (39.8)	157 (37.6)	14 (11.9)[b]	28 (23.0)[b]	20 (16.3)[b]	62 (17.1)[b]
LDI score, mean (SD)	46.2 (65.5)	93.9 (111.9)	58.1 (96.7)	40.6 (54.6)	55.8 (83.6)	37.3 (25.2)	31.5 (33.8)	53.9 (37.6)	40.1 (34.3)

[a]Defined as LEI > 0.[b]Defined as LDI-B score > 0.

*Derived from Mease et al, 2017; ** Derived from Nash et al, 2017.

Abbreviations: ADA40Q2W=adalimumab 40 mg every two weeks; BMI=body mass index; CASPAR=classification criteria for psoriatic arthritis; HAQ-DI=health assessment questionnaire-disability index; IXE80Q4W=ixekizumab 80 mg every four weeks; IXE80Q2W=ixekizumab 80 mg every two weeks; BSA = body surface area; BMI = body mass index; PsARC = Psoriasis Area and Severity Index; sPGA = static physician's global assessment; TNFi = tumour necrosis factor alpha inhibitor; DAS28-CRP = Disease Activity Score 28 diarthrodial joint count based on C-reactive protein; cDMARD = conventional disease-modifying antirheumatic drugs; CRP = C-reactive protein LEI=Leeds enthesitis index; LDI=Leeds dactylitis index; n=number of patients; N/A=not applicable; PASI=psoriasis area and severity index; PBO=placebo; SD=standard deviation.

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Efficacy analyses for the treatment period were conducted according to the treatment to which all randomised patients were assigned (intent-to-treat (ITT) population), even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Patients were analysed according to the treatment to which they were assigned. For inadequate responders at week 16, only data up to week 16 were included in the double-blind treatment analyses. Safety analyses were conducted on the safety population, defined as all randomised patients who received at least 1 dose of study treatment during the specific phase of the study (double-blind treatment phase and extension phase).

The primary and major secondary objectives were assessed using a gatekeeping testing strategy. An overview of the types of analyses of categorical and continuous efficacy variables that were conducted has been presented in Table 10.

Additionally, different subgroup analysis were performed:

The efficacy of ixekizumab independently of concomitant methotrexate use (post-hoc analysis) was assessed using a logistic regression model with treatment, subgroup, and the treatment-by-subgroup interaction included as factors. The treatment-by-subgroup interaction was tested at the significance level of 0.10. Treatment group differences were evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction was statistically significant. Missing data were imputed using NRI. Similar methodology was used in order to assess the efficacy of ixekizumab according to demographic, geographic region, as well as other baseline characteristics (pre-planned analysis).

The efficacy of ixekizumab in the subgroup of patients who would be eligible for treatment with bDMARDs under current NICE criteria (pre-planned analysis) was assessed using a logistic regression model with treatment and study as factors. Treatment differences were evaluated using Wald's exact test.

Table 10 Overview of analyses conducted of categorical and continuous efficacy variables

Study periods	Trial	Efficacy and health outcomes variables	
		Categorical	**Continuous**
Treatment Period	SPIRIT-P1 (69)	• Logistic regression with treatment, geographic region, and cDMARD baseline experience (naive, past use, and current use). • Missing data were imputed using non-responder imputation (NRI).	• A mixed-effects model repeated measures (MMRM) was used. The model included treatment, geographic region, baseline score, cDMARD experience at baseline (naive, past use, and current use), visit, and the interaction of treatment-by-visit as fixed factors. • MMRM analysis takes into account missing data, therefore no missing data was imputed.
	SPIRIT-P2 (70)	• Logistic regression with treatment, geographic region, and TNFi experience (IR to 1 TNFi, IR to 2 TNFi, or intolerance to a TNFi). • Missing data were imputed using non-responder imputation (NRI).	• The primary analysis for continuous outcome variables was MMRM analysis. The model included treatment, visit, geographic region, TNFi experience (IR to 1 TNFi, IR to 2 TNFi, or intolerance to a TNFi), treatment-by-visit interaction, geographic region-by-visit interaction, and TNFi experience-by-visit interaction as well as the continuous, fixed covariates of baseline value and baseline value-by-visit interaction. • MMRM analysis takes into account missing data, therefore no missing data was imputed.
Extension Period	SPIRIT-P1 (75)	• Summary descriptive statistics only. • Missing data were imputed using non-responder imputation (NRI).	• Summary descriptive statistics only. • Missing data were imputed using modified baseline observation carried forward (mBOCF) methodology except for the mTSS endpoint. • Linear extrapolation method* was used as the imputation method in the analysis of mTSS endpoint only.
	SPIRIT-P2 (76)	• Summary descriptive statistics only. • Missing data were imputed using non-responder	• Summary descriptive statistics only. Missing data were imputed using modified baseline observation carried

Study periods	Trial	Efficacy and health outcomes variables	
		Categorical	Continuous
		imputation (NRI).	forward (mBOCF**) methodology.

*The linear extrapolation method assumes that individual patients continued to accrue structural damage in their joints at the same rate that was observed at the time of last observation. For patients who discontinued the study or the study drug or for patients who missed a radiograph for any reason, baseline data and the most recent radiographic data prior to discontinuation or prior to the missed radiograph, adjusted for time, were used for linear extrapolation to impute missing data at subsequent scheduled time points, including the primary analysis at week 24. For patients who received rescue therapy starting at Week 16 or at any time point thereafter, baseline data and the most recent post-baseline radiographic data up to Week 16, adjusted for time, were used for linear extrapolation.

**Missing data was imputed using the modified baseline observation carried forward (mBOCF) methodology as follows: For patients who discontinued study drug due to an AE, the baseline observation was carried forward to Week 24. For patients who discontinued study drug for any other reason, the last nonmissing observation before discontinuation was carried forward to week 24, with the exception for patients eligible for rescue therapy at Week 16. Their last nonmissing observation up to Week 16 was carried forward to week 24. Randomized patients without at least 1 postbaseline observation were not included for evaluation with the exception of patients who discontinued study treatment due to an AE

Abbreviations: TNFi = tumour necrosis factor alpha inhibitor; cDMARD = conventional disease-modifying antirheumatic drugs; mTSS = modified Total Sharp Score; mBOCF = modified baseline observation carried forward; MMRM = Repeated measures mixed model.

A summary of the statistical analysis conducted for the primary and major secondary endpoints can be seen in Table 11.

Table 11 Summary of statistical analyses in the SPIRIT-P1 and SPIRIT-P2 studies

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SPIRIT-P1 (73)			
The primary objective of the study was to assess, after 24 weeks of treatment, whether Ixe 80 mg Q2W or 80 mg Q4W was superior to placebo as measured by the proportion of patients meeting ACR 20 response criteria at week 24	The primary objective was analysed using a logistic regression analysis (NRI) with treatment, geographic region, and cDMARD baseline experience (naive, past use, and current use). Missing data were imputed using non-responder imputation (NRI). A gatekeeping testing strategy for the primary and major secondary analyses was implemented to control the overall type I error rate at a 2-sided alpha level of 0.05 for the multiple comparisons. The order in which the primary and major secondary outcomes were tested for each dose is: • Primary (Test 1): Proportion of patients achieving ACR 20 response at Week 24 • Major Secondary 1 (Test 2): Change from baseline to Week 24 in HAQ-DI • Major Secondary 2 (Test 3): Change from baseline to Week 24 in mTSS • Major Secondary 3 (Test 4): Proportion of patients achieving ACR 20 response at Week 12 • Major Secondary 4 (Test 5): Proportion of patients achieving PASI 75 response at Week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA) • Major Secondary 5 (Test 6): Change from baseline to Week 12 in LEI in patients with enthesitis at baseline • Major Secondary 6 (Test 7): Change from baseline to Week 12 in Itch NRS (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA) The 7 statistical tests were grouped into 2 parallel branches, 1 for tests	The total planned sample size for SPIRIT-P1 was 412 patients randomized in a 1:1:1:1 ratio to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, adalimumab 40 mg Q2W or placebo. In order to account for multiple testing for the two ixe groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. This study had >99% power to test the superiority of each ixekizumab dose regimen to placebo for ACR 20 response criteria at week 24. The following assumptions were used for the power calculations at week 24: • 48% response rate for each ixekizumab treatment group • 15% response rate for the placebo group It was estimated that approximately 75% of the total sample size had cDMARD experience at baseline (approximately 77 patients per treatment group); this sample size would provide approximately 97% power to test the difference between each ixekizumab dose regimen and placebo in the cDMARD-experienced subpopulation, assuming ACR 20	Categorical endpoints: All missing data were imputed using NRI in which patients were defined as a non-responder if they: • did not meet the clinical response criteria at the timepoint of interest (week 12 or week 24) • Were eligible for rescue therapy at week 16 (ie, were analyzed as nonresponders after Week 16) • had missing clinical response data at the timepoint of interest • discontinued from the study at any time prior to week 24, for any reason • didn't have at least 1 post-baseline observation

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	of 80 mg Q4W versus placebo and another for tests of 80 mg Q2W versus placebo. For each dose schedule, if a test was not significant, all subsequent tests were not significant. The endpoints were assessed at baseline (week 0), and Weeks 1, 2, 4, 8, 12, 16, 20 and 24 during the double-blind treatment period and Weeks 28, 32, 36, 44 and 52 during the extension period.	response rate was 46% for each ixekizumab group and 15% for the placebo group.	
SPIRIT-P2 (74)			
The primary objective of the study was to assess, after 24 weeks of treatment, whether Ixe 80 mg Q2W or 80 mg Q4W was superior to placebo as measured by the proportion of patients meeting ACR 20 response criteria at week 24	The primary objective was analysed using a using logistic regression with treatment, geographic region, and TNFi experience (IR to 1 TNFi, IR to 2 TNFi, or intolerance to a TNFi). Missing data were imputed using non-responder imputation (NRI). A gatekeeping testing strategy for the primary and major secondary analyses was implemented to control the overall type I error rate at a 2-sided alpha level of 0.05 for the multiple comparisons. The order in which the primary and major secondary outcomes were tested for each dose is: • Primary (Test 1): Proportion of patients achieving ACR 20 response at Week 24 • Major Secondary 1 (Test 2): Change from baseline to Week 24 in HAQ-DI • Major Secondary 2 (Test 3): Proportion of patients achieving ACR 20 response at Week 12 • Major Secondary 3 (Test 4): Proportion of patients achieving PASI 75 response at Week 12 (restricted to patients with baseline psoriatic lesion(s) involving ≥3% BSA) • Major Secondary 4 (Test 5): Proportion of patients achieving Coates criteria for MDA at Week 24 (using LEI [E6] to assess enthesitis)	The total planned sample size for SPIRIT-P2 was 360 patients randomized in a 1:1:1 ratio to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo. In order to account for multiple testing for the two ixe groups, a 2-sided Fisher's exact test at the 0.025 level was assumed. This study had >90% power to test the superiority of each ixekizumab dose regimen to placebo for ACR 20 response criteria at week 24. The following assumptions were used for the power calculations at week 24: • 35% response rate for each ixekizumab treatment group • 15% response rate for the placebo group	Categorical endpoints: All missing data were imputed using NRI in which patients were defined as a non-responder if they: • Were eligible for rescue therapy at week 16 • had missing clinical response data at week 24 • discontinued from the study at any time prior to week 24, for any reason • didn't have at least 1 post-baseline observation

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	• Major Secondary 5 (Test 6): Proportion of patients achieving complete resolution in enthesitis as assessed by the LEI at Week 24 in patients with enthesitis at baseline The 6 statistical tests were grouped into 2 parallel branches, 1 for tests of 80 mg Q4W versus placebo and another branch for tests of 80 mg Q2W versus placebo. For each dose regimen, if a test was not significant, all subsequent tests were not significant. The endpoints were assessed at baseline (week 0), and Weeks 1, 2, 4, 8, 12, 16, 20 and 24 during the double-blind treatment period and Weeks 28, 32, 36, 44 and 52 during the extension period.		

Abbreviations: Q4W = every four weeks; Q2W = every two weeks; TNFi = tumour necrosis factor alpha inhibitor; cDMARD = conventional disease-modifying antirheumatic drugs; ACR 20 = at least 20% improvement in both tender and swollen joint counts; HAQ-DI=health assessment questionnaire-disability index; LEI=Leeds enthesitis index; n=number of patients; N/A=not applicable; PASI=psoriasis area and severity index; PsARC = Psoriasis Area and Severity Index; MDA =Minimum Disease Activity; NAPSI = Nail Psoriasis Severity Index; mTSS = modified Total Sharp Score; BSA = body surface area.

2.5 Quality assessment of the relevant clinical effectiveness evidence

An overview of the quality assessment results for the SPIRIT studies can be seen in Table 12. Given the design of the SPIRIT studies, in addition to the patient demographics/baseline demographics listed above and the recruitment of study participants from multiple sites in the UK, it can be assumed that the SPIRIT studies are reflective of UK clinical practice. For further details on the applicability of the trial results to the UK market, please refer to Section 2.13.1 (Strengths and limitations of the clinical evidence base for ixekizumab).

Table 12 Quality assessment results for the SPIRIT-P1 and SPIRIT-P2 studies

Trial number (acronym)	SPIRIT-P1	SPIRIT-P2
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes*	No
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Did the authors of the study publication declared any conflicts of interest?	Yes	Yes

*Itch NRS was a gated secondary endpoint in SPIRIT-P1, however, statistical testing was not performed as the prior gated endpoint was not significant.

The full quality assessment giving further details of the SPIRIT studies can be seen in Appendix D.

2.6 Clinical effectiveness results of the relevant trials

The primary objectives were met in both SPIRIT trials with both ixekizumab treatment groups showing greater efficacy than placebo at 24 weeks as measured by the proportion of patients achieving ACR 20 ($p<0.001$ for all comparisons). (69, 70)

Using multiplicity-controlled (gated) analyses, statistically significant differences for the ixekizumab 80 mg Q4W and Q2W versus placebo were observed for all major secondary endpoints in SPIRIT-P1 with the exception of the change from baseline to week 12 in LEI ($p>.25$ for each comparison) and the change from baseline to week 12 in Itch NRS (not

tested because of the multiplicity control strategy). (73) Using multiplicity-controlled analyses, statistically significant differences for the ixekizumab 80 mg Q4W group compared with the placebo group and for the ixekizumab 80 mg Q2W group compared with the placebo group were observed in the SPIRIT-P2 study for the primary endpoint of ACR 20 response rate at week 24 and all major secondary endpoints with the exception of the resolution of enthesitis as assessed by LEI at week 24. (70)

2.6.1 Primary objective: ACR 20 at week 24

In the SPIRIT-P1 trial, significantly greater proportions of biologic-naïve patients who received ixekizumab 80 mg Q4W or Q2W achieved an ACR 20 response at week 24, compared to placebo (57.9% and 62.1%, versus 30.2%, respectively, both p<0.001; Table 13 and Figure 4). (69) Similarly, in SPIRIT-P2, ACR 20 response rates were significantly greater in biologic-experienced patients who received ixekizumab 80 mg Q4W or Q2W compared to placebo (53.3% and 48.0%, versus 19.5%, respectively, both p<0.001; Table 13 and Figure 4). (70)

In the adalimumab arm of SPIRIT-P1, 57.4% of patients achieved ACR 20 at week 24; (69) these results are consistent with the ACR 20 response reported in the adalimumab ADEPT trial (57%). (51)

Table 13 ACR 20 response rates in SPIRIT-P1 and SPIRIT-P2 at week 24 - NRI (ITT population)

Study ***Endpoint***	**Placebo**	**Adalimumab**	**IXE80Q4W**	**IXE80Q2W**
SPIRIT-P1 (69)	**N=106**	**N=101**	**N=107**	**N=103**
ACR 20, *n (%)*	32 (30.2)	58 (57.4)	62 (57.9)	64 (62.1)
OR *95% CI[1]* *p-value[1]*	-	3.16 (1.78, 5.60) <0.001	3.24 (1.84, 5.72) <0.001	3.88 (2.18, 6.91) <0.001
SPIRIT-P2 (70)	**N=118**	**-**	**N=122**	**N=123**
ACR 20, *n (%)*	23 (19.5)	-	65 (53.3)	59 (48.0)
OR *95% CI[2]* *p-value[2]*	-	-	4.74 (2.65, 8.48) <0.001	3.79 (2.12, 6.78) <0.001

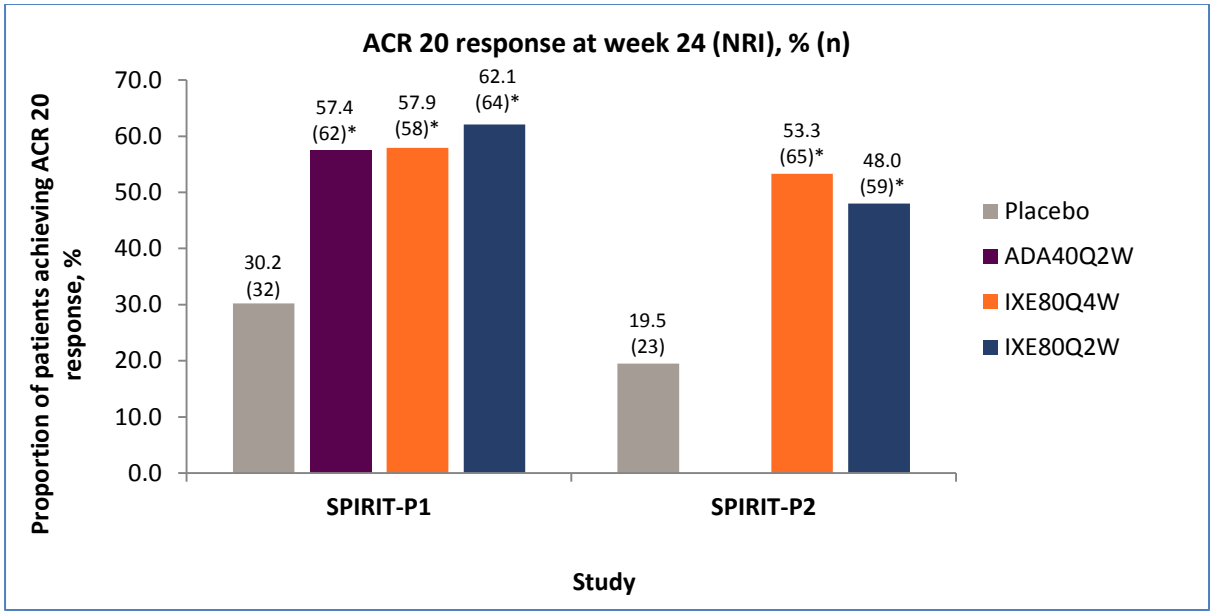
[1] A logistic regression analysis with treatment, geographic region and baseline cDMARD experience as factors. Comparison of active treatment versus placebo.

[2] A logistic regression analysis with treatment, geographic region and baseline TNFi experience as factors. Comparison of active treatment versus placebo.

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

Source: SPIRIT-P1: CSR RHAP, Table RHAP.11.4; SPIRIT-P2: CSR RHBE, Table RHBE.11.2 (Page 8 of 25)

Figure 4 ACR 20 response rates in SPIRIT-P1 and SPIRIT-P2 at week 24 (NRI), % (n)



*p<0.001 versus placebo. Note, the adalimumab 40 mg Q2W treatment arm served as an active reference for comparison with placebo; the study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab. Abbreviations: ACR 20=American College of Rheumatology criteria ≥20% improvement, ADA40Q2W=adalimumab 40 mg very two weeks, IXE80Q2W=ixekizumab 80 mg every two weeks, IXE80Q4W=ixekizumab 80 mg every four weeks, NRI=nonresponder imputation, n=number of patients.

2.6.2 Secondary outcomes

PsARC at Week 12 and 24

In both SPIRIT-P1 and -P2 trials, the percentage of patients who achieved a PsARC response at week 12 as well as week 24 was statistically significantly greater for the ixekizumab groups (80 mg Q2W and Q4W), compared to placebo (p<0.01 in all cases; Table 14).

The percentage of patients who received adalimumab, who achieved PsARC response at week 24 (58.4%) of the SPIRIT-P1 double-blind treatment period was comparable to that reported in the ADEPT trial (60%). (51)

Table 14 PsARC response rates in SPIRIT-P1 and SPIRIT-P2 at week 12 and week 24 - NRI (ITT population)

Study *Endpoint*	Placebo	Adalimumab	IXE80Q4W	IXE80Q2W
SPIRIT-P1 (73)	**N=106**	**N=101**	**N=107**	**N=103**
Week 12				
n (%)	36 (34.0%)	59 (58.4%)	59 (55.1%)	63 (61.2%)
OR *95% CI*[2] *p-value*[2]	-	2.8 (1.59, 5.02) <0.001	2.5 (1.41, 4.34) 0.002	3.2 (1.81, 5.71) <0.001
Week 24				
n (%)	34 (32.1%)	59 (58.4%)	62 (57.9%)	68 (66.0%)
OR *95% CI*[1] *p-value*[1]	-	3.0 (1.70, 5.35) <0.001	3.0 (1.69, 5.22) <0.001	4.2 (2.36, 7.57) <0.001
SPIRIT-P2 (74)	**N=118**	**-**	**N=122**	**N=123**
Week 12				
n (%)	28 (23.7%)	-	61 (50.0%)	64 (52.0%)
OR *95% CI*[2] *p-value*[2]	-	-	3.26 (1.87, 5.69) <0.001	3.47 (1.99, 6.05) <0.001
Week 24				
n (%)	24 (20.3%)	-	68 (55.7%)	58 (47.2%)
OR *95% CI*[2] *p-value*[2]	-	-	5.0 (2.81, 8.90) <0.001	3.55 (1.99, 6.32) <0.001

1 A logistic regression analysis with treatment, geographic region and baseline cDMARD experience as factors. Comparison of active treatment versus placebo.

2 A logistic regression analysis with treatment, geographic region and baseline TNFi experience as factors. Comparison of active treatment versus placebo.

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

Source: SPIRIT-P1: CSR RHAP, Table RHAP.14.58 (pages 3 and 4 of 5); SPIRIT-P2: CSR RHBE, Table RHBE.14.62 (page 5 and 8 of 9)

HAQ-DI at week 12

At week 12, patients in the two ixekizumab groups (Q4W and Q2W) achieved significantly greater mean change from baseline in HAQ-DI total scores both in SPIRIT-P1 and -P2 trials, relative to placebo (p<0.001 for all comparisons; Table 15). In SPIRIT-P1, the least squares mean (LSM) changes from baseline in the HAQ-DI total scores at week 12 were -0.13, -0.37, and -0.47 in the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, and placebo groups, respectively (Table 15). In SPIRIT-P2, the least squares mean (LSM) changes from baseline

in the HAQ-DI total scores at week 24 were -0.1, -0.4, and -0.4 in the ixekizumab 80 mg Q4W, ixekizumab 80 mg Q2W, and placebo groups, respectively (Table 15).

Table 15 Change from baseline to week 12 in HAQ-DI in SPIRIT-P1 and SPIRIT-P2 (ITT population)

Study *Endpoint*	Placebo	Adalimumab	IXE80Q4W	IXE80Q2W
SPIRIT-P1* (69, 73)	**N=106**	**N=101**	**N=107**	**N=103**
Number patients in model	n=100	n=95	n=96	n=95
Endpoint (LSM) Change (SE)	-0.13 (0.05)	-0.35 (0.05)	-0.37 (0.05)	-0.47 (0.05)
LSM Difference (95% CI)	-	-0.22 (-0.35, -0.09)	-0.24 (-0.36, -0.12)	-0.34 (-0.47, -0.21)
p-value[1]	-	<0.001	<0.001	<0.001
SPIRIT-P2*(74)	**N=118**	**-**	**N=122**	**N=123**
Number patients in model	n=102	-	n=114	n=113
Endpoint (LSM) Change (SE)	-0.1 (0.06)	-	-0.4 (0.06)	-0.4 (0.06)
LSM Difference (95% CI)	-	-	-0.3 (-0.5, -0.2)	-0.3 (-0.4, -0.1)
p-value[2]	-	-	<0.001	<0.001

[1] Repeated measures mixed model (MMRM) with treatment, region, baseline conventional DMARD experience, visit, and treatment-by-visit interaction as fixed factors, and response value at baseline as a covariate. Comparison of active treatment versus placebo.

[2] Repeated measures mixed model (MMRM) with treatment, region, baseline TNFi experience, visit, and treatment-by-visit interaction, region by visit interaction, TNFi by visit interaction, baseline value, baseline by visit interaction as a covariates. Comparison of active treatment versus placebo.

*Major secondary endpoint (gated); MMRM = mixed model for repeated measures; CI = confidence interval; PBO = placebo; ADA40Q2W = adalimumab; IXE80Q4W = ixekizumab 80 mg Q4W; IXE80Q2W = ixekizumab 80 mg Q2W; LS = least squares; SD = standard deviation; SE = standard error; HAQ-DI = health assessment questionnaire - disability index; LSM = least squares mean; N = number of patients in the analysis population; n = number of patients in the specified category;

Source: SPIRIT-P1: CSR RHAP, Table RHAP.11.5 (Page 9 of 19); Table RHAP.14.60 (Page 1 and 29 of 33); SPIRIT-P2: CSR RHAP, Table RHAP.11.5 (Page 9 of 10); Table RHAP.14.69 (Page 1 and 29 of 33);

PASI 75, PASI 90 and PASI 100 at week 12

For both, SPIRIT-P1 and –P2, for the patients with baseline psoriatic lesions ≥3% of BSA, there was a statistically significantly greater percentage of patients who achieved PASI 75 response at week 12 for each of the ixekizumab groups compared with the placebo group (p<0.001 in all cases; Table 16). In SPIRIT-P1, the PASI 75 response rates at week 12 (NRI) were 75.3% and 69.5% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 7.5% for the placebo group. In SPIRIT-P2, the PASI 75 response rates at week 12 (NRI) were 57.4% and 61.8% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 10.4% for the placebo group.

For both, SPIRIT-P1 and –P2, for the patients with baseline psoriatic lesions ≥3% of BSA, there was a statistically significantly greater percentage of patients who achieved PASI 90 and 100 response at week 12 for each of the ixekizumab groups compared with the placebo group (Table 16). The PASI 90/100 response rates at week 12 (NRI) were 52.1%/31.5% and 57.6%/40.7% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 1.5%/1.5% for the placebo group (Table 16).

Table 16 PASI 75, PASI 90 and PASI 100 response rates in SPIRIT-P1 and SPIRIT-P2 at week 12 - NRI (ITT population)

Study ***Endpoint***	**Placebo**	**Adalimumab**	**IXE80Q4W**	**IXE80Q2W**
SPIRIT-P1 (69, 73)	**N=67**	**N=68**	**N=73**	**N=59**
PASI 75, n (%)*	5 (7.5)	23 (33.8)	55 (75.3)	41 (69.5)
OR *95% CI[1]* *p-value[1]*	-	6.3 (2.2, 17.95) <0.001	38.8 (13.36, 112.72) <0.001	29.1 (9.87, 85.53) <0.001
PASI 90, n (%)	1 (1.5)	15 (22.1)	38 (52.1)	34 (57.6)
OR *95% CI[1]* *p-value[1]*	-	18.5 (2.36, 144.84) 0.006	71.6 (9.40, 545.52) <0.001	91.8 (11.86, 710.43) <0.001
PASI 100, n (%)	1 (1.5)	10 (14.7)	23 (31.5)	24 (40.7)
OR *95% CI[1]* *p-value[1]*	-	10.9 (1.35, 88.49) 0.025	29.7 (3.86, 228.18) 0.001	46.1 (5.94, 357.57) <0.001
SPIRIT-P2 (74)	**N=67**	**-**	**N=68**	**N=68**
PASI 75, n (%)*	7 (10.4)	-	39 (57.4)	42 (61.8)
OR *95% CI[2]* *p-value[2]*	-	-	14.03 (5.28, 37.27) <0.001	16.67 (6.28, 44.24) <0.001
PASI 90, n (%)	4 (6.0)	-	26 (38.2)	29 (42.6)
OR *95% CI[2]* *p-value[2]*	-	-	10.52 (3.36, 32.95) NA	17.96 (5.32, 60.62) <0.001
PASI 100, n (%)	4 (6.0)	-	13 (19.1)	16 (23.5)
OR *95% CI[2]* *p-value[2]*	-	-	3.82 (1.16, 12.55) NA	5.87 (1.78, 19.32) 0.004

1 A logistic regression analysis with treatment, geographic region and baseline cDMARD experience as factors. Comparison of active treatment versus placebo.

2 A logistic regression analysis with treatment, geographic region and baseline TNFi experience as factors. Comparison of active treatment versus placebo.

*Major secondary endpoint (gated); CI = confidence interval; IXE = ixekizumab; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio;

Source: SPIRIT-P1: CSR RHAP, Table RHAP.11.8 (page 9 and 10 of 17); SPIRIT-P2: CSR RHBE, Table RHBE.11.4 (page 5, 13 and 21 of 25).

ACR 50 and ACR 70 at week 24

In SPIRIT-P1, the proportion of biologic-naïve patients who achieved an ACR 50/ACR 70 response at week 24, was significantly greater in the ixekizumab 80 mg Q4W and Q2W groups compared to placebo (40.2%/23.4% and 46.6%/34.0%, versus 15.1%/5.7%, respectively, all p<0.001; Table 17). Similarly, in SPIRIT-P2, the proportion of biologic-experienced patients who achieved an ACR 50 response at week 24, was significantly greater for ixekizumab 80 mg Q4W or Q2W groups, relative to placebo (35.2 and 33.3%, versus 5.1, respectively, both p<0.001; Table 17).

In the adalimumab arm of SPIRIT-P1, 38.6% of patients achieved ACR 50 at week 24; these results are consistent with the ACR 50 response reported in the adalimumab ADEPT trial (39%) at week 24. (51)

Table 17 ACR 50 and ACR 70 response rates in SPIRIT-P1 and SPIRIT-P2 at week 24 - NRI (ITT population)

Study ***Endpoint***	**Placebo**	**Adalimumab**	**IXE80Q4W**	**IXE80Q2W**
SPIRIT-P1 (69, 73)	**N=106**	**N=101**	**N=107**	**N=103**
ACR 50, *n (%)*	16 (15.1)	39 (38.6)	43 (40.2)	48 (46.6)
OR *95% CI[1]* *p-value[1]*	-	3.6 (1.83, 6.94) <0.001	3.8 (1.97, 7.38) <0.001	5.0 (2.57, 9.64) <0.001
ACR 70, *n (%)*	6 (5.7)	26 (25.7)	25 (23.4)	35 (34.0)
OR *95% CI[1]* *p-value[1]*	-	5.8 (2.27, 14.79) <0.001	5.1 (2.00, 13.09) <0.001	8.7 (3.46, 21.80) <0.001
SPIRIT-P2 (70, 74)	**N=118**	**-**	**N=122**	**N=123**
ACR 50, *n (%)*	6 (5.1)	-	43 (35.2)	41 (33.3)
OR *95% CI[2]* *p-value[2]*	-	-	10.83 (4.31, 27.23) <0.001	9.31 (3.75, 23.13) <0.001
ACR 70, *n (%)*	0 (0.0)	-	27 (22.1)	15 (12.2)
OR *95% CI[2]*	-	-	NA NA	NA NA

Study *Endpoint*	Placebo	Adalimumab	IXE80Q4W	IXE80Q2W
p-value[2]				

1 A logistic regression analysis with treatment, geographic region and baseline cDMARD experience as factors. Comparison of active treatment versus placebo.

2 A logistic regression analysis with treatment, geographic region and baseline TNFi experience as factors. Comparison of active treatment versus placebo.

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

Source: SPIRIT-P1: CSR RHAP, Table RHAP.11.14 (page 11 of 12); SPIRIT-P2: CSR RHBE, Table RHBE.11.2 (page 16 and 24 of 25)

ACR 20, ACR 50 and ACR 70 at week 12

In SPIRIT-P1, the proportion of biologic-naïve patients who achieved an ACR 20 response at week 12 (major secondary endpoint), was significantly greater in the ixekizumab 80 mg Q4W and Q2W groups compared to placebo (51.5% and 57.0%, versus 31.1%, respectively, both p<0.001; Table 18). Similarly, in SPIRIT-P2, the proportion of biologic-experienced patients who achieved an ACR 20 response at week 12, was significantly greater in the ixekizumab 80 mg Q4W and Q2W groups compared to placebo (50.0% and 48.0%, versus 22.0%, respectively, both p<0.001;Table 18).

At week 12, patients in the two ixekizumab groups (Q4W and Q2W) achieved significantly greater ACR 50 response rates in the SPIRIT-P1 and -P2 trials, relative to placebo (p<0.001 for all comparisons; Table 18).

At week 12, the ACR 70 response rates in SPIRIT-P1 were 15.0, 16.5 and 0 respectively for ixekizumab 80 mg Q4W, Q2W and placebo, respectively. At week 12, the ACR 70 response rates in SPIRIT-P2 were 14.8, 10.6 and 1.7 respectively for ixekizumab 80 mg Q4W, Q2W and placebo, respectively (Table 18).

Table 18 ACR 20, ACR 50 and ACR 70 response rates in SPIRIT-P1 and SPIRIT-P2 at week 12 - NRI (ITT population)

Study *Endpoint*	Placebo	Adalimumab	IXE80Q4W	IXE80Q2W
SPIRIT-P1 (69, 73)	**N=106**	**N=101**	**N=107**	**N=103**
ACR 20,* *n (%)*	33 (31.1)	52 (51.5)	61 (57.0)	62 (60.2)
OR *95% CI*[1] *p-value*[1]	-	2.4 (1.34, 4.17) 0.003	2.9 (1.66, 5.14) <0.001	3.3 (1.88, 5.89) <0.001
ACR 50, *n (%)*	5 (4.7)	30 (29.7)	36 (33.6)	41 (39.8)
OR *95% CI*[1]	-	8.6 (3.19, 23.35)	10.3 (3.83, 27.48)	13.4 (5.01, 35.77)

Study *Endpoint*	Placebo	Adalimumab	IXE80Q4W	IXE80Q2W
p-value[1]		<0.001	<0.001	<0.001
ACR 70, *n (%)*	0	18 (17.8)	16 (15.0)	17 (16.5)
OR *95% CI*[1] *p-value*[1]	-	NA	NA	NA
SPIRIT-P2 (74)	**N=118**	**-**	**N=122**	**N=123**
ACR 20,* *n (%)*	26 (22.0)	-	61 (50.0)	59 (48.0)
OR *95% CI*[2] *p-value*[2]	-	-	3.56 (2.02, 6.26) <0.001	3.28 (1.85, 5.79) <0.001
ACR 50, *n (%)*	4 (3.4)	-	38 (31.1)	41 (33.3)
OR *95% CI*[2] *p-value*[2]	-	-	14.61 (4.82, 44.28) <0.001	14.58 (4.98, 42.68) <0.001
ACR 70, *n (%)*	2 (1.7)	-	18 (14.8)	13 (10.6)
OR *95% CI*[2] *p-value*[2]	-	-	11.9 (2.47, 57.41) 0.002	7.46 (1.63, 34.22) NA

[1] A logistic regression analysis with treatment, geographic region and baseline cDMARD experience as factors. Comparison of active treatment versus placebo.

[2] A logistic regression analysis with treatment, geographic region and baseline TNFi experience as factors. Comparison of active treatment versus placebo.

*Major secondary endpoint (gated); CI = confidence interval; IXE = ixekizumab; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; N = number of patients in the analysis population; n = number of patients in the specified category; NRI = non-responder imputation; OR = odds ratio;

Source: SPIRIT-P1: CSR RHAP, Table RHAP.11.7 (page 6 and 7 of 12); SPIRIT-P2: CSR RHBE, Table RHBE.11.2 (page 5, 13 and 21 of 25)

Open-label extension period data (up to week 108 for SPIRIT-P1 and week 52 for SPIRIT-P2)

Ixekizumab treatment maintained effectiveness in both joint symptoms (as measured by the ACR 20, 50 and 70, mTSS and PsARC) and skin clearance (as measured by the PASI 75, 90 and 100) over the open-label extension period. Additionally, ixekizumab has demonstrated to maintain clinically relevant improvements in functional capacity (as measured by the HAQ-DI) over the same period. Results from the extension period can be found in Appendix Q.

2.7 Subgroup analysis

Pre-specified subgroups from the two pivotal phase 3 trials (SPIRIT-P1 and SPIRIT-P2) were examined to determine if there were differences in the rates of achievement of treatment goals (as measured by the ACR 20 response rate at Week 24 and mTSS change from baseline at week 24). Subgroups evaluated included patient demographics (e.g., gender, age, geographic region, weight), concomitant cDMARD therapy (current use at baseline [yes/no]), cDMARD experience at baseline (naïve, past use, current use), prior TNFi experience (inadequate responder to 1 TNFi, inadequate responder to 2 TNFi, intolerant to a TNFi), baseline severity groups (CRP: <=6 or >6); previous therapy for PsA (yes,no); duration of PsA (0 to <2, ≥2 years). A list of all pre-specified subgroups analysis for SPIRIT-P1 and SPIRIT-P2 can be seen in Appendix E.

The efficacy and safety of ixekizumab was demonstrated regardless of age, race, baseline BMI, geographic region, baseline CRP, previous PsA therapy status, concomitant DMARD therapy (current use at baseline), cDMARD experience at baseline, duration since PsA onset, in both SPIRIT studies. For SPIRIT-P1, a statistical significant difference was observed in the baseline weight subgroup. For SPIRIT-P2, a statistical significant difference was observed in the gender subgroup.

Additionally, ixekizumab has shown to be consistently efficacious independently of concomitant methotrexate use (post-hoc analysis) as well as in the subgroup of patients who would be eligible for treatment with bDMARDs under current NICE criteria (pre-specified analysis). Results of these both subgroup analysis can be seen below. Results of other pre-specified subgroup analysis can be seen in Appendix E.

2.7.1 Efficacy of ixekizumab regardless of concomitant methotrexate use (post-hoc analysis)

Ixekizumab provides a high-level of efficacy in psoriatic arthritis symptoms in biological naïve as well as biologic experience patients with or without concomitant methotrexate use. ACR 20 response rates at week 24 by concomitant methotrexate use at baseline, can be seen in Figure 5 and Figure 6, respectively for SPIRIT-P1 and SPIRIT-P2.

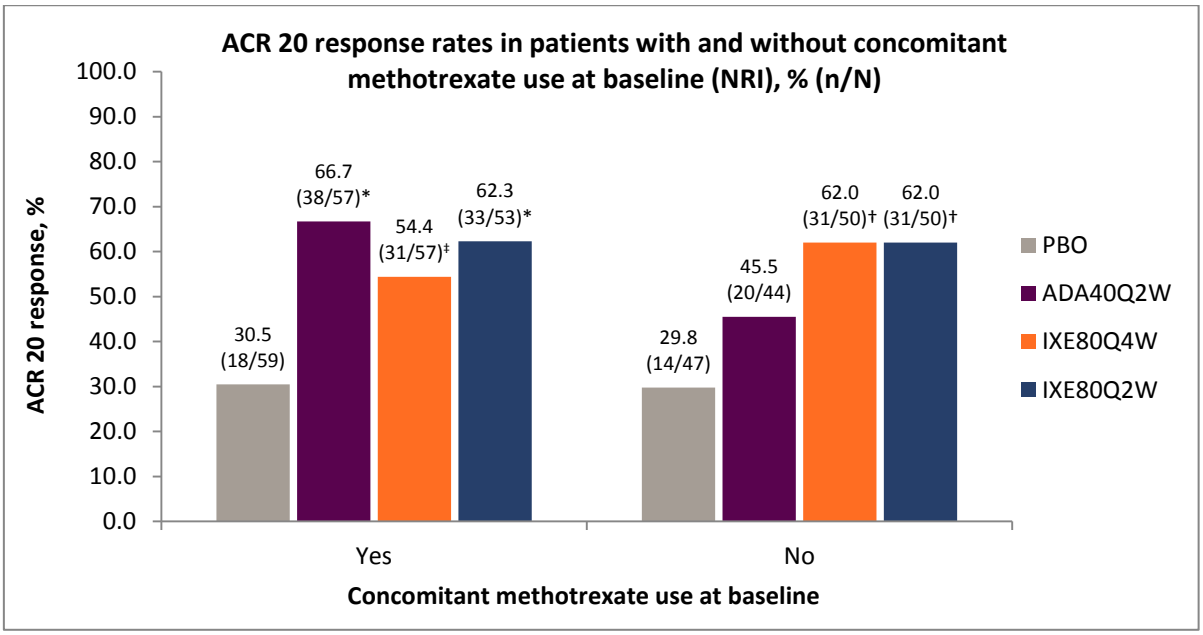
At week 24, ACR 20 response rates were comparable between patients with and without concomitant methotrexate at baseline in the SPIRIT-P1 trial. In patients who received ixekizumab 80 mg Q4W, with and without concomitant methotrexate at baseline, ACR 20 responses were achieved by 54.4% and 62.0%, respectively (Figure 5). Similarly, in patients

who received ixekizumab 80 mg Q2W, with and without concomitant methotrexate at baseline, ACR 20 responses were achieved by 62.3% and 62.0%, respectively (Figure 5).

In patients who received adalimumab 40 mg Q2W in the double-blind treatment period of the SPIRIT-P1 trial, ACR 20 response was substantially lower in patients treated with adalimumab monotherapy compared to patients who received concomitant methotrexate (45.5% versus 66.7%, respectively; Figure 5).

However, treatment by subgroup interaction (i.e. concomitant methotrexate versus no concomitant methotrexate) was not significant for ACR 20 response (p=0.199).

Figure 5 ACR 20 response rates rates at week 24 (NRI) by concomitant methotrexate use at baseline; SPIRIT-P1, % (n/N)



Logistic regression model with effect of treatment, subgroup and the treatment-by-subgroup interaction. The treatment-by-subgroup interaction was tested at the significance level of 0.10. P-values within each category of the subgroup are based on Fisher's exact test.

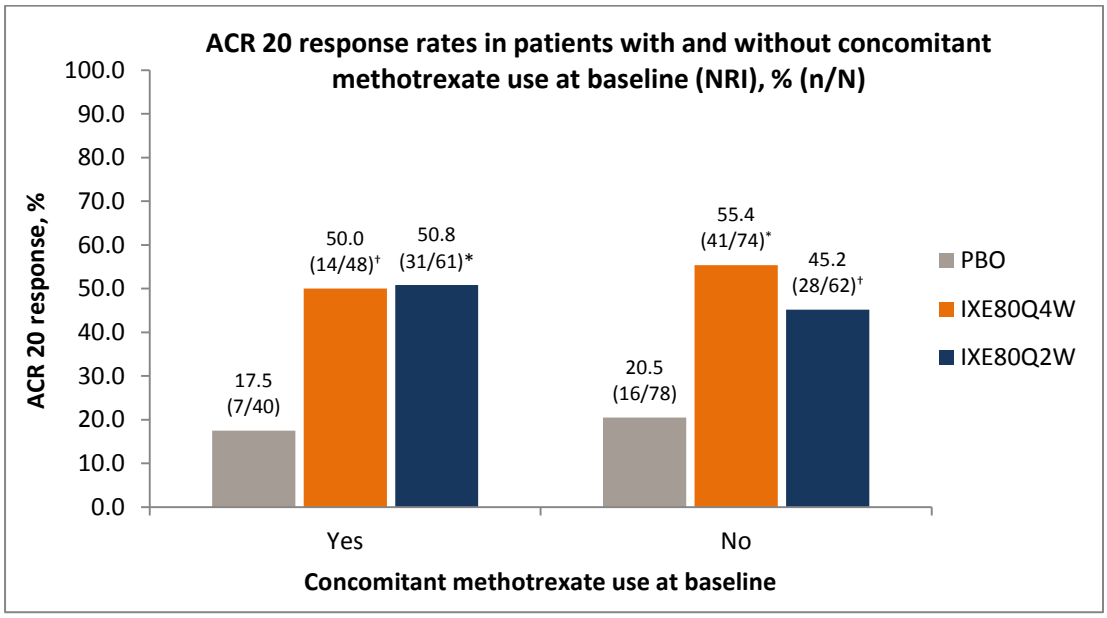
‡p<0.05 versus placebo ; †p<0.01 versus placebo; *p≤0.001 versus placebo.

Note, the adalimumab 40 mg Q2W treatment arm served as an active reference for comparison with placebo; the study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab.

Abbreviations: ACR 20=American College of Rheumatology criteria ≥20% improvement, ADA40Q2W=adalimumab 40 mg very two weeks, IXE80Q2W=ixekizumab 80 mg every two weeks, IXE80Q4W=ixekizumab 80 mg every four weeks, n=number of patients in the specified category, N=number of patients in each subgroup, NRI=non-responder imputation.

Source: Eli Lilly and Company, 2016, Data on File, ACR20 Response Rate at Week 24 (NRI) by Concomitant Therapy Subgroups (RHAP).

Figure 6 ACR 20 response rates rates at week 24 (NRI) by concomitant methotrexate use at baseline; SPIRIT-P2, % (n/N)



Logistic regression model with effect of treatment, MTX use and the treatment-by-MTX use interaction. The treatment-by-MTX use interaction was tested at the significance level of 0.10. P-values within each category of the subgroup are based on Fisher's exact test.

‡p<0.05 versus placebo ; †p<0.01 versus placebo; *p≤0.001 versus placebo.

Abbreviations: ACR 20=American College of Rheumatology criteria ≥20% improvement, IXE80Q2W=ixekizumab 80 mg every two weeks, IXE80Q4W=ixekizumab 80 mg every four weeks, NRI=nonresponder imputation, n=number of patients in the specified category.

Source: Eli Lilly and Company, 2016, Data on File, ACR20 Response Rate at Week 24 (NRI) by Methotrexate (MTX) Use at Baseline (RHBE).

2.7.2 Efficacy of ixekizumab in patients eligible for biologic therapy under current NICE criteria (pre-specified analysis)

Treatment with ixekizumab has demonstrated efficacy in patient populations who would be eligible for treatment with biologics according to NICE criteria based on failure of 2 prior cDMARDs and three or more tender joints and three or more swollen joints, demonstrating the efficacy of ixekizumab in a NICE-defined biologic eligible population (Table 19).

Due to the small number of patients eligible for treatment with biologics according to NICE criteria in each of the studies, this analysis was carried out on the PsA placebo-controlled integrated analysis set, which included the ixekizumab and placebo arms from the induction periods of both SPIRIT-P1 and SPIRIT–P2. Significantly greater proportions of patients who received ixekizumab 80 mg Q4W or Q2W achieved an ACR 20 response at week 24, compared to placebo ([redacted] Table 19).

Table 19 ACR 20 response rates at week 24 (NRI); Primary PsA placebo controlled integrated analysis set, n(%) (NICE ITT population)

Endpoint	Placebo	IXE80Q4W	IXE80Q2W	Total IXE	Total
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR 20, n (%)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR *95% CI*[1] *p-value*[1]	-	[redacted]	[redacted]	-	

[1]Odds ratio, CI, and p-value are from a logistic regression model using Wald's test with treatment and study as factors.

Abbreviations: IXE80Q4W = ixekizumab 80 mg Q4W; IXE80Q2W = ixekizumab 80 mg Q2W; IXE = ixekizumab; N = number of patients in the analysis population; Nx = number of patients with non-missing data in each category; n = number of responders; CI = confidence interval; NRI = non-responder imputation; ACR = American College of Rheumatology; NICE = National Institute for Health and Care Excellence.

Note: The NICE ITT Population is a subset of the ITT Population and is defined as all randomized patients with 1) peripheral arthritis with >=3 tender joints and >=3 swollen joints, and 2) PsA that has not responded to adequate trials of at least 2 standard DMARDs, administered either individually or in combination.

Note: Primary PsA Placebo-Controlled Integrated Analysis Set included patient data from the 2 pivotal Phase 3 PsA placebo-controlled studies (Studies RHAP and RHBE) from screening through Week 24. Analyses from baseline to Weeks 12 and 24 (and Week 16 for selected endpoints) were conducted. For patients who were inadequate responders at Week 16, observed data after Week 16 through Week 24 were not included to avoid falsely ascribing benefit from rescue medication to the randomized therapy. The adalimumab treatment group from Study RHAP was not included in this integrated analysis.

Source: Eli Lilly and Company, 2016, Data on File, ACR20 Response Rates at Week 24 (NRI), NICE Intent-to-Treat Population, Primary PsA Placebo-Controlled Integrated Analysis Set.

2.8 Meta-analysis

SPIRIT-P1 and SPIRIT-P2 were the only relevant trials identified in the systematic literature review to assess the efficacy and safety of ixekizumab. SPIRIT-P1 recruited bDMARD-naïve patients and only bDMARD-experienced patients were eligible to enrol in SPIRIT-P2. As these trial populations represent distinct patient groups and prior bDMARD exposure is a treatment effect modifier, a meta-analysis of the two trials would not have been appropriate. In the absence of head-to-head RCTs conducted between comparator treatments listed in the NICE scope, a comprehensive systematic literature review and network meta-analyses (NMA) were conducted to estimate the comparative efficacy of these treatments. As prior bDMARD exposure is a treatment effect modifier, Bayesian NMAs were conducted separately for the bDMARD-naïve population and bDMARD-experienced population to the extent possible, thus following the approach of the 2017 MTA of certolizumab pegol and secukinumab in PsA. (2) The outcomes of the NMAs are therefore more informative for the decision problem than conducting a meta-analysis of SPIRIT-P1 and SPIRIT–P2.

Indirect comparisons can provide relative measures of effect for all relevant comparators in the absence of direct evidence and is most suitable when there are multiple-arm trials included within networks. The use of an indirect comparison, in preference to pairwise meta-analysis, allowed the evidence of all available and relevant comparators listed in the scope to be included, enabling more precise relative treatment effects to be calculated using direct and indirect evidence. In addition, the indirect comparison feeds into the economic model to provide cost-effectiveness results for ixekizumab against relevant comparators. Indirect comparisons have been used to synthesise evidence in previous NICE STA and MTA submissions for biologics in psoriatic arthritis. (2, 26-29)

2.9 Indirect and mixed treatment comparisons

Bayesian NMAs were conducted to estimate treatment response in the bDMARD-naïve population and bDMARD-experienced populations. Joint response was measured by the proportion of patients achieving PsARC response and functional capacity was assessed as the absolute change from baseline in HAQ-DI score conditional on achieving PsARC response. Skin response was assessed as the proportion of patients achieving 50%, 75%, 90% and 100% reduction from baseline PASI score (PASI50, PASI75, PASI90, PASI100). Full details of the NMA methodology are presented in Appendix D.

2.9.1 Biologic-naïve population

A summary of trials used to carry out the NMA for the biologic-naïve population is presented in Table 20 and Figure 7.

Table 20 Summary of the trials used to carry out the PsARC, PASI 50/75/90/100 and CFB HAQ-DI network meta-analyses for the biologic-naïve population

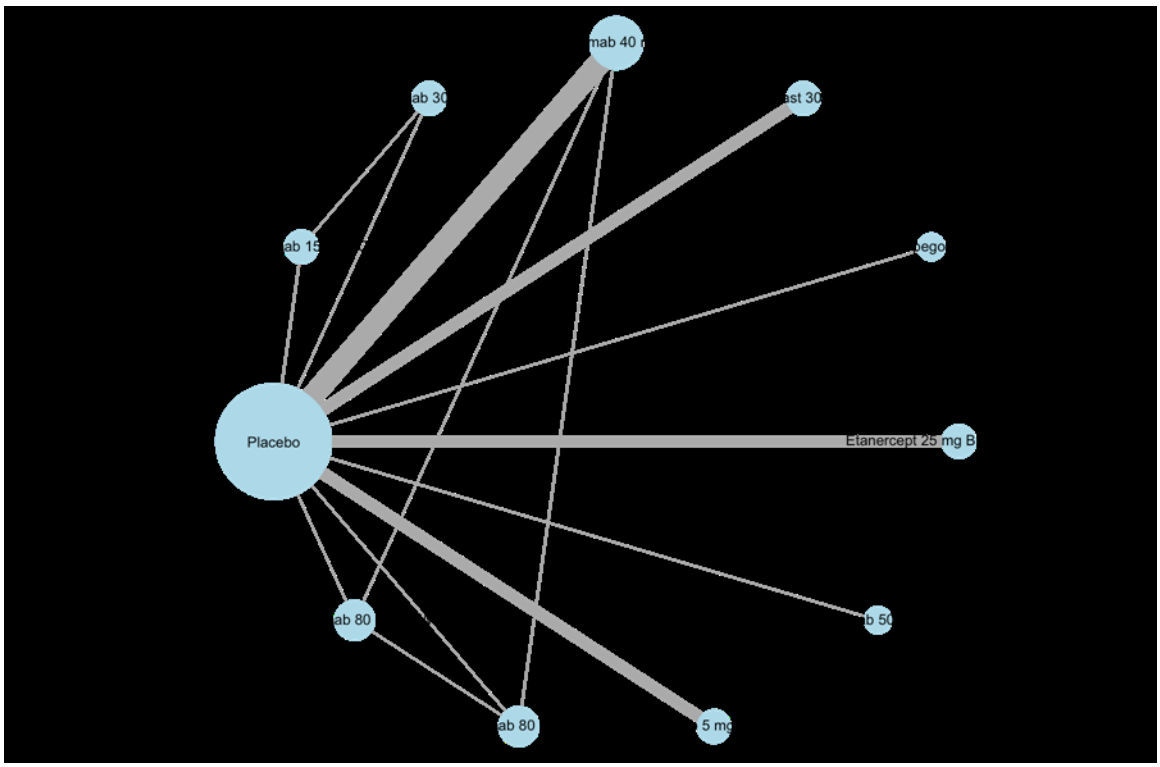
Trial	First author, year	Treatment arm	Timepoint (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
ADEPT	Mease 2005 (51)	Adalimumab 40 mg Q2W	12	Yes	Yes	Yes	Yes	No	Yes
ADEPT	Mease 2005 (51)	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2 *	Thom 2016 (77)	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2 *	Thom 2016 (77)	Secukinumab 150 mg Q4W	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2 *	Thom 2016 (77)	Secukinumab 300 mg Q4W	12	Yes	Yes	Yes	Yes	No	Yes
Genovese 2007	Genovese 2007 (52)	Adalimumab 40 mg Q2W	12	Yes	No	No	No	No	Yes
Genovese 2007	Genovese 2007 (52)	Placebo	12	Yes	No	No	No	No	Yes
GO-REVEAL	Kavanaugh 2009 (59)	Golimumab 50 mg Q4W	14	Yes	Yes	Yes	Yes	No	Yes
GO-REVEAL	Kavanaugh 2009 (59)	Placebo	14	Yes	Yes	Yes	Yes	No	Yes
IMPACT	Antoni 2005 (78)	Infliximab 5 mg/kg Q8W	16	Yes	Yes	Yes	Yes	No	Yes
IMPACT	Antoni 2005 (78)	Placebo	16	Yes	Yes	Yes	Yes	No	Yes
IMPACT 2	Antoni 2005 (50)	Infliximab 5 mg/kg Q8W	14	Yes	Yes	Yes	Yes	No	Yes
IMPACT 2	Antoni 2005 (50)	Placebo	14	Yes	Yes	Yes	Yes	No	Yes
Mease 2000	Mease 2000 (49)	Etanercept 25 mg BIW/50 mg QIW	12	Yes	Yes	Yes	No	No	Yes
Mease 2000	Mease 2000 (49)	Placebo	12	Yes	Yes	Yes	No	No	Yes
Mease 2004	Mease 2004 (79)	Etanercept 25 mg	12	Yes	No	No	No	No	Yes

Trial	First author, year	Treatment arm	Timepoint (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
		BIW/50 mg QIW							
Mease 2004	Mease 2004 (79)	Placebo	12	Yes	No	No	No	No	Yes
OPAL-BROADEN	Mease 2016 (80)	Adalimumab 40 mg Q2W	12	No	No	Yes	No	No	Yes
OPAL-BROADEN	Mease 2016 (80)	Placebo	12	No	No	Yes	No	No	Yes
PALACE 1 *	Kavanaugh 2014 (81)	Apremilast 30 mg BID	16	Yes	Yes	Yes	No	No	Yes
PALACE 1 *	Kavanaugh 2014 (81)	Placebo	16	Yes	Yes	Yes	No	No	Yes
PALACE 2 *	Cutolo 2016 (82)	Apremilast 30 mg BID	16	Yes	Yes	Yes	No	No	Yes
PALACE 2 *	Cutolo 2016 (82)	Placebo	16	Yes	Yes	Yes	No	No	Yes
PALACE 3	Edwards 2016 (83)	Apremilast 30 mg BID	16	No	Yes	Yes	No	No	Yes
PALACE 3	Edwards 2016 (83)	Placebo	16	No	Yes	Yes	No	No	Yes
RAPID-PsA*	Mease 2014 (55)	Certolizumab pegol	12	Yes	Yes	Yes	Yes	No	No
RAPID-PsA*	Mease 2014 (55)	Placebo	12	Yes	Yes	Yes	Yes	No	No
SPIRIT-P1	Eli Lilly and Company	Adalimumab 40 mg Q2W	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company	Ixekizumab 80 mg Q2W	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company	Ixekizumab 80 mg Q4W	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company	Placebo	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company	Adalimumab 40 mg Q2W	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company	Ixekizumab 80 mg Q2W	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company	Ixekizumab 80 mg Q4W	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company	Placebo	16	Yes	No	Yes	Yes	Yes	Yes

BID=Twice daily dosing regimen, BIW=Twice weekly dosing regimen, HAQ-DI=Health Assessment Questionnaire – Disability Index; PASI 50/75/90/100=reduction of (50/75/90/100)% from baseline Psoriasis Area and Severity Index score; PsARC=Psoriatic Arthritis Response Criteria; QIW=Once weekly dosing regimen, Q2/4/8/12W=Every 2nd/4th/8th/12th week dosing regimen

* Outcomes were not reported for bDMARD-naive subgroup at the response assessment timepoint specified in NICE guidance, therefore overall population data are used.

Figure 7 PsARC and PASI network for bDMARD-naïve population



BID=Twice daily dosing regimen, BIW=Twice weekly dosing regimen, QIW=Once weekly dosing regimen, Q2/4/8/12W=Every 2nd/4th/8th/12th week dosing regimen.
Circle size is proportional to the number of patients per treatment, line width is proportional to the number of studies per pairwise comparison of treatments.

Results are presented in Table 21, Table 22 and Table 23 for PsARC response rates, change from baseline HAQ-DI and PASI response rates, respectively.

Table 21 PsARC response (bDMARD-naïve; network 1A)

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]
Certolizumab pegol pooled doses	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]
Golimumab 50 mg Q4W	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]

Secukinumab 150 mg Q4W	[redacted]
Secukinumab 300 mg Q4W	[redacted]

Posterior median (95% credible interval). Mixed biologic naive and experienced population for the following treatments: Apremilast 30 mg BID, Certolizumab pegol pooled doses, Placebo, Secukinumab 150 mg Q4W, Secukinumab 300 mg Q4W

BID=Twice daily dosing regimen, BIW=Twice weekly dosing regimen, QIW=Once weekly dosing regimen, Q2/4/8/12W=Every 2nd/4th/8th/12th week dosing regimen. Certolizumab pegol pooled doses are 200 mg Q2W and 400 mg Q4W.

Table 22 PASI response rates (bDMARD-naïve; network 1A)

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30 mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]

Table 23 HAQ-DI response

Treatment	Mean change from baseline – PsARC responders	95% CrI	Mean change from baseline – PsARC non-responders	95% CrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

2.9.2 Biologic-experienced population

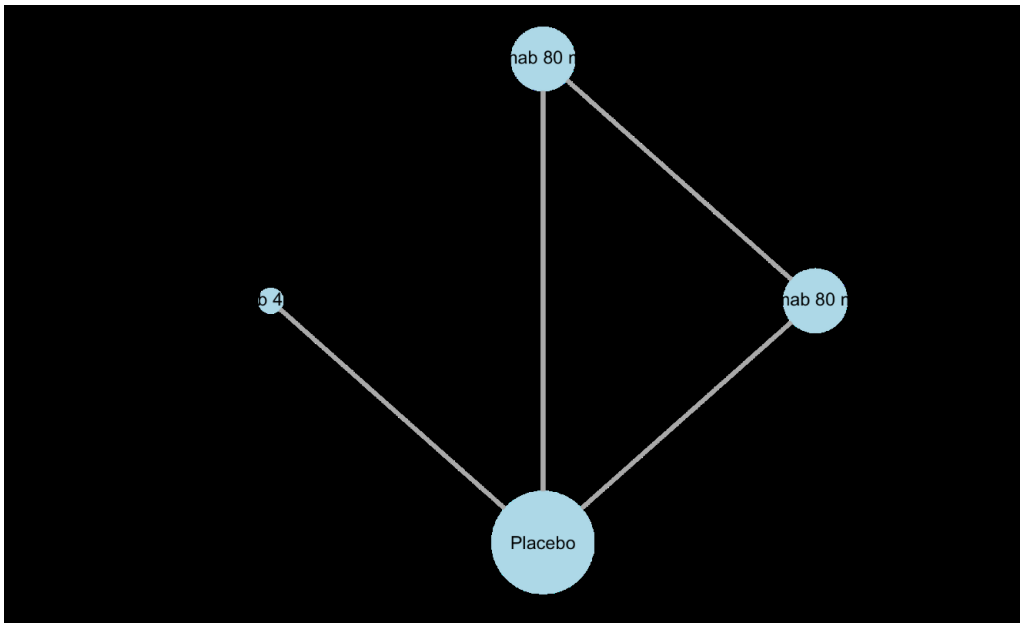
A summary of trials used to carry out the NMA for the bDMARD-experienced population is presented in Table 24. The base case is limited to trials that only look at TNF-IR patients, which are presented in the network diagram in Figure 8.

Table 24 Summary of the trials used to carry out the PsARC, PASI 50/75/90/100 and CFB HAQ-DI network meta-analysis for the biologic-naïve population

Trial	First author, year	Treatment arm	Timepoint (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
PSUMMIT 2	Ritchlin 2014 (57)	Placebo	24	Yes	No	Yes	No	No	Yes
PSUMMIT 2	Ritchlin 2014 (57)	Ustekinumab 45 mg Q12W	24	Yes	No	Yes	No	No	Yes
SPIRIT-P2	Nash 2017 (70)	Ixekizumab 80 mg Q2W	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017 (70)	Ixekizumab 80 mg Q4W	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017 (70)	Placebo	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017 (70)	Ixekizumab 80 mg Q2W	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017 (70)	Ixekizumab 80 mg Q4W	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017 (70)	Placebo	16	Yes	No	Yes	Yes	Yes	Yes
FUTURE 2 *	Thom 2016 (77)	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2 *	Thom 2016 (77)	Secukinumab 300 mg Q4W	12	Yes	Yes	Yes	Yes	No	Yes
RAPID-PsA*	Mease 2014 (55)	Certolizumab pegol	12	Yes	Yes	Yes	Yes	No	No
RAPID-PsA*	Mease 2014 (55)	Placebo	12	Yes	Yes	Yes	Yes	No	No

* Outcomes were not reported for bDMARD-experienced subgroup. As treatments are recommended by NICE in a bDMARD-experienced population, data for the overall population are included in a sensitivity analysis

Figure 8 PsARC and PASI network for bDMARD-experienced population (base case)



Results are presented in Table 25 and Table 26 for PsARC response rates and PASI response rates.

Table 25 PsARC response (bDMARD-experienced; network 1B)

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]
Ustekinumab 45 mg Q12W	[redacted]

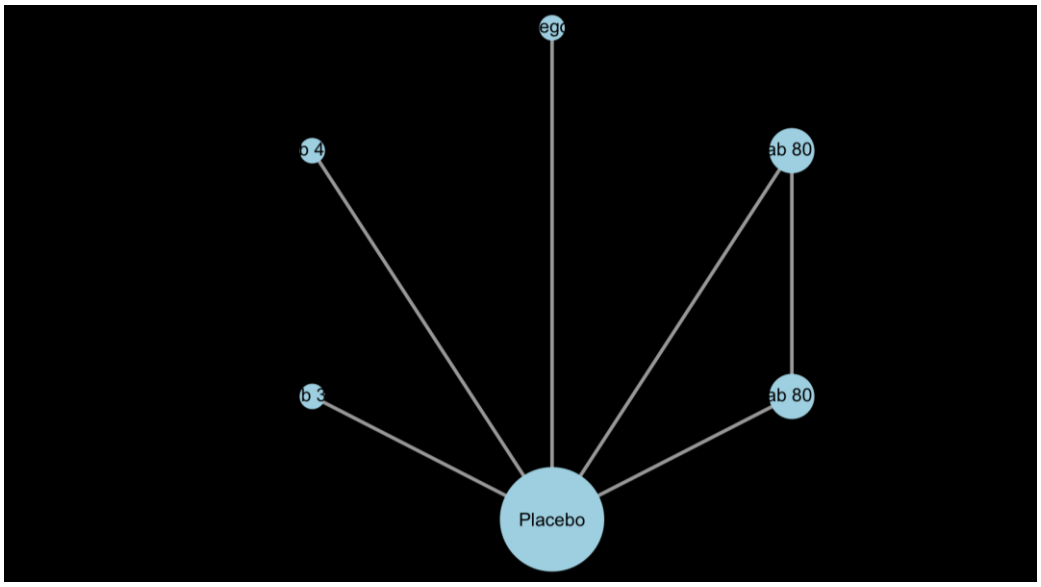
Table 26 PASI response rates (bDMARD-experienced; network 1B)

Treatment	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg Q12W	[redacted]	[redacted]	[redacted]

Secukinumab and certolizumab pegol were recommended by NICE for the treatment of PsA in a population with indadequate response to a previous TNF-alpha inhibitor. (2) Approximately 30% of patients in the FUTURE-2 and RAPID-PsA trials were bDMARD-experienced and in the RAPID-PsA trial, primary non-response to a prior TNF-alpha inhibitor was an exclusion criterion. Subgroup data by prior bDMARD exposure for these treatments were not publicly available at the time points for response assessment specified in NICE guidance TA445 (12 weeks for certolizumab pegol and 16 weeks for secukinumab),

therefore were not suitable for inclusion in the network. Furthermore, certolizumab pegol is recommended only in bDMARD-experienced patients who have had a secondary non-response to a prior TNF-alpha inhibitor. Data relating to the overall population for these two treatments were therefore included in the bDMARD-experienced network only as a sensitivity analysis (Figure 9). The results of this analysis are presented in Appendix D.

Figure 9 PsARC and PASI network for bDMARD-experienced population (sensitivity analysis)



2.9.3 Uncertainties in the indirect and mixed treatment comparisons

The number of studies in each NMA network was generally small, often with only one study per pairwise comparison of treatments. The networks were particularly small for the biologic-experienced population, usually consisting of at most five studies. Due to the small number of studies for each comparison, there were sometimes model-fitting and convergence difficulties with random effects models. As the majority of edges in the networks only consisted of one study, this made it very difficult to estimate between study heterogeneity accurately in random effects models, and in several cases the random effects models had fairly poor convergence diagnostics and large uncertainty in the between study heterogeneity parameter estimate. As random effects models were often difficult to fit, fixed effects model results are presented for all networks and selected for use in the economic model. There was occasionally a small amount of autocorrelation for some parameter estimates in the fixed effects models but satisfactory convergence appeared to have been achieved.

However, there may be undetectable heterogeneity in the network that cannot be adjusted for, which would indicate that the treatment effects from the fixed effects models are too

precise. For similar reasons, an assessment of inconsistency could not be performed, therefore it is not possible to assess if there is inconsistency in the network that could introduce heterogeneity and bias in results.

There was an insufficient number of studies in the bDMARD-experienced population to run a meta-regression on baseline risk, therefore a meta-regression was performed only for the bDMARD-naïve population and is used in a model scenario analysis.

To ensure that key comparators were included in the network, data from the full population, instead of a purely bDMARD-naïve or experienced population, was used for the following treatments: apremilast 30 mg BID (naïve networks only), certolizumab pegol 200 mg Q2W/400 mg Q4W, secukinumab 150 mg Q4W and secukinumab 300 mg Q4W. If prior biologic exposure is an effect modifier for these treatments, the NMA results will not be representative of the treatment effect in a pure biologic naïve/experienced population.

A key assumption of the probit model used to estimate PASI response rates was the assumption that the treatment effect on the probit scale is the same for all PASI response categories. This allows the model to use all studies in the network even if they do not report data for all PASI outcomes. However, as only the ixekizumab studies reported data in the PASI 100 category, the predicted PASI 100 results for the other treatments are all dependent on the ixekizumab trials. In the bDMARD-experienced population, the small sample of patients informing the two studies in the network results in a higher estimated PASI responses than would be expected based on a naïve comparison of the PASI 75 outcomes from the SPIRIT-P2 and PSUMMIT2 trials.

2.10 Adverse reactions

The safety and tolerability of ixekizumab during a 24 week Treatment Period was assessed by study drug discontinuation, adverse events (AEs) (including treatment emergent adverse events [TEAEs], serious adverse events [SAEs], and discontinuation due to AEs), haematology and laboratory measurements, vital signs, physical exam findings, concomitant medications, ECGs, and drug immunogenicity. A similar approach was taken to assess the safety and tolerability of ixekizumab during the Extension Period (week 24 to week 52).

A serious adverse event (SAE) is any AE from these studies that resulted in one of the following outcomes: death, initial or prolonged inpatient hospitalisation, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, or any other outcome considered significant by the investigator for any other reason. TEAEs were further examined within topics of special

interest (AESIs). Adverse events of special interest included categories of infections, cytopaenias (leukopenia, neutropenia, and thrombocytopenia), allergic/hypersensitivity reactions, injection site reactions, cerebrovascular events, hepatic events, malignancies, depression, pneumocystis pneumonia (SPIRIT-P1 only), interstitial lung disease, Crohn's disease, and ulcerative colitis.

In the SPIRIT studies, ixekizumab was well tolerated and safety findings were consistent with those in patients with moderate to severe psoriasis. (69, 70) The majority of TEAEs which occurred following treatment with ixekizumab were of mild or moderate severity and did not lead to discontinuation from study drug.

2.10.1 SPIRIT-P1

Treatment Period

During the 24-week double-blind treatment period, safety data were obtained from 416 patients who took at least one dose of study drug and who were randomised to receive placebo (N=106), adalimumab 40 mg Q2W (N=101), ixekizumab Q4W (N=107), or ixekizumab Q2W (N=102). This phase of the study was completed by 91.8% of all patients. Table 27 provides an overview of the adverse events reported during the double-blind treatment period. (69, 73)

The proportion of patients with ≥1 TEAE and TEAEs judged to be possibly related to study drug was statistically significantly higher in each of the ixekizumab groups compared with the placebo group ($p<0.05$ for all comparisons). At week 24 the proportion of patients who experienced ≥1 TEAE was 66.4% in the ixekizumab 80 Q4W group, 65.7% in the ixekizumab 80 Q2W group and 47.2% in the placebo group, respectively. The proportion of patients who experienced TEAEs judged to be possibly related to study drug was 29.9% in the ixekizumab 80 Q4W group, 36.3% in the ixekizumab 80 Q2W group and 11.3% in the placebo group, respectively. The majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication (Table 27). (69, 73)

The proportion of patients who discontinued study medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab and placebo groups (IXE Q4W: 1.9%; IXE Q2W: 3.9%; PBO: 1.9%) (Table 27). (69, 73)

SAEs occurred in 3.8% of all patients (IXE Q4W: 5.6%; IXE Q2W: 2.9%; PBO: 1.9%) with no statistically significant differences between ixekizumab and placebo groups (Table 27). (69, 73) The most frequently reported categories of AESI were infections (reported by 25.7% of all patients) and injection site reactions (reported by 15.4% of all patients). Injection site

reactions were statistically significantly more common in both ixekizumab treatment groups occurring at a frequency of 24.3%, 26.5% and 4.7% in the ixekizumab Q4W, ixekizumab Q2W and placebo group, respectively (p<0.001 for both comparisons). There were no statistically significant differences between either of the ixekizumab groups and the placebo group for the incidence of infections (Table 27). (69, 73)

TEAEs reported by ≥1.0% of patients in the total ixekizumab group were injection-site reactions and injection-site erythema. Injection site reactions were statistically significantly more common in both ixekizumab treatment groups occurring at a frequency of 12.1%, 15.7% and 0.0% in the ixekizumab Q4W, ixekizumab Q2W and placebo group, respectively (p<0.001 for both comparisons). Similarly, injection site erythema were statistically significantly more common in both ixekizumab treatment groups occurring at a frequency of 6.5%, 12.7% and 0.0% in the ixekizumab Q4W, ixekizumab Q2W and placebo group, respectively (p<0.05 and p<0.001, respectively). The AEs associated with the adalimumab treatment reference arm are also presented in Table 27 for completeness.

Table 27 Overview of AEs in the SPIRIT-P1 study - safety population (double-blind treatment period)

SPIRIT-P1 (69, 73)	Placebo (N=106) n (%)	ADA40Q2W (N=101) n (%)	IXE80Q4W (N=107) n (%)	IXE80Q2W (N=102) n (%)	Total IXE (N=209) n (%)	Total (N=416) n (%)
Patients with ≥1 TEAE	50 (47.2)	65 (64.4)	71 (66.4)	67 (65.7)	138 (66.0)	253 (60.8)
Discontinuations from Study Drug due to AE (including death)	2 (1.9)	2 (2.0)	2 (1.9)	4 (3.9)	6 (2.9)	10 (2.4)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs	2 (1.9)	5 (5.0)	6 (5.6)	3 (2.9)	9 (4.3)	16 (3.8)
TEAEs possibly related to study drug	12 (11.3)	21 (20.8)	32 (29.9)	37 (36.3)	69 (33.0)	102 (24.5)
TEAE reported by ≥1% patients in Total Ixekizumab group (MedDRA Preferred Term)						
Injection site reaction	0 (0)	2 (2.0)	13 (12.1)	16 (15.7)	29 (13.9)	31 (7.5)
Injection site erythema	0 (0)	2 (2.0)	7 (6.5)	13 (12.7)	20 (9.6)	22 (5.3)
Treatment-Emergent AE of Special Interest						
Cytopenias	6 (5.7)	4 (4.0)	1 (0.9)	4 (3.9)	5 (2.4)	15 (3.6)
Hepatic	7 (6.6)	13 (12.9)	5 (4.7)	9 (8.8)	14 (6.7)	34 (8.2)
Infection	27 (25.5)	26 (25.7)	30 (28.0)	24 (23.5)	54 (25.8)	107 (25.7)
Injection-site reactions	5 (4.7)	6 (5.9)	26 (24.3)	27 (26.5)	53 (25.4)	64 (15.4)
Allergic reactions/ Hypersensitivities	3 (2.8)	5 (5.0)	2 (1.9)	5 (4.9)	7 (3.3)	15 (3.6)
Cerebrocardiovascular	0 (0)	3 (3.0)	0 (0)	0 (0)	0 (0)	3 (0.7)

SPIRIT-P1 (69, 73)	Placebo (N=106) n (%)	ADA40Q2W (N=101) n (%)	IXE80Q4W (N=107) n (%)	IXE80Q2W (N=102) n (%)	Total IXE (N=209) n (%)	Total (N=416) n (%)
events						
Malignancies	1 (0.9)	1 (1.0)	0 (0)	0 (0)	0 (0)	2 (0.5)
Depression	0 (0)	1 (1.0)	2 (1.9)	1 (1.0)	3 (1.4)	4 (1.0)
Antithrombotic Trialists' Collaboration (ATTC)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumocystis pneumonia (PCP) and Interstitial lung disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Crohn's Disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ulcerative Colitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AE = adverse event; ADA40=Adalimumab 40 mg; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: CSR RHAP, Table RHAP.12.2 (Page 1 and 2 of 3) and Table RHAP.12.3 (Page 1 of 3)

Extension Period

A total of 381 patients entered the extension period and received at least one dose of study drug in the extension period (extension period population): total ixekizumab Q4W group (N=191); total ixekizumab Q2W group (N=190). The total ixekizumab Q4W and total ixekizumab Q2W groups were defined as all patients who were randomized to receive or continued to receive ixekizumab Q4W and ixekizumab Q2W, respectively, during the extension period. Of the patients who entered the extension period, 79.8% completed the extension period; the percentages of patients who completed the extension period were greater in the ixekizumab/ixekizumab groups, compared with the placebo/ixekizumab and adalimumab/ixekizumab groups. Table 28 provides an overview of the adverse events reported during the extension period.

The proportion of patients who reported a TEAE during the SPIRIT-P1 extension period was comparable across the treatment groups, ranging from 40.8–58.7%. Overall, a total of 53.5% of patients in the Extension Period Population reported a TEAE (53.4% and 53.7% in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). Most TEAEs were mild or moderate in severity; with severe TEAEs being reported in 3% or fewer patients in both total ixekizumab 80 mg Q4W and Q2W treatment groups (2.1% and 1.6%, respectively). (75)

The proportion of patients with TEAEs judged by the investigator as possibly related to the study drug was 17.1% (15.7% and 18.4% in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). (75)

A total of 12 patients (3.1%) experienced a SAEs (10 (5.2%) and 2 (1.1%) patients in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). Overall, across treatment arms discontinuation rates due to AEs were low (ranging from 0–2.2%). Three (0.8%) patients discontinued the study drug because of AEs (2(1.0%) and 1 (0.5%) in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). (75)

Infections were reported by 27.7% and 27.9% of patients in the total ixekizumab 80 mg Q4W and Q2W groups, respectively. Injection site reactions were reported by 10.5% and 11.1% of patients in the total ixekizumab 80 mg Q4W and Q2W groups, respectively. (75)

Table 28 Overview of AEs in the SPIRIT-P1 study - safety population (extension period)

	SPIRIT-P1 Extension Period Population							
SPIRIT-P1 (75)	**PBO/IXE 80Q4W (N=45) n (%)**	**ADA/IXE80Q4W (N=49) n (%)**	**IXE80Q4W /IXE80Q4W (N=97) n (%)**	**Total IXE80Q4W (N=191) n (%)**	**PBO/ IXE80Q2W (N=46) n (%)**	**ADA/ IXE80Q2W (N=48) n (%)**	**IXE80Q2W/IXE80Q2W (N=96) n (%)**	**Total IXE80Q2W (N=190) n (%)**
Patients with ≥ 1 TEAEs	28 (62.2)	20 (40.8)	54 (55.7)	102 (53.4)	27 (58.7)	21 (43.8)	54 (56.3)	102 (53.7)
Discontinuation from study drugs due to AE (including death)	1 (2.2)	0 (0)	1 (1.0)	2 (1.0)	1 (2.2)	0 (0)	0 (0)	1 (0.5)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs	1 (2.2)	5 (10.2)	4 (4.1)	10 (5.2)	1 (2.2)	1 (2.1)	0 (0)	2 (1.1)
Patients with ≥ 1 TEAE possibly related to study drug	13 (28.9)	5 (10.2)	12 (12.4)	30 (15.7)	13 (28.3)	4 (8.3)	18 (18.8)	35 (18.4)
Treatment-Emergent AE of Special Interest								
Cytopenias	3 (6.7)	0 (0)	3 (3.1)	6 (3.1)	2 (4.3)	1 (2.1)	1 (1.0)	4 (2.1)
Hepatic	1 (2.2)	0 (0)	1 (1.0)	2 (1.0)	2 (4.3)	1 (2.1)	4 (4.2)	7 (3.7)
Infection	14 (31.1)	8 (16.3)	31 (32.0)	53 (27.7)	9(19.6)	12 (25.0)	32 (33.3)	53 (27.9)
Injection-site reactions	6 (13.3)	5 (10.2)	9 (9.3)	20 (10.5)	8 (17.4)	4 (8.3)	9 (9.4)	21 (11.1)
Allergic reactions/ Hypersensitivities	3 (6.7)	0 (0)	2 (2.1)	5 (2.6)	1 (2.2)	0 (0)	4 (4.2)	5 (2.6)
Cerebrocardiovascular	1 (2.2)	3 (6.1)	0 (0)	4 (2.1)	1 (2.2)	0 (0)	2 (2.1)	3 (1.6)

events								
Malignancies	0 (0)	0 (0)	1 (1.0)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)
Depression	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	1 (0.5)
Antithrombotic Trialists' Collaboration (ATTC)	0 (0)	1 (2.0)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumocystis pneumonia (PCP) and Interstitial lung disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Crohn's Disease/ Ulcerative Colitis	0 (0)	1 (2.0)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)

AE = adverse event; ADA40=Adalimumab 40 mg; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; PCP = pneumocystis pneumonia; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: CSR w52 RHAP, Table RHAP.12.2 and Table RHAP.12.3 (Page 1 and 2 of 3)

For SPIRIT-P1, safety data up to 2 years of treatment is available. The safety profile of ixekizumab through 2 years of treatment was similar to that observed in the double-blind treatment period of SPIRIT-P1. (84)

2.10.2 SPIRIT-P2

Treatment Period

During the 24-week treatment period, safety data were obtained from 363 patients who were randomised to receive placebo (N=118), ixekizumab Q4W (N=122), or ixekizumab Q2W (N=123). This phase of the study was completed by 86.5% of all patients. Table 29 provides an overview of the adverse events reported during the treatment period. (70, 74)

The number of patients with one or more TEAEs in the ixekizumab 80 Q4W and ixekizumab 80 Q2W groups was higher than in the placebo group (83 (68%),90 (73%) and 76 (64%), respectively) (Table 29). (70, 74) The proportion of patients with TEAEs judged to be possibly related to study drug was statistically significantly higher in each of the ixekizumab 80 mg Q2W group compared with the placebo group ($p<0.05$). The proportion of patients who experienced TEAEs judged to be possibly related to the study drug was 28.7% in the ixekizumab 80 Q4W group, 40.7% in the ixekizumab 80 Q2W group and 24.6% in the placebo group, respectively. The majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of the study medication (Table 29). (70, 74) The proportion of patients who discontinued the study medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab and placebo groups (IXE Q4W: 4.1%; IXE Q2W: 6.5%; PBO: 5.1%) (Table 29). (70, 74) SAEs occurred in 4.1% of all patients (IXE Q4W: 2.5%; IXE Q2W: 6.5%; PBO: 3.4%) with no statistically significant differences between ixekizumab and placebo groups (Table 29). (70, 74) The number of patients with treatment emergent infections in the ixekizumab 80 Q4W and ixekizumab 80 Q2W groups was higher than in the placebo group (Table 29). (74) However, these differences were not statistically significant. Injection site reactions were statistically significantly more common in the ixekizumab 80 mg Q2W treatment group (23.6%) compared to the placebo group (4.2%) ($p<0.001$). A greater percentage of patients had at least 1 injection-site reaction in the ixekizumab 80 mg Q4W group (11.5%) compared with the placebo group (4.2%). (70, 74)

Table 29 Overview of AEs in the SPIRIT-P2 study - safety population (double-blind treatment period)

SPIRIT-P2 (70, 74)	Placebo (N=118) n (%)	IXE80Q4W (N=122) n (%)	IXE80Q2W (N=123) n (%)	Total IXE (N=245) n (%)	Total (N=363) n (%)
Patients with ≥1 TEAE	76 (64.4)	83 (68.0)	90 (73.2)	173 (70.6)	249 (68.6)
Discontinuations from Study Drug due to AE (including death)	6 (5.1)	5 (4.1)	8 (6.5)	13 (5.3)	19 (5.2)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAEs	4 (3.4)	3 (2.5)	8 (6.5)	11 (4.5)	15 (4.1)
TEAEs possibly related to study drug	29 (24.6)	35 (28.7)	50 (40.7)	85 (34.7)	114 (31.4)
Treatment-Emergent AE of Special Interest					
Cytopenias	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic	2 (1.7)	2 (1.6)	5 (4.1)	7 (2.9)	9 (2.5)
Infection	35 (29.7)	47 (38.5)	47 (38.2)	94 (38.4)	129 (35.5)
Injection-site reactions	5 (4.2)	14 (11.5)	29 (23.6)	43 (17.6)	48 (13.2)
Allergic reactions/ Hypersensitivities	6 (5.1)	13 (10.7)	14 (11.4)	27 (11.0)	33 (9.1)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non-anaphylaxis	6 (5.1)	13 (10.7)	14 (11.4)	27 (11.0)	33 (9.1)
Cerebrocardiovascular events	2 (1.7)	0 (0)	0 (0)	0 (0)	2 (0.6)
Malignancies	0 (0)	2 (1.6)	0 (0)	2 (0.8)	2 (0.6)
Depression	3 (2.5)	2 (1.6)	2 (1.6)	4 (1.6)	7 (1.9)
Interstitial lung disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Inflammatory Bowel Disease (IBD) †	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

†Inflammatory bowel disease includes the following narrow terms: inflammatory bowel disease, Crohn's disease, and ulcerative colitis.

AE = adverse event; IXE = ixekizumab; IXE80 = ixekizumab 80 mg; N = number of patients in the analysis population; n = number of patients in the specified category; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: CSR RHBE, Table RHBE.12.2 (Page 1 and 2 of 3) and Table RHBE.12.3 (Page 1 of 5)

Extension Period

A total of 310 patients entered the Extension Period and received at least one dose of study drug in the Extension Period (Extension Period Population): total ixekizumab Q4W group (N=157); total ixekizumab Q2W group (N=153). The total ixekizumab Q4W and Q2W groups were defined as all patients who were randomized to receive or continued to receive

ixekizumab Q4W and ixekizumab Q2W, respectively, during the Extension Period. Table 30 provides an overview of the adverse events reported until week 52 of the Extension Period.

The proportion of patients who reported a TEAE during the SPIRIT-P2 extension period was comparable across the treatment groups, ranging from 58.7%-71.2%. Overall, a total of 66.5% of patients in the extension period population reported at least one TEAE (70.7% and 62.1% in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). Most TEAEs were mild or moderate in severity; with severe TEAEs being reported in 5.5% of patients in both total ixekizumab 80 mg Q4W and Q2W treatment groups (4.5% and 6.5%, respectively). (76) The proportion of patients with TEAEs judged by the investigator as possibly related to the study drug was 28.4% (28.0% and 28.8% in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). (76)

A total of 15 patients (4.8%) experienced a SAEs (8 (5.1%) and 7 (4.6%) patients in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). One death, caused by cardiorespiratory arrest, was reported in the SPIRIT-P2 extension period.

Overall, across treatment arms discontinuation rates due to AEs were low (ranging from 0–7.5%). A total of twelve (3.9%) patients discontinued study drug because of AEs (2(1.3%) and 10 (6.5%) in the total ixekizumab 80 mg Q4W and Q2W groups, respectively). The percentage of patients with AEs that led to study drug discontinuation was numerically greater in the total ixekizumab 80 mg Q2W group compared to the ixekizumab 80 mg Q4W group but the overall number of patients was small (10 (6.5%) and 2(1.3%), respectively).(76)

The most frequently reported categories of AESI were infections and injection site reactions, reported by 45.2% and 8.4% of all patients, respectively. Infections were reported by 49.0% and 41.2% of patients in the total ixekizumab 80 mg Q4W and Q2W groups, respectively. Injection site reactions were reported by 7.0% and 9.8% of patients in the total ixekizumab 80 mg Q4W and Q2W groups, respectively. (76)

Table 30 Overview of AEs in the SPIRIT-P2 Study - Safety population (extension period up to week 52)

	SPIRIT-P2 Extension Period Population					
SPIRIT-P2 (76)	**PBO/ IXE80Q4W (N=46) n (%)**	**IXE80Q4W/ IXE80Q4W (N=111) n (%)**	**Total IXE80Q4W (N=157) n (%)**	**PBO/ IXE80Q2W (N=46) n (%)**	**IXE80Q2W/ IXE80Q2W (N=107) n (%)**	**Total IXE80Q2W (N=153) n (%)**
Patients with ≥1 TEAEs	32 (69.6)	79 (71.2)	111(70.7)	27 (58.7)	68 (63.6)	95 (62.1)
Discontinuation from study drugs due to TEAE (including death)	0	2 (1.8)	2 (1.3)	2 (4.3)	8 (7.5)	10 (6.5)
Death*	0	0	0	1 (2.2)	0	1 (0.7)
SAEs	2 (4.3)	6 (5.4)	8 (5.1)	3 (6.5)	4 (3.7)	7 (4.6)
TEAEs possibly related to study drug	17 (37.0)	27 (24.3)	44 (28.0)	12 (26.1)	32 (29.9)	44 (28.8)
Treatment-Emergent AE of Special Interest						
Cytopenias	0 (0)	1 (0.9)	1 (0.7)	1 (2.2)	0 (0)	1 (0.7)
Hepatic	2 (4.3)	3 (2.7)	5 (3.2)	1 (2.2)	3 (2.8)	4 (2.6)
Infection	23 (50.0)	54 (48.6)	77 (49.0)	16 (34.8)	47 (43.9)	63 (41.2)
Injection-site reactions	6 (13.0)	5 (4.5)	11 (7.0)	6 (13.0)	9 (8.4)	15 (9.8)
Allergic reactions/ Hypersensitivities	2 (4.3)	4 (3.6)	6 (3.8)	0 (0)	7 (6.5)	7 (4.6)
Anaphylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non-anaphylaxis	2 (4.3)	4 (3.6)	6 (3.8)	0 (0)	7 (6.5)	7 (4.6)
Cerebrocardiovascular events	0 (0)	3 (2.8)	0 (0)	1 (2.2)	3 (2.8)	4 (2.6)
Malignancies	1 (2.2)	1 (0.9)	2 (1.3)	0 (0)	0 (0)	0 (0)
Depression	0 (0)	3 (2.7)	3 (1.9)	0 (0)	1 (0.9)	1 (0.7)
Interstitial lung disease	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)	1 (0.7)
Inflammatory Bowel Disease (IBD) †	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

†Inflammatory bowel disease includes the following narrow terms: inflammatory bowel disease, Crohn's disease, and ulcerative colitis.

*Deaths are also included as serious adverse events and study treatment discontinuations due to adverse events.
Abbreviations: AE=adverse event, IXE=ixekizumab, IXE80Q2W=ixekizumab 80 mg every two weeks, IXE80Q4W=ixekizumab 80 mg every four weeks, N= number of patients in the analysis population; n=number of patients in the specified category, SAE=Serious adverse event, TEAE=treatment emergent adverse event.

Source: CSR w52 RHBE, Table RHBE.12.2, Table RHBE.12.3 (Page 1 of 4) and Table RHBE.14.92 (Page 1 of 7)

2.11 Ongoing studies

In addition to SPIRIT-P1 and SPIRIT-P2, two other ixekizumab Phase 3 Studies, I1F-MC-RHBF (SPIRIT-P3) and I1F-MC-RHCF (SPIRIT-H2H), are currently ongoing. The dosing regimen being evaluated in the SPIRIT-P3 study (ixekizumab 80mg Q2W) was administered in all patients regardless of psoriasis severity and therefore not in line with the licence. For this reason, no further details of this study are presented. SPIRIT-H2H has only recently (Aug 2017) been initiated and is currently actively recruiting patients. Therefore, no data is available yet from this study. A summary of the ongoing Phase 3 SPIRIT-H2H study can be found in Table 31 below.

Table 31 Summary of ongoing ixekizumab PsA RCTs

Trial	**SPIRIT-H2H (RHCF)**
Trial overview	Phase III, randomized, open-label, parallel-group, active-controlled RCT. The study consisted of a 52 weeks double-blind treatment period followed by a 132 weeks extension period.
Main eligibility criteria for participants	Patients with a documented diagnosis of PsA for at least 6 months fulfilling the Classification for Psoriatic Arthritis (CASPAR) and the activity of disease as defined by the presence of at least 3 swollen joints (66 joints) and at least 3 tender joints (68 joints) in patients who are bDMARD naive. Patients must have active psoriatic skin lesions (plaque) of plaque psoriasis with a BSA of at least 3%.
Number of patients randomised	Anticipated randomization 550
Trial arms and dosage for each arm (n=number randomised/not randomised; treatment period)	Anticipate 275 patients in the ixekizumab arm and 275 patients in the adalimumab arm. All patients randomized to ixekizumab will receive a starting dose of 160 mg at randomization (Visit 2 [Week 0]). Patients with moderate-to-severe plaque psoriasis will receive ixekizumab 80 mg Q2W from week 2 to week 12 and Q4W thereafter. Patients not meeting criteria for moderate-to-severe plaque psoriasis at randomization will receive ixekizumab 80 mg Q4W starting at Week 4. Patients randomized to adalimumab with moderate-to-severe plaque psoriasis will receive a starting dose of 80 mg at randomization (Visit 2 [Week 0]) followed by 40 mg Q2W starting at week 1. Patients not meeting criteria for moderate-to-severe plaque psoriasis will receive a starting dose of 40 mg at randomization (Visit 2) followed by 40 mg Q2W starting at week 2.
Trial duration	52 weeks
Start Date or FPV	FPV: August 24, 2017
Proposed End Date or LPV	Projected LPV: April 22, 2019

Primary objective	To assess whether ixekizumab is superior to adalimumab at week 24 in the treatment of patients with active PsA as measured by American College of Rheumatology 50 (ACR 50) and Psoriasis Area and Severity Index 100 (PASI 100)

2.12 Innovation

Biologics have improved outcomes for PsA patients, but despite their availability, there are still a group of patients who fail to achieve ACR 20. Additionally, the literature demonstrates an overall decline in drug survival rates among patients receiving second- or third-line biologic therapies relative to first line. This may be related to treatment effectiveness, which has been shown to decrease as patients are treated with several lines of biologic therapy. (47) These results demonstrate the clear need for new and effective therapeutic options which allow patients to obtain effectiveness independently of prior biologic experience as well as maintain long-term responses.

Ixekizumab is the first monoclonal antibody to block both active forms of IL-17A (IL-17A is expressed in both homodimer and heterodimer forms) with high binding affinity. (64) It is the second anti IL-17 to offer an alternative mechanism of action to TNF-alpha inhibitors and IL12/23.

Both SPIRIT-P1 and SPIRIT-P2 studies were phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient trials comparing the efficacy and safety of ixekizumab to placebo in two sub-groups of patients: i) biologic disease-modifying antirheumatic drug (bDMARD)-naive patients (I1F-MC-RHAP [SPIRIT-P1]) and ii) tumour necrosis factor (TNF) inhibitor–experienced patients (I1F-MC-RHBE [SPIRIT-P2]). In addition, SPIRIT-P1 also included an active control reference (adalimumab) arm. Across the SPIRIT studies, the proportion of patients who achieved ACR 20 at week 24 ranged from 48.0% to 62.1% the ixekizumab Q2W group, 53.3% to 57.9% in the ixekizumab Q4W group. Similarly, ACR 50 at week 24 ranged from 33.3% to 46.6% the ixekizumab Q2W group, 35.2% to 40.2% in the ixekizumab Q4W group. While ACR 70 at week 24 ranged from 12.2% to 34.0% the ixekizumab Q2W group, 22.1% to 23.4% in the ixekizumab Q4W group. Across the studies, PASI 100 response rates at week 24 ranged from 27.9% to 52.5% in the ixekizumab Q2W group, 35.3% to 42.5% in the ixekizumab Q4W group (See Section 1.1.6 Appendix P). (69, 70)

Long-term efficacy data from the SPIRIT studies also demonstrate the sustained responses achieved by patients treated with ixekizumab – an important factor in the treatment of chronic diseases such as psoriatic arthritis. In the SPIRIT-P1 and -P2 studies, which included an open-label extension period (week 24-152) significant proportions of patients

treated with either ixekizumab 80 mg Q4W achieved or maintained ACR 20/ 50/ 70 response rates at week 108 (SPIRIT-P1) and week 52 (SPIRIT-P2) (Appendix Q).

Overall, RCT data show that most biologic treatments do not effectively address the extra-articular symptoms including, enthesitis, dactylitis, and nail psoriasis. For example, in most RCTs no more than half of all patients treated with biologics achieve a PASI 90 response, whilst dactylitis and enthesitis persisted in 12–65% and 20–76% of patients after 24 weeks, respectively. (55-57) With the exception of secukinumab, the current biologics fail to achieve high levels of PASI 90 and 100 skin clearance in PsA patients. Ixekizumab has demonstrated efficacy in treating the extra-articular symptoms of PsA such as psoriasis, nail psoriasis, dactylitis and structural progression (Appendix P).

Ixekizumab has demonstrated consistent benefits across a variety of PsA patient subgroups. In particular, ixekizumab has shown to be consistently efficacious independently of previous biologic drug exposure, concomitant methotrexate use as well as in the subgroup of patients who would be eligible for treatment with bDMARDs under current NICE criteria (Section 2.7 and Appendix E).

These factors all contribute to the argument that ixekizumab is an innovative treatment option for PsA patients. Furthermore, there are aspects of the treatment benefits of ixekizumab that are unlikely to be captured in the QALY calculation such as the potential limitations of generic preference-based utility instruments such as EQ-5D for skin conditions. Additionally, the presentation of skin symptoms in difficult-to-treat areas (e.g. nail) can be an additional burden that further reduces patient HRQoL but the impact may not be adequately captured by the EQ-5D instrument.(85)

2.13 Interpretation of clinical effectiveness and safety evidence

In patients with active PsA, either biologic-naïve or experienced, treatment with ixekizumab demonstrated efficacy across the major symptom domains (including joint symptoms, joint structural damage [in SPIRIT-P1 only], skin, dactylitis, and nail disease), resulting in associated improvements in functional ability and health-related quality of life (HRQoL) of patients. Additionally, the SPIRIT-P1 and SPIRIT-P2 studies show similar efficacy and safety results across biologic naïve and biologic experienced population.

The clinical efficacy and safety of ixekizumab has been demonstrated in the two pivotal phase III studies – SPIRIT-P1 and –P2. Ixekizumab demonstrated significant improvements in joint (ACR 20/50/70, PsARC) and skin symptoms (PASI 50/ 75/100), functional capacity

(HAQ-DI) of psoriatic arthritis compared with placebo, while maintaining an acceptable safety profile.

The primary objective was met in both SPIRIT studies with both ixekizumab treatment groups (ixekizumab 80 mg Q2W and 80 mg Q4W) showing greater efficacy than placebo at week 24 as measured by the proportion of patients achieving ACR 20 ($p<0.001$ for all comparisons). (69, 70)

The key findings from the SPIRIT studies are highlighted below:

- Across both studies, the proportion of patients who achieved ACR 20 response at week 24 were statistically superior in each of the ixekizumab treatment groups (Q4W, 57.9% ; Q2W, 62.1% and Q4W, 53.3%; Q2W, 48.0% for SPIRIT-P1 and –P2 respectively) compared to placebo (30.2% and 19.5%, for SPIRIT-P1 and –P2, respectively) ($p<0.001$ for all comparisons).

- There was a statistically significantly greater percentage of patients in each of the ixekizumab groups compared with the placebo group achieving a PsARC response in both SPIRIT studies ($p<0.01$ in all cases). At week 24, the PsARC response rates (NRI) were 57.9% and 66.0% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 32.1% for the placebo group in SPIRIT-P1. In SPIRIT-P2, at week 24, the PsARC response rates (NRI) were 55.7% and 47.2% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 20.3% for the placebo group. Slightly higher rates were observed at week 12.

- At week 12, patients in the two ixekizumab groups (Q4W and Q2W) achieved significantly greater mean change from baseline in HAQ-DI total scores both in SPIRIT-P1 and -P2 trials, relative to placebo ($p<0.001$ for all comparisons).

- In SPIRIT-P1, a statistically significant difference in mean mTSS change from baseline at week 24 was reported in the biologic-naïve patients. The greatest change from baseline in mTSS scores was reported in the placebo group by comparison with ixekizumab 80 mg Q4W and 80 mg Q2W ($p<0.01$ and $p<0.001$ versus placebo, respectively), demonstrating the greatest level of structural joint damage (see Appendix P).

- For both SPIRIT studies, the proportion of patients achieving complete clearance (PASI 100) and high-level responses (PASI 90) was significantly greater with ixekizumab compared with placebo at week 12. PASI 100 response rates (NRI) were 31.5% and 40.7% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 1.5% for the

placebo group in SPIRIT-P1. In SPIRIT-P2, the PASI response rates (NRI) were 19.1% and 23.5% for the ixekizumab 80 mg Q4W and Q2W groups, respectively, and 6.0% for the placebo group.

- At week 24, the proportion of patients who achieved Coates criteria for minimal disease activity at week 24 (MDA_{PASI} [6 entheseal points]) was significantly greater for the ixekizumab 80 mg Q4W and Q2W groups, compared to placebo, in both SPIRIT-P1 and SPIRIT-P2 trials ($p<0.05$, in all cases) (see Appendix P).

- In SPIRIT- P1, the percentage of patients with complete resolution of dactylitis (as measured by the Leeds Dactylitis Index – Basic (LDI-B) score of 0) at week 24 was statistically significantly greater in the ixekizumab 80 mg Q4W and Q2W groups compared with placebo ($p<.001$ in both cases). In SPIRIT-P2, the percentage of patients with complete resolution in dactylitis (as measured by the Leeds Dactylitis Index – Basic [LDI-B] score of 0) was statistically significantly greater in the ixekizumab 80 mg Q4W group at week 24 compared with the placebo group (see Appendix P).

- At week 24, a statistically significantly greater proportion of patients who received ixekizumab 80 mg Q2W achieved complete resolution of fingernail involvement (as measured by a Nail Psoriasis Severity Index (NAPSI) score of 0), relative to placebo, in both SPIRIT-P1 and -P2 trials. In SPIRIT-P2, NAPSI score of 0 response was statistically significantly greater in the ixekizumab 80 mg Q4W group compared to placebo ($p<0.05$ versus placebo) (see Appendix P).

- Responses achieved with ixekizumab treatment are sustained during the maintenance dosing period (SPIRIT-P1 and -P2 trials). At week 108, significant proportions of patients treated with ixekizumab 80 mg Q4W achieved or maintained ACR 20, 50 and 70 response (56.1%, 42.1% and 26.2%, respectively), in SPIRIT-P1. At week 52, 61.5%, 41.8% and 26.2% of patients treated with ixekizumab 80 mg Q4W achieved or maintained ACR 20, 50 and 70 response, respectively, in SPIRIT-P2.

- Ixekizumab demonstrated efficacy in improvement of psoriatic arthritis signs and symptoms with or without concomitant methotrexate use. All patients in the two ixekizumab groups (Q4W and Q2W) achieved significantly greater ACR 20 response rates compared to placebo in both SPIRIT-P1 and -P2 trials, irrespective of methotrexate use ($p<0.05$ for all comparisons).

- There were no major safety signals identified in the SPIRIT clinical development programme. Ixekizumab was well tolerated across the SPIRIT studies with a predictable

safety profile which was comparable to other biologic treatments. The similar number of ixekizumab and placebo treated patients discontinued due to TEAE in the SPIRIT studies.

- The proportion of patients with TEAEs judged to be possibly to study drug was generally higher in the ixekizumab groups compared with the placebo group at week 24. However, the majority of these TEAEs were of mild to moderate severity and did not lead to discontinuation of study medication.
- In both SPIRIT studies there were no statistical differences in terms of the percentages of patients with treatment-emergent infections, however, in SPIRIT-P2 the number of patients with treatment-emergent infections were higher in the ixekizumab groups than in the placebo group.
- The incidence of SAEs and discontinuations due to AEs did not differ between the ixekizumab and placebo groups in either of the SPIRIT studies at week 24.
- The most frequent AESIs which were reported with ixekizumab treatment in the SPIRIT studies included infection and injection site reactions. A statistically significantly greater percentage of patients experienced injection-site reactions in each of the ixekizumab groups compared with the placebo group.
- Since many AEs take time to emerge, the safety of ixekizumab was evaluated beyond the 24-week efficacy primary endpoint. Ixekizumab was well tolerated in the extension period with similar AEs to those seen in the induction period.

Results for other clinical endpoints of interest have been presented in Appendix P and Appendix Q.

2.13.1 Strengths and limitations of the clinical evidence base for ixekizumab

The clinical evidence base provided by the phase III SPIRIT clinical development programme clearly demonstrates the efficacy and safety of ixekizumab in patients with psoriatic arthritis. Both studies met their primary endpoint and all the major secondary endpoints except for enthesitis (in SPIRIT-P1, the itch endpoint not tested due to the statistical testing gated approach) and demonstrated consistent improvements in psoriatic arthritis symptoms compared with placebo. The consistency of the results across the different clinical endpoints between the SPIRIT-P1 and –P2 studies demonstrates the efficacy of ixekizumab in treating biologic naïve PsA patients as well as biologic experienced patients. The ixekizumab clinical program is unique in that available licensed biologics, have

not conducted a separate study to evaluate efficacy in bio-experienced patients. To date, effectiveness of treating bio-experienced patients with competitor biologics has been based on underpowered subgroup analysis. The design also provided an opportunity to assess consistency in maintenance of response among initial ixekizumab responders. Additionally, the SPIRIT-P1 trial included a reference arm (adalimumab 40 mg every other week). Adalimumab currently remains the most prescribed PsA treatment. Compared to adalimumab, ixekizumab 80 mg Q4W demonstrated similar response rates (not powered) which were consistent with the ADEPT trial results adding to the external validity of SPIRIT-P1. Further evidence for the short and long-term efficacy of ixekizumab will come from the superiority SPIRIT-H2H study which includes adalimumab as an active comparator.

The evidence base from the SPIRIT studies is highly relevant to the NICE decision problem. Given biologics are required to be prescribed in line with NICE criteria, the baseline patient characteristics reported by the British Society for Rheumatology Biologics Register (BSRBR) are similar to the baseline characteristics of patients in SPIRIT-P1 and –P2, indicating that the SPIRIT studies have evaluated a relevant patient population. Table 32 compares demographics and clinical characteristics from the BSRBR to those of the patients included in SPIRIT-P1 and –P2.

Additionally, the primary and secondary outcomes measures included in the studies are highly relevant to UK clinical practice and reflect the severity of the symptoms of PsA (ACR, PsARC, HAQ-DI, PASI mTSS, dactylitis, enthesitis, NAPSI).

Table 32 Demographics and Baseline Characteristics of UK Clinical Practice Compared with Studies RHAP and RHBE

Demographic/ Characteristic	UK BSRBR(45) (N=566)	RHAP (73) (N=417)	RHBE (74) (N=363)
Age, mean	45.7	49.5	51.9
Female, %	53	54	53.4
Disease Duration, years	12.4	10.1	12.2
TJC, mean x/total number counted	13.4/28	20.1/68	23.4/68
SJC, mean x/total number counted	8.9/28	11/66	12.3/66
DAS-28	6.4	4.9	5.1
HAQ-DI	1.9	1.2	1.2

Abbreviations: BSRBR= British Society of Rheumatology Biologics Register; DAS-28 = Disease Activity Score 28 diarthrodial joint count; HAQ-DI = Health Assessment Questionnaire; SJC = swollen joint count; TJC = tender joint count.

In England and Wales there are predicted to be 86,118 people suffering from PsA in 2018. Of these, 2,067 patients are estimated to be eligible for ixekizumab treatment.

Table 33 Adult population with PsA who are eligible for biologic treatment in England and Wales

Details	%	Population	Source
Adult population in England, 2018		47,894,664	
Estimated prevalence of psoriatic arthritis	0.19	86,118	Ogdie et al, 2013 (17)
People with psoriatic arthritis eligible for treatment (prevalence population only)	2.4	2,067	NICE 2011, Golimumab in psoriatic arthritis, resource impact report [TA220] (27)

Additionally, ixekizumab has also been approved for use in patients with moderate to severe psoriasis. The number of patients with psoriasis who are eligible for psoriatic biologic treatment in England and Wales is forecasted to be 19,236 in 2018 (Table 34).

Table 34 Adult population with psoriasis who are eligible for biologic treatment in England and Wales

Details	%	Population	Source
Adult population in England and Wales		47,894,664	
Estimated prevalence of psoriasis	1.75	838,157	Parisi et al (2011) (86)
People with plaque psoriasis	90	754,341	National Institute for Health and Care Excellence 2016. TA442.(87)
People eligible for biologic treatment	2.55	19,236	NICE clinical guideline on psoriasis: assessment and management. (67)

3 *Cost effectiveness*

3.1 Published cost-effectiveness studies

A systematic literature review was conducted to identify relevant cost-effectiveness studies and HTA appraisals in psoriatic arthritis. Full details of the methods and findings of the review are discussed in Appendix G. A summary of the peer-reviewed studies and HTA appraisals identified in the UK setting is presented in Table 35.

Table 35 Summary list of published cost-effectiveness studies

Study	Summary of model	Patient age (years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Stated drivers of CE results
Published CEMs						
Bansback et al. (2006) (88)	Individual sampling model	47	10 year time horizon: ETAN: 4.49 CICLO: 3.67 LEF: 3.84	10 year time horizon: ETAN: £51,122 CICLO: £28,010 LEF: £26,822	ETAN vs. CICLO: £28 189 per QALY ETAN vs. LEF: £37 066 per QALY	- Baseline HAQ-DI - Annual HAQ-DI progression of biologics - Annual HAQ-DI progression of patients on best standard care
Bojke et al. (2011) (89)	Probabilistic cohort model	47	- palliative care: 5.241 - ADA: 6.642 - ETAN: 7.115 - INF: 7.430	- palliative care: £42,205 - ADA: £66,408 - ETAN: £72,178 - INF: £89,107	vs. Palliative care: ADA: extendedly dominated; ETAN: £15,986 per QALY; INF: £53,750 per QALY	- Length of treatment effect for biologics (10 years rather than 40 years); - assumptions about the prescription cost; - alternative costs of treating patients who do not achieve a response to biologics for the PsO component of PsA; - assumptions about progression of HAQ-DI on and off treatment
Bravo Vergel et al. (2007) (90)	Short-term: Cohort model in form of modified decision tree Long-term: Markov model	47	Rebound equal to gain (10 yrs): - INF: 4.636 - ETAN: 4.514 - palliative care: 3.248 Rebound equal to natural history (10 yrs): - INF: 4.455 - ETAN: 4.356	Rebound equal to gain (10 yrs): - INF: £64,274 - ETAN: £44,111 - palliative care: £10,718 Rebound equal to natural history (10 yrs): - INF: £64,418 - ETAN: £44,169	Rebound equal to gain (10 yrs): - INF vs. ETAN: £165 363 - ETAN vs. palliative care: £26 361 Rebound equal to natural history (10 yrs): - INF vs. ETAN: £205 345 - ETAN vs. palliative care: £30 628	- Estimates of rebound assumptions at withdrawal and the time horizon - Alternative structural assumptions (such as rebound effect and HAQ-DI progression whilst responding to treatment)

Study	Summary of model	Patient age (years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Stated drivers of CE results
			- palliative care: 3.263	- palliative care: £10,679		
Cawson et al. (2014) (91)	Markov cohort model	NR	40 year time horizon Conventional management strategy: 5.2 ADA: 6.7 GOL: 7.1 ETAN: 7.2 INF: 7.4	40 year time horizon Conventional management strategy: £43,391 ADA: £69,332 GOL: £76,976 ETAN: £75,563 INF: £88,362	ICER vs. conventional management strategy): ADA: Ext Dom'd £17,222 per QALY GOL: Dom'd £17,435 per QALY ETAN: £16,426 per QALY INF: £20,789 per QALY	NR
Cummins et al. (2011) (92)	Short-term: Cohort model in form of modified decision tree Long-term: Markov model	45	Palliative care: 6.10 ADA: 7.89 ETAN: 8.62 INF: 8.65 Psoriasis patients: Palliative care: 5.79 ADA: 7.63 ETAN: 8.35 INF: 8.40	Palliative care: £64,704 ADA: £99,278 ETAN: £108,481 INF: £107,954-£123,475 Psoriasis patients: Palliative care: £76,402 ADA: £109,682 ETAN: £118,925 INF: £117,606-133,128	ICER vs. palliative care: All patients - ADA £19,246 - ETAN £17,327 - INF £16,942–£23,022 Psoriasis patients - ADA £18,170 - ETAN £16,613 - INF £15,788–£21,736	Results were sensitive to change in structural assumptions: - Utility estimates - HAQ-DI score rebound after TNF-alpha inhibitor withdrawal - Halving rate of HAQ-DI score progression
Cummins et al. (2012) (93)	Short-term: Cohort model in form of modified decision tree Long-term: Markov model	47	All patients (total QALYs): Palliative care: 5.44 GOL: 7.34 ADA: 6.97 ETAN: 7.69	All patients (total costs): Palliative care: £62,224 GOL: £94,151 ADA: £86,410 ETAN: £94,578	ICER vs. Palliative care: All patients: GOL £16,811 ADA £15,820 ETAN £14,402	Changing rebound assumption to "rebound to natural history" had significant impact on ICER

Study	Summary of model	Patient age (years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Stated drivers of CE results
			PsO patients: Palliative care: 5.30 GOL: 7.21 ADA: 6.83 ETAN: 7.55 Non-PsO patients (total QALYs): Palliative care: 5.85 GOL: 7.71 ADA: 7.35 ETAN: 8.06	PsO patients (total costs): Palliative care: £70,342 GOL: £101,403 ADA: £93,820 ETAN: £101,609 Non-PsO patients (total costs): Palliative care: £40,275 GOL: £74,542 ADA: £66,377 ETAN: £74,767	Psoriasis patients: GOL £16,245 ADA £15,249 ETAN £13,982 Non-psoriatic patients: GOL £18,378 ADA £17,405 ETAN £15,557	
Mughal et al. (2015) (94)	Markov model		APR before anti-TNFs: Incremental QALY: 0.71	Incremental cost: £11,695	£16,507/QALY gained	Results were sensitive to parameters: - HAQ-DI increase on BSC - Discount rates - BSC cost
Rencz et al. (2015) (95)	Probabilistic Markov model		NR	NR	ICUR of biosimilar INF-standard care treatment sequence versus standard care: 50,103/QALY (Belgium), 60,141/QALY (France), 79,730/QALY (Germany), 40,897/ QALY (Hungary), 48,059/QALY (Italy), 49,212/QALY (the Netherlands), 53,602/QALY (Spain), 74,773/QALY (Sweden) and 68,697/QALY (UK)	Results were sensitive to: - Changes in the perspective - Utility weights - Time horizon (10-year)

Study	Summary of model	Patient age (years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Stated drivers of CE results
NICE appraisals						
Ustekinumab for treating active psoriatic arthritis (2014) (28)	A short-term decision tree, which evaluated patients' initial response to treatment; followed by a longer-term Markov model		Anti-TNFα naïve patients: Conventional management: 5.60 GOL: 8.03 ADA: 7.53 UST: 7.33 ETAN: 8.11 INF: 8.30	Anti-TNFα naïve patients, total costs: Conventional management: £28,825 GOL: £58,723 ADA: £60,425 UST: £66,186 ETAN: £68,131 INF: £131,953	ICERs vs. conventional management Anti-TNFα naïve patients: GOL: £12,288 per QALY ADA: £16.386 per QALY UST: £21,550 per QALY ETAN: £15,662 per QALY INF: £38,149 per QALY	TNF-α inhibitor- naive population: - Change in HAQ-DI score over time associated with the natural history of PsA - the proportion of people who had a PsARC response - HAQ-DI change associated with PsARC response TNF-α inhibitor- exposed population: - Change in HAQ-DI score over time associated with the natural history of PsA - HAQ-DI change associated with PsARC response
Golimumab for the treatment of psoriatic arthritis (2011-12) (27)	Markov cohort model	47	Palliation: 6.61 ADA: 7.89 GOL: 8.21 ETAN: 8.49 INF: 8.49	Palliation: £62,224 ADA: £86,410 GOL: £94,151 ETAN: £94,578 INF: £106,620	Base case results calculated by the manufacturer are incorrect. Correct ICERs are: Pallation: Referent ADA: Extendedly dominated GOL: Extendedly dominated ETN: £14,379 INF: Dominated	- when compared to the next most effective alternative, all alternatives to ETAN were either dominated or extendedly dominated - weakness of evidence suggesting clinically important differences in the effectiveness of GOL compared to other TNF inhibitors
Etanercept, infliximab and adalimumab for the treatment of	Probabilistic decision analytic cost-utility model (Markov cohort model)	47	Palliative care: 5.171 ADA: 6.580 ETAN: 7.001 INF: 7.308	Palliative care: £42,168 ADA: £68,638 ETAN: £74,841 INF: £88,442	ICER vs. palliative care: ADA: extendedly dominated ETAN: £15,986 per QALY INF: £53,750 per QALY	- INF prescription cost - Cost of treating patients who do not achieve a response to biologics for the PsO component of PsA

Study	Summary of model	Patient age (years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Stated drivers of CE results
psoriatic arthritis (2010) (26)						- Progression of HAQ-DI on and off treatment
Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (2016) (2)	Markov cohort model with 3-monthly cycles. -Treatment sequences modelled - Six subgroups: 1. Only 1 prior cDMARD 2. At least 2 prior cDMARDs 3. Failure on TNF-alpha inhibitor 4. Contraindicated to TNF-alpha inhibitor Psoriasis severity: - a=moderate to severe - b=mild-moderate - c=no PsO	47	Subpopulation 1a: BSC: 5.312 CZP: 8.377 SEC 300mg: 8.524 Subpopulation 1b: BSC: 5.676 CZP: 8.667 SEC 150mg: 8.685 Subpopulation 1c: BSC: 6.188 SEC 150mg: 9.067 CZP: 9.074 Subpopulation 2a: BSC: 5.312 CZP: 7.226 SEC 300mg: 7.379 ADA: 7.411 GOL: 7.637 ETAN: 7.719 INF: 7.890 Subpopulation 2b: BSC: 5.676 CZP: 7.537	Subpopulation 1a: BSC: £95,965 CZP: £159,951 SEC 300mg: £179,692 Subpopulation 1b: BSC: £67,000 CZP: £135,946 SEC 150mg: £132,500 Subpopulation 1c: BSC: £51,436 SEC 150mg: £120,303 CZP: £122,832 Subpopulation 2a: BSC: £95,965 CZP: £137,240 SEC 300mg: £157,086 ADA: £138,109 GOL: £142,850 ETAN: £144,585 INF: £167,126 Subpopulation 2b: BSC: £67,000 CZP: £111,856	Pairwise ICER vs. BSC Subpopulation 1a: CZP: £20,870 SEC 300mg: £26,064 Subpopulation 1b: CZP: £23,052 SEC 150mg: £21,772 Subpopulation 1c: SEC 150mg: £23,928 CZP: £24,744 Subpopulation 2a: CZP: £21,564 SEC 300mg: £29,569 ADA: £20,074 GOL: £20,074 ETAN: £20,197 INF: £27,599 Subpopulation 2b: CZP: £24,103 SEC 150mg: £22,032 ADA: £23,149 GOL: £23,419 ETAN:£22,274 INF: £31,616 Subpopulation 2c:	Different sources of disease management costs

Study	Summary of model	Patient age (years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Stated drivers of CE results
			SEC 150mg: 7.560 ADA: 7.708 GOL: 7.923 ETAN: 8.025 INF: 8.161 Subpopulation 2c: BSC: 6.188 CZP: 7.972 SEC 150mg: 7.974 ADA: 8.125 GOL: 8.325 ETAN: 8.456 INF: 8.543 Subpopulation 3a: BSC: 5.312 UST: 6.334 SEC 300mg: 6.632 Subpopulation 3b: BSC: 5.676 UST: 6.666 SEC 300mg: 6.945 Subpopulation 3c: BSC: 6.188 UST: 7.132 SEC 300mg: 7.384	SEC 150mg: £108,508 ADA: £114,039 GOL: £119,624 ETAN: £119,326 INF: £145,569 Subpopulation 2c: BSC: £51,436 CZP: £95,632 SEC 150mg: £98,060 ADA: £100,893 GOL: £106,895 ETAN: £105,592 INF: £133,664 Subpopulation 3a: BSC: £95,965 UST: £118,127 SEC 300mg: £143,534 Subpopulation 3b: BSC: £67,000 UST: £91,246 SEC 300mg: £118,564 Subpopulation 3c: BSC: £51,436 UST: £76,712 SEC 300mg: £104,973	CZP: £24,773 SEC 150mg: £26,105 ADA: £25,532 GOL: £25,951 ETAN:£23,883 INF: £34,930 Subpopulation 3a: UST: £21,685 SEC 300mg:£36,013 Subpopulation 3b: UST: £24,510 SEC 300mg:£40,639 Subpopulation 3c: UST: £26,797 SEC 300mg: £44,774 Subpopulation 4a: UST: £19,969 SEC 300mg: £34,445 Subpopulation 4b: UST: £22,708 SEC 150mg: £19,349 Subpopulation 4c: UST: £24,781 SEC 150mg: £22,334	

Study	Summary of model	Patient age (years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Stated drivers of CE results
			Subpopulation 4a: BSC: 5.312 UST: 6.276 SEC 300mg: 6.530 Subpopulation 4b: BSC: 5.676 UST: 6.613 SEC 150mg: 6.739 Subpopulation 4c: BSC: 6.188 UST: 7.088 SEC 150mg: 7.190	Subpopulation 4a: BSC: £95,965 UST: £115,216 SEC 300mg: £137,936 Subpopulation 4b: BSC: £67,000 UST: £88,280 SEC 150mg: £87,559 Subpopulation 4c: BSC: £51,436 UST: £73,717 SEC 150mg: £73,798		
Apremilast for treating active psoriatic arthritis (2015-2017) (29)	Markov cohort model comparing sequences APR-ADA-ETN-BSC to ADA-ETN-BSC	50.3 (pooled across apremilast trials)	APR sequence 8.01 Comparator sequence 7.27	APR sequence: £116,199 Comparator sequence: £105,321	£14,691/QALY	Assumptions for HAQ-DI (improvements and progressions)

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

3.2 Economic analysis

A de novo economic analysis was developed to assess the cost-effectiveness of ixekizumab versus other recommended treatments in the treatment of PsA. The model was developed in Visual Basic for Applications with a user interface in Microsoft Excel. The publications summarised in Table 35 helped to inform key features of the model, such as patient population, model structure, utilities, costs and resource use. The way in which the studies identified in the review have informed patient population, model structure and treatments in the model are described in the sections below. In particular, the second revision of the York model (2016) served as the foundation of the current de novo analysis, most notably with its treatment sequencing approach in a fully incremental framework; and stratification of patient subgroups by prior bDMARD exposure and baseline psoriasis severity. (2) The de novo analysis was also designed to incorporate additional PASI response thresholds, i.e. PASI 50, PASI 90 and PASI 100.

3.2.1 Patient population

Ixekizumab, either alone or in combination with methotrexate, is indicated for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD therapies. This amendment to the marketing authorisation was granted by the EMA on January 18th 2018. (1) The licence wording of “one or more DMARD therapies” covers a broader patient population than the patient populations of interest in the current economic analysis, who are assumed to have met NICE criteria for eligibility for bDMARD therapy: diagnosis of psoriatic arthritis with three or more tender joints and three or more swollen joints, and prior treatment with and inadequate response to two cDMARDs, administered either individually or in combination. Inclusion criteria in the SPIRIT trials included patients diagnosed with three or more tender joints and three or more swollen joints; with presence of active psoriatic skin lesions or personal history of plaque psoriasis, and meeting the CASPAR criteria for diagnosis; diagnosis. In SPIRIT-P2, prior treatment with one or more cDMARDs was an inclusion criterion.

The published peer-reviewed models and NICE appraisals identified in the systematic review estimated the cost-effectiveness in a population with active PsA after non-response to two prior cDMARDs. Prior biologic-treatment subgroups were considered in the ustekinumab model submitted to NICE and the 2016 York model. The 2016 York model also incorporates subgroups relating to previous cDMARD use and skin involvement. The 2016 MTA considered a patient subgroup that had been treated with only one prior cDMARD therapy.

However, it was believed that prescribing a bDMARD in this position of the pathway did not reflect clinical practice in the NHS in England and Wales, therefore bDMARDs were not recommended in this subgroup. For this reason, this subgroup has not been included in the current analysis, therefore only a patient population that has been treated with at least two prior cDMARDs is considered.

The de novo economic analysis considers separately 1) bDMARD-naïve patients and 2) bDMARD-experienced patients. Each of these subpopulations is further stratified by presence or severity of concomitant psoriasis: a) no psoriasis, b) mild-to-moderate psoriasis (BSA≥3% and PASI≤10), and c) moderate-to-severe psoriasis (BSA>3% and PASI>10), thus comprising a total of six subgroups of interest. Baseline PASI and HAQ-DI scores for these subgroups in the SPIRIT-P1 and SPIRIT-P2 trials are presented in Table 36 and are assumed to be reflective of patients prior to initiating biologic or targeted synthetic DMARD (b/tsDMARD) therapy.

Table 36 Baseline PASI and HAQ-DI scores in model subgroups

	bDMARD-naive	bDMARD-experienced
No psoriasis	Baseline PASI = 0 Baseline HAQ-DI = 1.17	Baseline PASI = 0 Baseline HAQ-DI =1.39
Mild-to-moderate psoriasis	Baseline PASI = 3.9 Baseline HAQ-DI = 1.17	Baseline PASI = 3.7 Baseline HAQ-DI = 1.2
Moderate-to-severe psoriasis	Baseline PASI = 20.4 Baseline HAQ-DI = 1.19	Baseline PASI = 23.4 Baseline HAQ-DI = 1.16

Source: SPIRIT-P1 CSR; (73) SPIRIT-P2 CSR (74)

3.2.2 Model structure

The 2011 York model (89) is a widely accepted framework for modelling PsA, having been used in the ustekinumab and golimumab submissions and with similar frameworks also applied in three more recent peer-reviewed CEMs publications identified in the literature review. (27, 28, 91-93) All patients were assumed to receive cDMARDs or BSC after the failure of the initial biologic in these models. Initial response determined the criteria for continuing treatment and was defined as meeting the PsARC response criteria at 12-24 weeks. Patients who did not achieve a response at the appropriate time point were considered non-responders and subsequently received cDMARDs or BSC. Clinical and health economic expert opinion was sought during an expert workshop in London (May 2015) on an appropriate modelling structure for the current model for ixekizumab, during which the experts agreed that the structure of the York model would be appropriate to use.

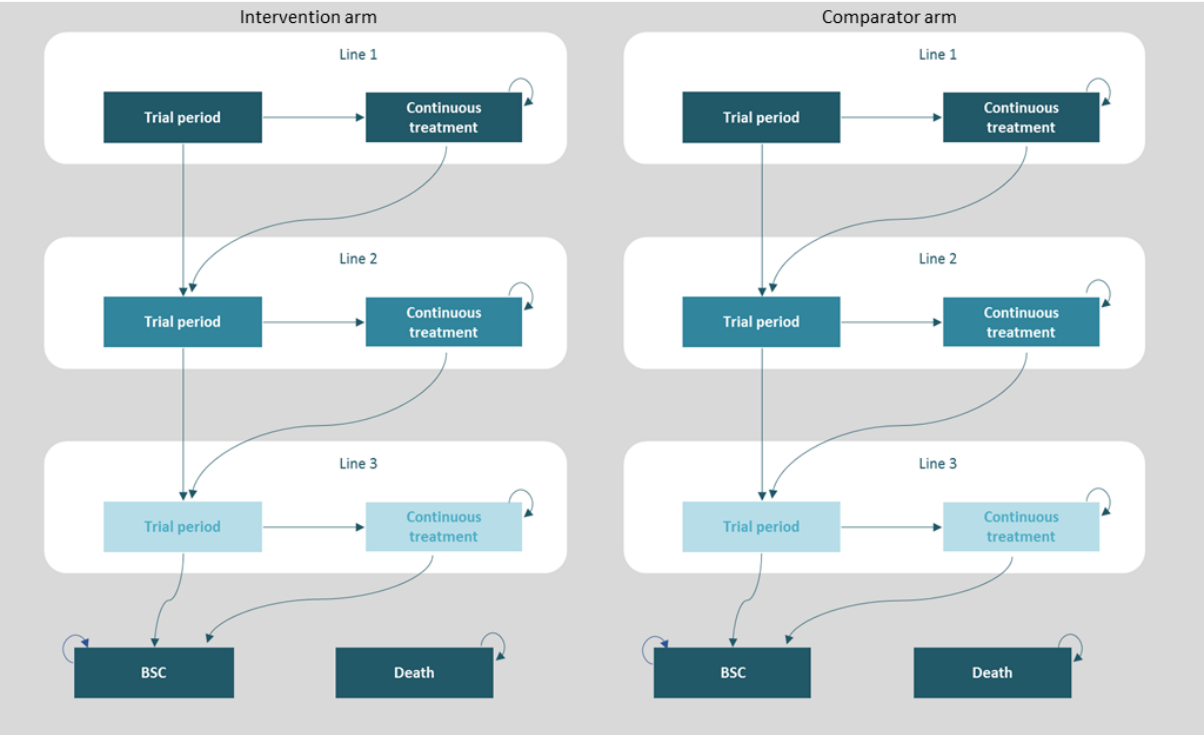
The 2011 York model, 2016 revision of the York model and the manufacturer models since 2009 were designed to incorporate the impact of both the joint and skin components of PsA in estimating costs, health outcomes and cost-effectiveness. (27-29, 96, 97) In particular, the 2016 York model incorporated important changes, including treatment sequences and subpopulations regarding previous treatment and skin involvement. Following the publication of the Assessment Group report for TA445, the 2016 York model was considered to be an appropriate foundation for the de novo model for ixekizumab. In addition to the features of the 2016 York model, additional PASI health states (PASI50, PASI90, and PAS100) were considered important to include in the current analysis, given the greater efficacy in skin outcomes of the newer generation biologics, such as the IL-17 agents.

Ixekizumab is expected to be used in the same position of the NICE clinical pathway of care as other bDMARDs that are approved in England and Wales, i.e. following failure on two csDMARDs, as presented in Figure 1. Treatment continuation in the clinical pathway is determined by whether patients have achieved PsARC response

The clinical outcomes of interest in the model are PsARC response, HAQ-DI and, if the patient has concomitant psoriasis, PASI response. Accordingly, in the model, PsARC response determines the proportion of patients who transition from the trial period to the continued treatment period. HAQ-DI and PASI response are not used as the basis of treatment continuation in the clinical pathway and therefore do not determine transition probabilities in the model. As they relate to functional capacity and psoriasis symptoms, respectively, they have the potential to affect patients' HRQoL and healthcare resource utilisation, therefore these endpoints are used to derive health state costs and utilities.

Moreover, the NICE pathway recommends initiating certain treatments in the case of inadequate response at the response assessment time point (primary failure); in the continued treatment period after an initially adequate level of response (secondary failure), or if the drug cannot be tolerated or becomes contraindicated. (68) Patients may therefore receive more than one b/tsDMARD over the course of their disease management. The de novo analysis captures this through modelling treatment sequences as depicted in Figure 10.

Figure 10 Model schematic with treatment sequencing



Note: Arrows denote transition is possible. Transition to death is possible from all treatment states but not presented for simplicity.

The current analysis takes the form of a Markov state-transition model with a cycle length of one month and lifetime time horizon. In alignment with the NICE reference case, costs and benefits are discounted at 3.5% annually. No half-cycle correction is applied as the model cycle length of one month was considered to be sufficiently short and patients repeatedly enter tunnel states. The model consists of four treatment period health states that constitute a set of mutually exclusive and collectively exhaustive states in the model, which are described in further detail below:

- Trial period
- Continued treatment period
- BSC
- Death

Trial period

The trial period consists of a series of tunnel states from which patients either die or transition to the next temporary state. In the final temporary state, patients are assessed for response to treatment. The trial period length is dependent on the biologic and can last from

10 to 16 weeks in alignment with the response assessment time points in NICE guidance for each treatment of interest. At the end of the trial period, patients are assessed for PsARC response and PASI response. Patients also experience a change from baseline in their HAQ-DI score, which is conditioned on PsARC response.

Patients who achieve PsARC response move to the continued treatment period whereas patients who do not achieve response enter the trial period for the next active treatment in the sequence or BSC, i.e. another series of tunnel states at the end of which they are again assessed for PsARC response.

Continued treatment period

During the continued treatment period, patients maintain PsARC response while they continue to receive treatment. A constant risk of discontinuation due to any cause, such as safety or loss of joint or skin efficacy, is applied in each cycle.

Upon discontinuing, patients lose PsARC response and revert to their baseline HAQ-DI and PASI score. These patients proceed to the trial period of the subsequent active treatment in the sequence or BSC.

BSC

When patients have exhausted the active treatment options in the sequence, they proceed to BSC, the final treatment option in the sequence, which is assumed to consist of a mix of cDMARDs and palliative care. The model uses placebo rates from the NMAs for all endpoints as a proxy for BSC. All patients, including non-responders, continue to receive BSC and maintain their level of PsARC and PASI response until death whereas HAQ-DI progresses according to natural history.

Death

Death is an absorbing health state to which transition is possible from any other state . Mortality rates have been derived from UK life tables and adjusted for the excess mortality risk associated with PsA, and are applied equally across all treatments irrespective of joint or skin symptom response.

Overview of the economic analysis

Features of the economic analysis and a comparison with previous TAs in PsA are presented in Table 37.

Table 37 Features of the economic analysis

	Previous appraisals					Current appraisal	
Factor	**TA313 Ustekinumab**	**TA220 Golimumab**	**TA 199; 2011 York Model**	**TA 445; 2016 York model**	**TA433 Apremilast**	**Chosen values**	**Justification**
Time horizon	52 years	40 years				40 years	Alignment with NICE reference case and previous appraisals
Treatment waning effect?	**On treatment:** PsARC response, HAQ-DI improvement and PASI response maintained **Off treatment:** PsARC response is lost, and HAQ-DI and PASI scores revert to baseline. If the patient discontinues active treatment and goes on to receive BSC, HAQ-DI worsens over time in line with natural history progression.						Alignment with previous appraisals
Source of utilities	York model equation used in base case: EQ-5D utility = 0.897 – 0.298*HAQ – 0.004*PASI					bDMARD-naïve: Utility=[redacted]- [redacted] *HAQ - [redacted] *PASI bDMARD-experienced: Utility=[redacted]- [redacted] *HAQ - [redacted] *PASI	SPIRIT trials used to estimate coefficients in York utility function. Prior bDMARD subgroups analysed separately to reflect inherent differences in terms of functional capacity between the two populations.
Source of costs	UK NHS PSS perspective Drug costs: BNF; MIMS (98, 99) Administration costs: PSSRU Unit Costs of Health and Social Care, NHS reference costs (100, 101) Monitoring costs: NHS reference costs (101) HAQ-DI-related costs: Kobelt et al. (2002) (102) PASI-related costs: manufacturer estimates; Hartman et al (2003); Poyner et al (1999) (103, 104)						Alignment with NICE reference case and 2016 MTA

3.2.3 Intervention technology and comparators

The comparators of interest are b/tsDMARDs recommended by NICE for patients with PsA whose disease has not responded to two prior cDMARDs. Dosing regimens for each treatment are in line with their marketing authorisation and the stopping rules used in the model align with the corresponding NICE guidance. These are presented in Table 38.

In the base case analysis, the model stopping rule for ixekizumab is set to 12 weeks. This is based on the assessment timepoint in the SPIRIT trials for the clinical endpoints used in the model and aligns with the stopping rules for TNF-alpha inhibitors. The SmPC for ixekizumab states that consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. The impact of a stopping rule of 16 weeks is considered in a sensitivity analysis using data collected at this timepoint in the SPIRIT trials.

The analysis assesses treatments using a sequencing approach in which patients switch from one b/tsDMARD to another treatment sequentially. Treatment sequences align with those used in the 2016 York model and are presented for the biologic-naïve subpopulation in Table 39 and for the biologic-experienced subpopulation in Table 40. Switching from one biologic to another is recommended as a strategy when patients fail to respond or no longer respond due to lack of efficacy or safety (68, 105), particularly switching between mechanisms of action. The cost-effectiveness of ixekizumab and these treatments is therefore assessed in the model as part of a treatment sequencing approach. This approach is important for two reasons.

First, a treatment sequencing approach is reflective of clinical practice in the UK with potential variation in bDMARD treatment algorithms between Clinical Commissioning Groups (CCG). (106, 107) Furthermore, NICE's recommendation of ustekinumab as a treatment following failure on TNF-alpha inhibitor and the use of sequences in the 2016 York model suggests that a sequencing approach would be appropriate in the current analysis. Second, there may be costs and benefits associated with the end of a treatment sequence that are only apparent if a sequence is modelled. For example, as BSC is associated with poorer clinical outcomes than active treatments, upstream treatments that reduce the time during which patients are treated with BSC will be associated with a greater QALY improvement. Modelling treatment sequences may therefore be important to reflect the decision problem accurately and consequently, the ixekizumab CEM incorporates treatment sequences.

Table 38 Treatment stopping rules and annual doses

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
Ixekizumab Q2W	If patient has concomitant moderate-to-severe psoriasis, 80 mg every two weeks for 12 weeks, following a 160 mg starting dose in the trial period; thereafter 80 mg every 4 weeks	N/A	Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.	Base case: 12 Sensitivity analysis: 16	8	13	18
Ixekizumab Q4W	80 mg every four weeks, following a 160 mg starting dose.	N/A	Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks.	Base case: 12 Sensitivity analysis: 16	5	13	15
Adalimumab	Injection, 40 mg administered every other week	Adalimumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks (26)	Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period (108)	12	6	26	26
Apremilast	Oral tablet, 30 mg twice daily after an initial titration schedule: Day 1: 10mg qd; Day 2: 10 mg bid; Day 3: 10mg AM, 20 mg PM; Day 4: 20 mg biw; Day 5 20 mg AM, 30 mg PM	Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate response using the PsARC (29)	If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered (109)	16	223	730	725

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
Certolizumab pegol 200 mg Q2W	Injection, loading dose 400 mg at weeks 0,2 and 4; 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered	Certolizumab pegol should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks (2)	Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment. (110)	12	10	26	29
Etanercept 50 mg QW	Injection, 50mg once weekly	Etanercept should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks (26)	Treatment should be discontinued in patients who show no response after 12 weeks (111)	12	12	52	52
Golimumab 50mg	Injection, 50 mg once a month	Golimumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks (27)	Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within 12 to 14 weeks of treatment (after 3-4 doses). (112)	12	3	12	12
Infliximab	By intravenous infusion, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks	Infliximab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks (26)	If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given (113)	12	3	6.5	8
Ustekinumab 45 mg	Injection, body-weight <100 kg, initially 45 mg, then 45 mg 4 weeks after initial dose, then 45 mg every 12 weeks	Ustekinumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 24 weeks (28)	Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment (114)	24	3	4.33	5
Secukinumab 150 mg	Injection of 150mg at weeks 0, 1, 2 and 3 followed by monthly	Secukinumab should be discontinued in people whose	Consideration should be given to discontinuing treatment in	16	7	13	16

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
	dosing from week 4 for bDMARD-naïve patients without concomitant moderate-to-severe psoriasis	PsA has not shown an adequate response using the PsARC at 16 weeks (2)	patients who have shown no response up to 16 weeks of treatment (115)				
Secukinumab 300 mg	Dose of 300mg (two 150 mg injections) at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4 for TNF-naïve patients with concomitant moderate-to-severe psoriasis or patients with prior exposure to TNF-alpha inhibitors	Secukinumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 16 weeks (2)	Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment (115)	16	7	13	16

Table 39 Treatment sequences in bDMARD-naïve population by psoriasis severity

1st Line	2nd Line	3rd Line
Biologic-naïve: no psoriasis and mild-to-moderate psoriasis		
Ixekizumab Q4W	Ustekinumab	BSC
Adalimumab	Ustekinumab	BSC
Apremilast	Ustekinumab	BSC
Certolizumab pegol	Ustekinumab	BSC
Etanercept 50 mg	Ustekinumab	BSC
Golimumab	Ustekinumab	BSC
Infliximab	Ustekinumab	BSC
Secukinumab 150 mg	Ustekinumab	BSC
Biologic-naïve: moderate-to-severe psoriasis		
Ixekizumab Q2W+Q4W	Ustekinumab	BSC
Adalimumab	Ustekinumab	BSC
Apremilast	Ustekinumab	BSC
Certolizumab pegol	Ustekinumab	BSC
Etanercept 50 mg	Ustekinumab	BSC
Golimumab	Ustekinumab	BSC
Infliximab	Ustekinumab	BSC
Secukinumab 300 mg	Ustekinumab	BSC

Table 40 Treatment sequences in bDMARD-experienced population by psoriasis severity

2nd Line	2nd Line
Biologic- experienced; no psoriasis, mild-to-moderate psoriasis	
Ixekizumab	BSC
Ustekinumab	BSC
Certolizumab pegol	BSC
Secukinumab 300 mg	BSC
Biologic-experienced; moderate-to-severe psoriasis	
Ixekizumab	BSC
Ustekinumab	BSC
Certolizumab pegol	BSC
Secukinumab 300 mg	BSC

3.3 Clinical parameters and variables

3.3.1 Clinical outcomes

The outcomes of interest in the model are PsARC, HAQ-DI and PASI, which are sourced from the NMA described in Section 2.9. In the base case analysis, all outcomes of interest have been taken directly from the NMA. Response rates for PsARC and PASI used in the model are specific to whether the patient has had prior bDMARD exposure whereas change in HAQ-DI conditional on PsARC response is not stratified by prior bDMARD exposure. While it would have been ideal to estimate treatment effects specific to each of the six subgroups, evidence was not available to estimate PsARC, PASI or HAQ-DI response by presence of severity of psoriasis.

In a sensitivity analysis, efficacy estimates from meta-regression analyses with baseline risk (i.e. placebo response) as the covariate are used in the economic model. Placebo response rates have been observed to rise over time across clinical trials in PsA, referred to as 'placebo creep'. (2) As a control arm, higher placebo response rates may limit the maximum value of relative risks, which could dilute effect estimates. Initial analyses within the NMA identified placebo response rate as a potential source of heterogeneity. However, a meta-regression analysis was feasible only for the biologic-naïve network and the interaction term was not significant. The placebo-adjusted efficacy estimates are therefore only used in the biologic-naïve population in a sensitivity analysis.

PsARC

In the base case analysis, the treatment continuation rule is defined as the treatment effectiveness on joint outcomes, measured as the proportion of patients achieving PsARC response at the end of the trial period. This aligns with current UK practice in assessing response to b/tsDMARD therapies (68) and with the cost-effectiveness models identified in the SLR.

Patients who meet the response criteria transition to the continued treatment period and are assumed to maintain their improvement in joint and/or skin outcomes until treatment discontinuation due to any cause. Non-responders discontinue treatment and may receive a subsequent b/tsDMARD or BSC. Patients who receive a subsequent b/tsDMARD are assessed again for PsARC response at the end of the trial period.

HAQ-DI

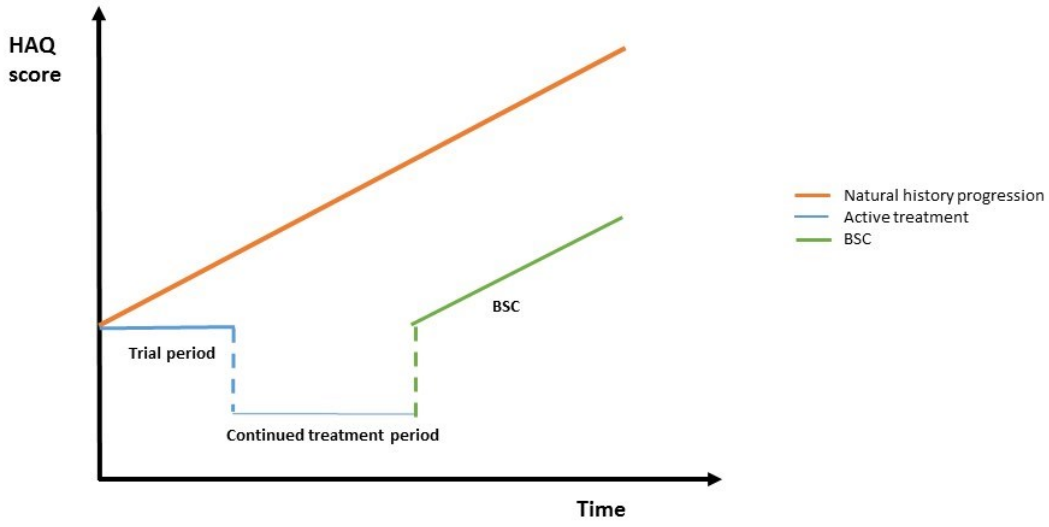
The impact on functional capacity due to joint symptoms is modelled as change from baseline HAQ-DI score at the end of the trial period. HAQ-DI is used in the model as an intermediate outcome that is used to calculate health state costs and utility values, which affects, in turn, QALYs. Baseline HAQ-DI values are presented in Table 36 for each model subgroup. Change from baseline HAQ-DI is specific to each treatment and conditioned on

PsARC response. As change from baseline HAQ-DI conditional on response was not publicly available for certolizumab pegol, the value for golimumab has been used instead.

All patients are assumed to experience an improvement in baseline HAQ-DI score, which is applied instantaneously in the trial period and is specific to each treatment and conditioned on achieving PsARC response. PsARC responders experience a greater change from baseline HAQ-DI than PsARC non-responders. Responders maintain their improvement in HAQ-DI as long as they are on treatment throughout the trial period and continued treatment period. For non-responders who did not achieve PsARC response at the end of the trial period and responder patients who discontinue treatment during the continued treatment period, the HAQ-DI score is assumed to rebound to baseline. As with PsARC, when a patient discontinues and receives a subsequent active treatment, they experience the corresponding improvement in HAQ-DI score conditional on PsARC response.

When patients discontinue from active treatment and receive BSC, HAQ-DI rebounds to baseline in the base case and progresses at a rate equivalent to natural history progression until it plateaus at the maximum value of 3. The rate at which HAQ-DI deteriorates is 0.072 per year. This is based on the mean annual change in HAQ-DI score over three years in patients with arthritis from the NOAR registry. (27) The rebound to initial gain (i.e. baseline) is depicted in Figure 11.

Figure 11 Change in HAQ-DI



PASI

Treatment effect on skin symptoms in patients with psoriatic arthritis and concomitant psoriasis is captured through percentage reduction from baseline PASI score. PASI is also used in the model as an intermediate outcome in the derivation of health state utilities and

cost. Baseline PASI values are presented in Table 36 for each model subgroup. PASI response is measured in terms of the proportion of patients who achieve at least a specific percentage reduction from baseline PASI score, i.e. 50% (PASI 50), 75% (PASI 75) 90% (PASI 90) and 100% (PASI 100). Improvement in PASI is applied instantaneously in the trial period.

The distribution of PASI 75 responders amongst patients who achieve a PsARC response is derived using a correlation coefficient (ρ) of 0.4 sourced from the 2016 York model. (97) The correlation coefficient is applied to all patients irrespective of prior bDMARD exposure, psoriasis severity and treatment. When etanercept is included in the comparator set, the feasible upper bound of ρ is 0.26. Using the approach laid out in Appendix 10 of Rodgers et al (2011), the formulae to calculate the proportions of PsARC responders and non-responders achieving PASI 75 or less is presented in Table 41. (96)

Table 41 Bivariate probabilities of observing PsARC and PASI 75 response or non-response

	PsARC responder	PsARC non-responder
PASI 75	(A) $= \rho * \sqrt{PsARC * PASI\ 75 * (1 - PsARC) * (1 - PASI\ 75)} + PsARC * PASI\ 75.$	(C) $= \text{PASI } 75 - (A)$
PASI < 75	(B) $= \text{PsARC} - (\text{A}))$	(D) $= 1 - (\text{PASI } 75 + \text{PsARC} - (A))$

In the absence of information on the distribution of PASI 50 responder patients, the assumption was made that patients referred to in cell (B) of Table 41 achieved PASI 50-74 response. If the PASI 50-74 response rate estimated from the NMA exceeded the value of the formula in column B, the remaining proportion of PASI 50-74 responders were allocated to cell D.

In the base case analysis, the formulae in Table 41 informs only the calculation of health state utilities and costs associated with psoriasis. In sensitivity analyses, when PASI 75, 90 or 100 response are incorporated into the treatment continuation rule, the formulae in cell A

is used to inform a combined PsARC and PASI response rate. The estimated rates are presented in Appendix T.

Response rates are applied to the baseline PASI score and used to calculate an absolute change from baseline PASI based on the distribution of patients across the relative PASI response categories. Similar to HAQ-DI, PASI responders obtain a greater reduction in baseline PASI score than non-responders.

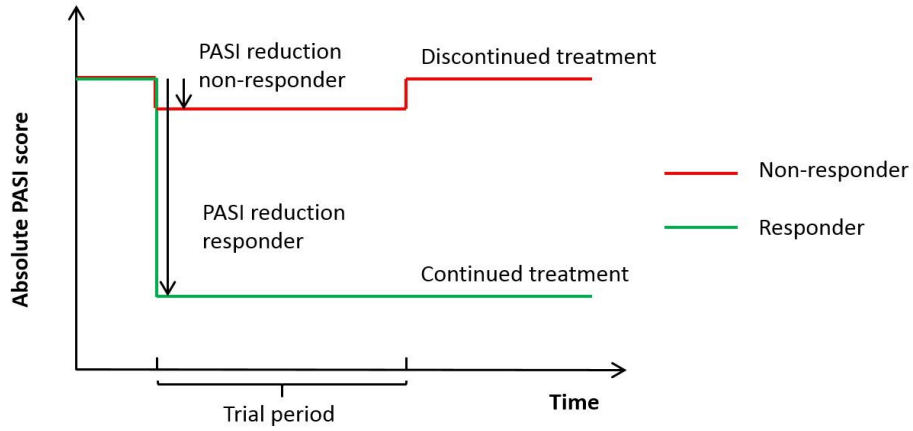
The formulae for absolute PASI scores for responders is presented in Table 42 for the PsARC only response criterion, and PsARC and PASI response criteria. To illustrate, when the response criterion is either PsARC only or PsARC and PASI 75, the total PASI score for responders is calculated as the baseline PASI score decreased by 75%. For non-responders, the total PASI score is calculated as a weighted average score of patients who achieve a PASI 50 response and those who do not.

Table 42 Change in PASI conditional on PsARC response alone and PsARC and PASI response

Response criterion	Response group	Formula for absolute PASI during treatment
PsARC	Responders	*Baseline*0.25*
	Non-responders	*Baseline*(0.5(PASI50-PASI75)/(1-PASI75)+(1-PASI50)/(1-PASI75))*
PsARC and PASI 75	Responders	*Baseline*0.25*
	Non-responders	*Baseline*(0.5(PASI50-PASI75)/(1-PASI75)+(1-PASI50)/(1-PASI75))*
PsARC and PASI 90	Responders	*Baseline*0.1*
	Non-responders	*Baseline*(0.25*(PASI75-PASI90)/(1-PASI90)+ 0.5(PASI50-PASI75)/(1-PASI90)+(1-PASI50)/(1-PASI90))*
PsARC and PASI 100	Responders	*Baseline*0*
	Non-responders	*Baseline*(0.1*(PASI90-PASI100)/(1-PASI100) +0.25*(PASI75-PASI90)/(1-PASI100)+ 0.5*(PASI50-PASI75)/(1-PASI100)+(1-PASI50)/(1-PASI100))*

Responder patients maintain the improvement in PASI in the continuous treatment period. When patients discontinue treatment from the trial period or the continuous treatment period, their PASI score reverts to baseline. Change in PASI score is depicted graphically in Figure 12.

Figure 12 Change in PASI score for responders and non-responders



3.3.2 Transition probabilities

Psoriatic arthritis is associated with a progressive natural history. This is captured in part by the natural history progression of HAQ-DI when patients are not receiving active treatment and by PsARC rates specific to the biologic-naïve and biologic-experienced subgroups. Psoriasis is associated with an unpredictable natural history, therefore in the absence of data to model otherwise and in alignment with the 2016 York model and previous TAs in moderate-to-severe plaque psoriasis, PASI scores are assumed to either improve on treatment or remain at baseline while off-treatment. (29, 97)

However, as these data are not publicly available at all time points for all treatments in order to inform the evidence syntheses, it is not possible to derive time-varying transition probabilities. In the absence of data for ixekizumab and other treatments to model time-varying transition probabilities, fixed transition probabilities are used with the exception of mortality, which is derived from UK life tables. The derivation of transition probabilities between treatment states is described below.

Trial period

After initiating treatment in the trial period, patients transition to the next temporary state in the tunnel unless they die within the temporary state. At the end of the trial period, transition to the continued period is conditional on achieving PsARC response or a combined PsARC and PASI response. Response is assessed in the model at the same time point as recommended in the NICE clinical pathway (Table 38). Non-responder patients transition to the trial period for the next treatment. No further adjustment is required to the response rates obtained from the NMA in order for these to be applied as transition probabilities.

Response rates for subsequent lines of treatment are taken from the biologic-experienced network. As these response rates can be applied directly in the model, it is assumed that no effect modification of first-line response is needed in a biologic-experienced population.

Continued treatment period

Patients transition to the continued treatment period through achieving PsARC response and are assumed to continue treatment until they discontinue due to any cause. A constant annual discontinuation rate of 16.5% is applied in the continued treatment state and represents discontinuation due to any cause, e.g. loss of efficacy and safety concerns. The annual drop-out rate, d_a, is converted to a monthly drop-out rate, d_m, using Equation 1 and applied in each model cycle in the continued treatment state to patients receiving any biologic therapy to arrive at a monthly drop-out rate of 1.49%.

Equation 1 – Formula for converting annual discontinuation rate to monthly rate

$$d_m = 1 - e^{\left(\frac{ln(1-d_a)}{12}\right)}$$

This discontinuation rate has first been established by Rodgers et al. (2011) based on a meta-analysis of registry data from multiple countries. (96) The analysis resulted in an estimate of -1.823 (SE 0.2044) on a log scale, which was then transformed to an exponential scale, resulting in an annual rate of 16.5%. This rate has been consistently used in subsequent NICE submissions. (27, 96, 97) In the absence of alternative data, this treatment discontinuation rate is applied to all comparators and treatment lines in the base case and is independent of HAQ-DI and PASI scores.

Mortality

Patients can transition from any treatment state to the death state. Mortality is modelled using UK general population life tables and applies an increased disease-specific mortality risk in the base case, which is set at 1.36 for PsA patients based on the relative risk of mortality observed in a Canadian PsA cohort. (21) Although the effect on results from modelling excess mortality is limited, some impact can be expected as a smaller proportion of patients end up in later treatment lines and BSC. The increased risk is applied at all times in the model. As there is no evidence to suggest that mortality differs between treatments, the increased mortality is not modified by treatment or treatment response. In scenario analyses, the increased disease-specific mortality risk can be excluded or an alternative estimate of disease-specific mortality presented by Wong et al can be used. (116)

3.4 Measurement and valuation of health effects

Health effects in the current analysis are expressed in QALYs, in accordance with NICE's reference case, which combine quality of life and life expectancy into a single index. Life expectancy is assumed not to differ across therapies, therefore the key driver behind the valuation of health effects is the HRQoL measure used.

3.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D health status questionnaire is a standardized instrument self-completed by patients to assess their general health states (117) and is not specific to a disease condition. The questionnaire is made up from two components, a health state description and a single index evaluation, which consists of a visual analogue scale ranging from 0-100. The health state description component comprises five dimensions of health status: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression.

The EQ-5D-3L rates each dimension under three levels of severity (no problems, some problems, or extreme problems/unable to undertake any tasks in the dimension). The EQ-5D-5L is a recent development in which each of these dimensions is rated under five levels of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems/unable to undertake any tasks in the dimension). The valuation of HRQoL measured in patients is based on a valuation of public preferences from a representative sample of the UK in the 3L questionnaire or for England specifically in the 5L questionnaire. Both questionnaires use choice-based methods: time trade-off (TTO) for the 3L and a hybrid of TTO and discrete choice experiments (DCE) for the 5L. These are used to derive utility weights associated with each possible health state.

The EQ-5D-5L questionnaire was administered to patients in the SPIRIT-P1 and SPIRIT-P2 trials for ixekizumab at baseline and at week 12. (73, 74). These two studies were analysed separately so that the utility equations could reflect the inherent differences in terms of functional disability and skin involvement between these two populations. No imputation method was applied in case of missing information on EQ-5D as only a small proportion of patients in each trial had a missing EQ-5D score (20/417 in SPIRIT-P1 and 32/331 in SPIRIT-P2).

3.4.2 Mapping

NICE's position statement on the EQ-5D-5L recommended that the EQ-5D-3L continue as the reference case in HTA appraisals with the EQ-5D-5L to be used in sensitivity analyses. In accordance with the position statement, the EQ-5D-5L data collected in the trial has been

mapped to EQ-5D-3L using the indirect mapping approach with a non-parametric model outlined in van Hout et al. (2012). (118)

3.4.3 Health-related quality-of-life studies

A systematic search was carried out for HRQoL data in psoriatic arthritis. The full details of the methodology is described in Appendix H along with a summary of utility values identified from the SLR. Based on the review of cost-effectiveness studies described in Appendix G, the model followed the approach of the 2016 York model by modelling utility as a function of HAQ and PASI. (97) As the studies identified in the HRQoL review reported only health state utility values, these were not used to inform the model.

3.4.4 Adverse reactions

Only one manufacturer model was identified in the SLR that considered the cost of adverse events: Novartis' model for secukinumab based adverse event costs on the approach used in a NICE appraisal for ankylosing spondylitis. (2) In all other economic models submitted to HTA agencies, the HRQoL and cost impact associated with adverse events were not explicitly modelled. (2, 26-29) Instead, adverse events were thought to be captured only to the extent that they affect the initial response and the long-term withdrawal rates. Similarly, this assumption is made in the current model, therefore the HRQOL impact of AEs is not modelled.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The cost-effectiveness analysis estimates health utilities at each point in time using an algorithm based on patients' HAQ-DI and PASI scores. Baseline utility is derived from this algorithm using baseline HAQ-DI and PASI scores presented in Table 36 for each model subgroup and utility values in subsequent model cycles are based on the treatment-specific combinations of HAQ-DI and PASI score in subsequent model cycles.

Improvements from baseline HAQ-DI and PASI associated with active treatments are applied instantaneously in the trial period with different values for PsARC responders and non-responders. The improvements in HAQ-DI and PASI are constant in each model cycle, therefore the utilities estimated for PsARC responders and non-responders are constant in each cycle in the trial period. In the continued treatment period, only PsARC responders continue to maintain their HAQ-DI and PASI scores. PsARC non-responders revert to baseline HAQ-DI, PASI and utility and proceed to the trial period of the subsequent treatment. In the continued treatment period, therefore the estimated utility for PsARC responders remains the same as in the trial period. In the BSC treatment state, patients may

experience an improvement in PASI score; however, HAQ-DI progresses at a rate of 0.072 points per year until a maximum of a score of three. The estimated utility associated with the BSC treatment state changes over time until the maximum HAQ-DI score is reached.

The algorithm describing the relationship between HAQ-DI, PASI and EQ-5D utilities is estimated based on an ordinary least squares regression analysis of SPIRIT-P1 and SPIRIT-P2 trial data for the active treatment sub-sample for bDMARD-naïve and bDMARD-experienced patients, respectively. The functional form of the regression analysis used in the York models (Equation 2) was tested and provided a better goodness of fit than other tested variations on the model, which included an interaction term between HAQ-DI and PASI and /or were adjusted for age and gender.

Equation 2 - Utility regression model

$$Utility = \beta_0 - \beta_{HAQ} * HAQ - \beta_{PASI} * PASI$$

EQ-5D-5L data from the SPIRIT trials were cross-walked to the 3L and valued using the UK tariff. The coefficients derived from the cross-walked utility data are used in the base case analysis and are presented in Table 43. Coefficients derived using the unadjusted EQ-5D-5L data and coefficients from the York model (26) are utilised in scenario analyses.

Table 43 Coefficients of linear regression of utility versus HAQ-DI and PASI

	Intercept		HAQ-DI		PASI	
Source	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
bDMARD-naïve: SPIRIT-P1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bDMARD-experienced: SPIRIT-P2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No further adjustment is made in the cost-effectiveness analysis to the utilities estimated using the algorithm in Equation 2. No other health effects were identified in the literature or clinical trials.

3.4.6 Summary of utility values for cost-effectiveness analysis

Table 44 Summary of utility values used for cost-effectiveness analysis

State	Utility value (PsARC responders)	Utility value (PsARC non-responders)	Reference in submission	Justification
bDMARD-naïve, no psoriasis				
Trial period	0.624		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period			Table 36, Equation 2	Baseline utility at start of trial period

IXE Q4W	0.744	0.624	Table 21, Table 22, Table 23, Table 36, Equation 2	Derived from treatment-specific response rates in the biologic-naïve NMA and from baseline HAQ score
ADA	0.717	0.647		
APR	0.693	0.641		
CZP	0.702	0.637		
ETN	0.750	0.662		
GOL	0.702	0.637		
INF	0.756	0.661		
SEC 150	0.735	0.652		
bDMARD-naïve, mild-moderate psoriasis				
Trial period	0.605		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE Q4W	0.739	0.613	Table 21, Table 22, Table 23, Table 36, Equation 2	Derived from treatment-specific response rates in the biologic-naïve NMA and from baseline PASI and HAQ scores
ADA	0.709	0.629		
APR	0.683	0.622		
CZP	0.692	0.618		
ETN	0.736	0.642		
GOL	0.694	0.619		
INF	0.750	0.649		
SEC 150	0.729	0.639		
bDMARD -naïve, moderate-severe psoriasis				
Trial period	0.518		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE Q2W	0.716	0.600	Table 21, Table 22, Table 23, Table 36, Equation 2	Derived from treatment-specific response rates in the biologic-naïve NMA and from baseline PASI and HAQ scores
ADA	0.669	0.550		
APR	0.638	0.539		
CZP	0.642	0.533		
ETN	0.675	0.556		
GOL	0.657	0.539		
INF	0.723	0.596		
SEC 300	0.701	0.590		
bDMARD -experienced, no psoriasis				
Trial period	0.589		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE Q4W	0.763	0.634	Table 23, Table 25, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline HAQ score
UST	0.737	0.675		
bDMARD -experienced, mild-moderate psoriasis				

Trial period	0.577		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE Q4W	0.711	0.586	Table 23, Table 25, Table 26, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline PASI scores, which determines the severity of psoriasis.
UST	0.683	0.637		
bDMARD -experienced, moderate-severe psoriasis				
Trial period	0.310		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE Q2W+Q4W	0.497	0.422	Table 23, Table 25, Table 26, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline PASI scores, which determines the severity of psoriasis.
UST	0.453	0.493		
BSC	Point estimate N/A	NA	NA	HAQ-DI progresses each cycle according to natural history in BSC
Death	0	NA	NA	No utility assigned in death state

3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic literature review of costs and healthcare resource use data was carried out to identify relevant information for the model. The full details of the methodology are presented in Appendix I. In line with recent NICE TAs of treatments in PsA, cost and healthcare resource use inputs considered in the base case analysis are as follows:

- Acquisition cost of b/tsDMARDs
- Treatment administration
- Monitoring and tests
- Disease management

Only direct medical costs are included in the model. Costs were sourced from the NHS Reference Costs 2015-16, Monthly Index of Medical Specialities (MIMS), Personal Social Services Research Unit (PSSRU) and published literature. (2, 99, 101, 102, 119) Where not available for 2015-16, costs are inflated to 2016 using the Hospital and Community Health

Services Index sourced from the Unit Costs of Health and Social Care (Appendix R). (100, 120)

The NHS Reference Costs were chosen as the preferred source over the Payment by Results (PbR) tariff as the former contains national average unit costs to the NHS of providing defined services to NHS patients in England whereas the PbR tariff is reflective of the payment system within the NHS in which commissioners pay healthcare providers for each patient seen or treated. (101, 121)

Although healthcare resource utilisation estimates were collected in the SPIRIT trials on the number of visits to healthcare providers, emergency room admissions, hospital admissions and concomitant medications, the resource use estimates in the model are aligned with those used in previous published cost-effectiveness models and submissions.

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition cost

Drug acquisition costs have been derived from the online version of MIMS. The drug unit costs are presented in Table 45. A confidential simple discount patient access scheme (PAS) for ixekizumab was approved by Patient Access Scheme Liaison Unit (PASLU)/Department of Health in February 2016 and would apply to the current appraisal. Secukinumab and apremilast were recommended for the treatment of PsA by NICE under a confidential simple price discount PAS. As these prices are not publicly available, the base case analysis uses the list price for all treatments, including ixekizumab.

Certolizumab pegol was recommended by NICE under a PAS that requires the manufacturer to provide the first 12 weeks of treatment free of cost to the NHS; this has been incorporated in the current analysis. Under the complex PAS for ustekinumab, the manufacturer provides the higher dose of 90 mg needed for people who weigh more than 100 kg at the same total cost as the lower dose of 45 mg for people who weigh 100 kg or less. In line with previous appraisals, a common evidence base has been assumed for both doses of ustekinumab, therefore the model simply refers to 'ustekinumab' and does not differentiate between the low and high dose. The baseline weight of all patients in the SPIRIT trial programme was used to calculate a weighted average of 87.02 kg, which informs the weight-based dosing of infliximab.

Biosimilar infliximab was launched in the UK in February 2015 and biosimilar etanercept became available in the UK in February 2016.(122, 123) A common evidence base was assumed in the NMA for these biosimilar therapies and their branded counterparts. In the

base case analysis, biosimilar prices are used for both infliximab and etanercept and is associated with a more conservative estimate of the cost-effectiveness of ixekizumab versus these treatments. The branded prices of these treatments are used in a sensitivity analysis.

Drug administration cost

All therapies of interest are administered as a SC injection with the exception of oral apremilast and infliximab, which is administered via intravenous (IV) infusion.

Patients who received SC injections incurred administration costs only for nurse training for self-administration in the trial period and no further administration costs in the continued treatment period. Self-administration training was assumed to require one hour of nurse time. Patients who received infliximab received an IV infusion cost three times in the trial period and an average of 6.5 times each year they remain on treatment. No administration costs were applied to oral administration of apremilast.

The cost of administration was obtained from the PSSRU Unit Costs of Health and Social Care 2016 and the NHS Reference Costs 2015-16. (101, 119)

Table 45 Drug acquisition costs

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (trial period)	Total annual cost (continued treatment)	Source
IXE Q2W	1	80 mg	£1,125	£1,125	£9,000	£14,625	List price: MIMS 2017 (99)
IXE Q4W	1	80 mg	£1,125	£1,125	£5,625	£14,625	List price: MIMS 2017 (99)
IXE Q2W	1	80 mg	[redacted]	[redacted]	[redacted]	[redacted]	PAS price
IXE Q4W	1	80 mg					PAS price
ADA	2	40 mg/0.8ml	£704.28	£352.14	£2,112.84	£9,155.64	MIMS 2017 (99)
APR*	56	30 mg	£550.00	£9.82	£2,190.18	£7,150.00	MIMS 2017 (99)
CZP†	2	200 mg	£715.00	£357.50	£0†	£9,295.00	MIMS 2017; NICE FAD TA445 (2, 99)
ETN (Enbrel)	4	50 mg	£715.00	£178.75	£2,145.00	£9,295.00	MIMS 2017 (99)
ETN biosimilar (Benepali)	4	50 mg	£656.00	£164.00	£1,968.00	£8,528.00	MIMS 2017 (99)
GOL	1	50 mg	£762.97	£762.97	£2,288.91	£9,155.64	MIMS 2017 (99)
INF (Remicade)‡	1	100 mg	£419.62	£2,056.40	£6,169.21	£13,366.63	MIMS 2017 (99)
INF biosimilar (Remsima) ‡	1	100 mg	£377.00	£1,847.54	£5,542.62	£12,009.01	MIMS 2017 (99)
SEC 150 mg*	2	150 mg	£1218.78	£609.39	£4,265.73	£7,922.07	MIMS 2017 (99)
SEC 300 mg*	2	150 mg	£1218.78	£1,218.78	£8,531.46	£15,844.14	MIMS 2017 (99)
UST 45	1	45 mg	£2,147.00	£2,147.00	£4,294.00	£9,303.67	MIMS 2017 (99)

*List price used in model due to confidential discount PAS; †CZP is associated with a PAS that provides the first 12 weeks of treatment free; ‡Infliximab dose based on a baseline weight of 87.02 kg. MIMS = Monthly Index of Medical Specialities; PAS = Patient Access Scheme.

Table 46 Drug administration cost

Administration method	Admin cost	Admin: trial period	Annual admin	Total cost: trial period	Total annual cost	Source
SC self-injection: a hour-long nurse training sessions	£43.00	1	0	£108.00	£0.00	PSSRU, Unit Costs of Health and Social Care 2016, section 10, cost per hour of Nurse in GP practice (119)
IV infusion, outpatient procedure	£236.19	3	6.5	£291.24	£631.02	NHS Reference Cost 2015-2016, Deliver Simple Parenteral Chemotherapy

Administration method	Admin cost	Admin: trial period	Annual admin	Total cost: trial period	Total annual cost	Source
						at First Attendance, code SB12Z (101)
Oral administration	£0.00	N/A	N/A	£0.00	£0.00	Assumption

GP = general practitioner; IV = intravenous; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; SC = subcutaneous

Monitoring

Costs for monitoring during treatment have been obtained from the NHS Reference Costs. (101)

Table 47 Costs for administration and monitoring of treatment

Resource	Price	Reference	Cost year
Rheumatologist visit	£142.74	NHS Reference Cost 2015-2016, , code DAPS05 (101)	2016
Full blood count	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 (101)	2016
Liver function test	£1.00	NHS Reference Cost 2015-2016, , code DAPS04 (101)	2016
Urea and electrolytes	£1.00	NHS Reference Cost 2015-2016, , code DAPS04 (101)	2016
ESR	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 (101)	2016
Chest X-Ray	£30.00	NHS Reference Cost 2015-2016, , code DAPF (101)	2016
TB Heaf test	£8.91	Rodgers et al 2011 (96)	2016
ANA test	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 (101)	2016
ds DNA test	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 (101)	2016

ANA: Antinuclear antibody; ds: Double-stranded; ESR: Erythrocyte sedimentation rate; FBC = full blood count; LFT = liver function test; NHS = National Health Service; TB: Tuberculosis; U&E = urea and electrolytes test

Unless otherwise noted, resource use estimates associated with monitoring and routine laboratory tests were taken from Corbett et al. (2016) (97) and are in line with the guidelines from the British Society for Rheumatology (BSR) for the use of biologics. Resource use is stratified by method of administration. The frequency of physician visits and monitoring tests for ixekizumab is assumed equivalent to resource use rates for other SC administered biologic treatments. (2)

Table 48 Resource use for SC, oral and IV administration of therapies in the trial and continued treatment periods

Treatment period	SC	Oral	IV
Trial period			
Rheumatologist visit	2	2	2
Full blood count	2	2	2
Liver function test	2	2	2
Urea and electrolytes	2	2	2
ESR	2	2	2
Chest X-Ray	1	1	1
TB Heaf test	1	1	1
ANA test	1	1	1
ds DNA test	1	1	1
Continued treatment period			
Rheumatologist visit	0	1	0
Full blood count	2	0	2
Liver function test	2	0	2
Urea and electrolytes	2	0	2
ESR	2	0	2
Chest X-Ray	0	0	0
TB Heaf test	0	0	0
ANA test	0	0	0
ds DNA test	0	0	0

FBC = full blood count; IV = intravenous; LFT = liver function test; NHS = National Health Service; SC = subcutaneous; U&E = urea and electrolytes test

Healthcare resource use associated with joint and skin symptoms

Costs related to HAQ-DI and PASI are applied in each model cycle to capture the impact of arthritis and psoriasis severity on health care costs, in accordance with previously published models and NICE TAs. Monthly costs based on absolute HAQ-DI and PASI in the modelled cohort are calculated in two separate algorithms detailed below. These algorithms are also assumed to capture the cost of BSC.

Costs associated with HAQ-DI

Annual healthcare costs associated with arthritis are estimated using a linear regression from Kobelt et al (2002), which is based on data from a study on patients with rheumatoid arthritis (RA). (88, 102) The reported coefficients presenting the cost per point-increase in HAQ-DI have been updated to 2017 GBP and are presented in Equation 3.

Equation 3 – Health state costs associated with HAQ-DI

$$Annual\ direct\ costs = £565.64\ x\ HAQ + £1{,}867.56$$

Kobelt et al. (2002) estimated that costs for cDMARDs would account for 15% of the direct cost. To avoid double-counting with drug acquisition costs applied elsewhere in the current model, patients on biologic treatment are modelled to incur 85% of the costs from Kobelt et al. (2002). Patients receiving BSC are assigned 100% of the cost estimated from the algorithm, thereby capturing the cost of cDMARDs. An alternative algorithm by Poole et al. (2010) is used in a scenario analysis. (124)

Costs related to PASI

Costs related to the treatment of controlled and uncontrolled psoriasis are presented in Table 49 with controlled psoriasis defined as achieving a PASI 75 response. Patients with mild to moderate and moderate to severe concomitant psoriasis are assumed to incur the same costs as in the study by Rodgers et al.(89), due to lack of data that would allow differential costing. For patients without concomitant psoriasis, it is assumed that no additional psoriasis-related costs occur.

Costs for treating patients with mild to moderate concomitant psoriasis who are not treated with or have not responded to active therapy (i.e. uncontrolled psoriasis) are based on UK unit costs for phototherapy and other treatment costs such as drug costs and physician visits estimated from a UK RCT. (97, 104) For patients with uncontrolled moderate to severe concomitant psoriasis, costs are based on a Dutch RCT (including short contact treatment, UVB therapy and inpatient treatment) which has been adjusted to UK price levels. (103) These costs are annualised and presented in Table 49.

Table 49 Annual costs for controlled and uncontrolled psoriasis

Description	No psoriasis	Mild to moderate	Moderate to severe
Costs for uncontrolled psoriasis	£0	£892	£2,552
Costs for controlled psoriasis (PASI75 response)	£0	£72	£72

Source: Harman et al (2002) (103), Poyner et al (1998) (104); annualised costs from Corbett et al. 2016 (97).

3.5.2 Health-state unit costs and resource use

Cost categories associated with each PASI response health state are presented in Table 50.

Table 50 List of health states and associated costs in the economic model

Health states	Item	Value	Reference
PsARC response and non-response	*Treatment costs*		
	Ixekizumab	£1,125 per dose	MIMS, January 2017 (99)
	Adalimumab	£352.14 per dose	MIMS, January 2017 (99)
	Apremilast	£9.82 per dose	MIMS, January 2017 (99)
	Certolizumab pegol	£357.50 per dose	MIMS, January 2017 (99)
	Etanercept	£164 per dose	MIMS, January 2017 (99)

Health states	Item	Value	Reference
	(biosimilar)		
	Golimumab	£762.97 per dose	MIMS, January 2017 (99)
	Infliximab (biosimilar)	£1,847.54 per dose	MIMS, January 2017 (99)
	Secukinumab 150mg	£609.39 per dose	MIMS, January 2017 (99)
	Secukinumab 300mg	£1,218.78 per dose	MIMS, January 2017 (99)
	Ustekinumab	£2,147.00 per dose	MIMS, January 2017 (99)
	BSC	£0	Captured in HCRU due to skin and joint symptoms
	Administration costs		
	Nurse training for SC administration	£43.00 per hour of nurse time	PSSRU, Unit Costs of Health and Social Care 2015, Nurse (GP practice), wage cost per hour (100)
	IV infusion	£236.19 per administration	NHS Reference Cost 2015-2016, Deliver Simple Parenteral Chemotherapy at First Attendance, code SB12Z (101)
	Monitoring costs		
	Rheumatologist visit costs	£142.74 per visit	NHS Reference Cost 2015-2016 (101)
	FBC	£3.00 per test	NHS Reference Cost 2015-2016 (101)
	LFT	£1.00 per test	NHS Reference Cost 2015-2016 (101)
	U&E	£1.00 per test	NHS Reference Cost 2015-2016 (101)
	- ESR	£3.00	NHS Reference Cost 2015-2016 (101)
	- Chest X-Ray	£30.00	NHS Reference Cost 2015-2016 (101)
	- TB Heaf test	£8.91	NHS Reference Cost 2015-2016 (101)
	- ANA test	£3.00	NHS Reference Cost 2015-2016 (101)
	- ds DNA test	£3.00	NHS Reference Cost 2015-2016 (101)
HCRU due to skin and joint symptoms			
Joint symptoms	HAQ-DI	£565.64 per unit change + £1,867.56	Kobelt et al (2002) (102)
No psoriasis		£0	Annualised cost from Corbett et al (2016) (97)
Mild-to-moderate psoriasis	PASI≥75	£72.00	Annualised cost from Corbett et al (2016) (97)
	PASI<75	£892	Annualised cost from Corbett et al (2016) (97)
Moderate-to-severe psoriasis	PASI≥75	£72.00	Annualised cost from Corbett et al (2016) (97)
	PASI<75	£2,552	Annualised cost from Corbett et al (2016) (97)

BSC = best supportive care; FBC = full blood count; IV = intravenous; LFT = liver function test; NHS = National Health Service; PASI = Psoriasis Area and Severity Index; SC = subcutaneous; U&E = urea and electrolytes test NHS: National Health Service; PSSRU: Personal Social Services Research Unit; ESR: Erythrocyte sedimentation rate; TB: Tuberculosis; ANA: Antinuclear antibody; ds: Double-stranded

3.5.3 Adverse reaction unit costs and resource use

As noted in Section 3.4.4, the major impact of adverse events is expected to be on treatment discontinuation rates. In line with previous NICE TAs and the 2016 York model, the current analysis does not model the cost impact of adverse events.

3.5.4 Miscellaneous unit costs and resource use

No additional costs or resource use items were included in the model that have not already been listed above.

3.6 Summary of base-case analysis inputs and assumptions

3.6.1 Summary of base-case analysis inputs

The inputs used in the base case analysis are presented in Table 51.

Table 51 Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Model settings			
Discount rate (costs)	3.5%	NA	Section 3.2.2
Discount rate (benefits)	3.5%	NA	Section 3.2.2
Patient age	51	NA	
Patient weight	87.02	SD 21.40	
% male	51.8%	NA	
Baseline HAQ; bDMARD-naive			
No psoriasis	1.17	NA	Table 36
Mild-to-moderate psoriasis	1.17	NA	
Moderate-to-severe psoriasis	1.19	NA	
Baseline HAQ; bDMARD-experienced			
No psoriasis	1.39	NA	Table 36
Mild-to-moderate psoriasis	1.2	NA	
Moderate-to-severe psoriasis	1.16	NA	
Baseline PASI; bDMARD-naive			
No psoriasis	0	NA	Table 36
Mild-to-moderate psoriasis	3.9	NA	
Moderate-to-severe psoriasis	20.4	NA	
Baseline PASI; bDMARD-experienced			
No psoriasis	0	NA	Table 36
Mild-to-moderate psoriasis	3.7	NA	
Moderate-to-severe psoriasis	23.4	NA	
PsARC response			
bDMARD-naive			
Placebo	[redacted]	[redacted]	Table 21
Adalimumab 40 mg Q2W			
Apremilast 30 mg BID			

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Certolizumab pegol pooled doses	[redacted]	[redacted]	
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	
Golimumab 50 mg Q4W	[redacted]	[redacted]	
Infliximab 5 mg/kg Q8W			
Ixekizumab 80 mg Q2W			
Ixekizumab 80 mg Q4W			
Secukinumab 150 mg Q4W			
Secukinumab 300 mg Q4W			
bDMARD-experienced			
Placebo	[redacted]	[redacted]	Table 25
Ixekizumab 80 mg Q2W			
Ixekizumab 80 mg Q4W			
Ustekinumab 45 mg Q12W			
PASI 50			
bDMARD-naive			
Placebo	[redacted]	[redacted]	Table 22
Adalimumab 40 mg Q2W			
Apremilast 30 mg BID			
Certolizumab pegol pooled doses			
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	
Golimumab 50 mg Q4W	[redacted]	[redacted]	
Infliximab 5 mg/kg Q8W			
Ixekizumab 80 mg Q2W			
Ixekizumab 80 mg Q4W			
Secukinumab 150 mg Q4W			
Secukinumab 300 mg Q4W			
PASI 75			
bDMARD-naive			
Placebo	[redacted]	[redacted]	Table 22
Adalimumab 40 mg Q2W			
Apremilast 30 mg BID			
Certolizumab pegol pooled doses			
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	
Golimumab 50 mg Q4W	[redacted]	[redacted]	
Infliximab 5 mg/kg Q8W			
Ixekizumab 80 mg Q2W			
Ixekizumab 80 mg Q4W			
Secukinumab 150 mg Q4W			
Secukinumab 300 mg Q4W			
bDMARD-experienced			
Placebo	[redacted]	[redacted]	Table 26
Ixekizumab 80 mg Q2W			
Ixekizumab 80 mg Q4W			
Ustekinumab 45 mg Q12W			
Change from baseline HAQ-DI for PsARC responders			

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Placebo	[redacted]	[redacted]	Table 23
Ixekizumab Q4W	[redacted]	[redacted]	
Ixekizumab Q2W	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Apremilast	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
Infliximab	[redacted]	[redacted]	
Secukinumab	[redacted]	[redacted]	
Ustekinumab	[redacted]	[redacted]	
Change from baseline HAQ-DI for PsARC non-responders			
Placebo			Table 23
Ixekizumab Q4W	[redacted]	[redacted]	
Ixekizumab Q2W	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Apremilast	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
Infliximab	[redacted]	[redacted]	
Secukinumab	[redacted]	[redacted]	
Ustekinumab	[redacted]	[redacted]	
Drug costs (per dose)			
Ixekizumab	£1,125 per dose	NA	Table 45
Adalimumab	£352.14 per dose	NA	
Apremilast	£9.82 per dose	NA	
Certolizumab pegol	£357.50 per dose	NA	
Etanercept (biosimilar)	£164 per dose	NA	
Golimumab	£762.97 per dose	NA	
Infliximab (biosimilar)	£1,847.54per dose	NA	
Secukinumab 150mg	£609.39 per dose	NA	
Secukinumab 300mg	£1,218.78 per dose	NA	
Ustekinumab	£2,147.00 per dose	NA	
BSC	£0	NA	
Drug administration			
Nurse training for SC administration	£43.00	NA	Table 46
IV infusion	£236.19	NA	
Oral administration	£0	NA	
Frequency of drug administration cost			
SC administration (trial)	1	NA	Table 46

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
SC administration (continued)	0	NA	
IV administration (trial)	3	NA	
IV administration (continued)	7	NA	
Monitoring costs			
Rheumatologist visit costs	£142.74 per visit	NA	Table 47
FBC	£3.00 per test	NA	
LFT	£1.00 per test	NA	
U&E	£1.00 per test	NA	
- ESR	£3.00	NA	
- Chest X-Ray	£30.00	NA	
- TB Heaf test	£8.91	NA	
- ANA test	£3.00	NA	
- ds DNA test	£3.00	NA	
Monitoring frequency (trial period)			
Rheumatologist visit	2	NA	Table 48
FBC	2	NA	
LFT	2	NA	
U&E	2	NA	
ESR	2	NA	
Chest X-Ray	1	NA	
TB Heaf test	1	NA	
ANA test	1	NA	
ds DNA test	1	NA	
Monitoring frequency (continued treatment period)			
Rheumatologist visit (SC, IV)	0	NA	Table 48
Rheumatologist visit (oral)	1	NA	
FBC (SC, IV)	2	NA	
FBC (oral)	0	NA	
LFT (SC, IV)	2	NA	
LFT (oral)	0	NA	
U&E(SC, IV)	2	NA	
U&E(oral)	0	NA	
ESR (SC, IV)	2	NA	
ESR (oral)	0	NA	
Chest X-Ray	0	NA	
TB Heaf test	0	NA	
ANA test	0	NA	
ds DNA test	0	NA	
Disease management costs (HAQ)			
HAQ intercept	£1,867.56	£657.28	Equation 3
HAQ coefficient	£565.64	£364.98	
Disease management (PASI)			
Without psoriasis	£0	NA	Table 49
Mild-to-moderate psoriasis; uncontrolled	£892	NA	
Mild-to-moderate psoriasis; controlled	£72	NA	
Moderate-to-severe psoriasis; uncontrolled	£2,552	NA	

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Moderate-to-severe psoriasis; controlled	£72	NA	
Utility			
bDMARD-naive			
Intercept	[redacted]	[redacted]	Equation 2
HAQ coefficient			
PASI coefficient			
bDMARD-experienced			
Intercept	[redacted]	[redacted]	Equation 2
HAQ coefficient			
PASI coefficient			

3.6.2 Assumptions

Maintaining response in continued treatment period

Responder patients are assumed to maintain the improvement in joint and/or skin outcomes achieved by the end of the trial period throughout the continued treatment period until discontinuation from treatment.

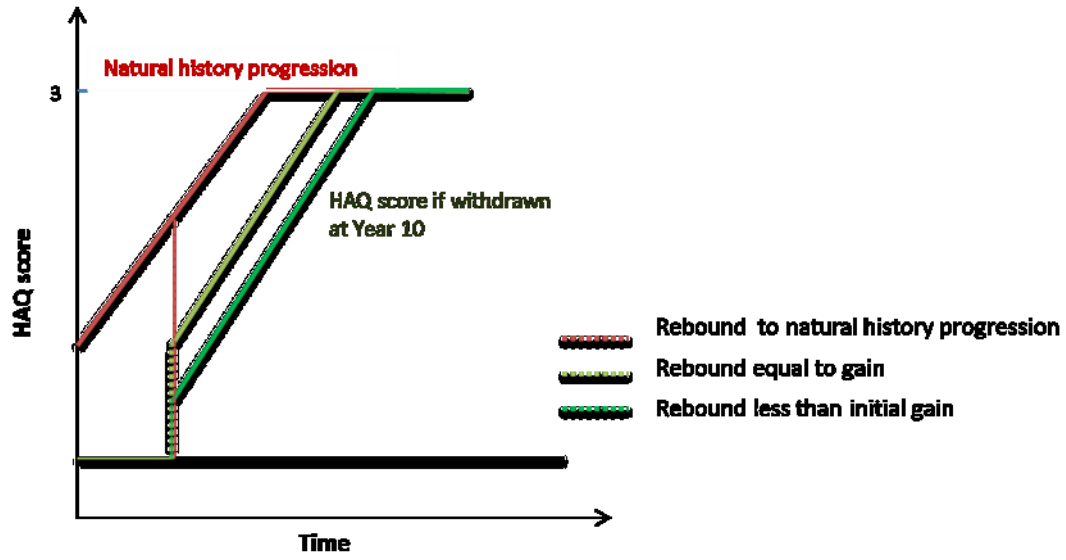
Discontinuation in the continued treatment period

A constant annual discontinuation rate of 16.5% is applied on a cyclical basis to all patients on active treatment in the continued treatment period to capture discontinuation due to any cause, such as loss of efficacy or adverse events. This was derived from a meta-analysis of registry data from multiple countries and has been used in previous NICE TAs for biologic treatments and apremilast in PsA. (96)

Disease progression in joint and/or skin symptoms in BSC

When patients discontinue from all active treatments within a sequence, they proceed to the BSC treatment state where they experience disease progression in joint symptoms measured by the HAQ-DI, which then deteriorates at the underlying rate of natural history progression. In the base case, when patients enter the BSC state, HAQ-DI returns to baseline, i.e. the rebound is equal to the initial improvement in HAQ-DI, and then deteriorates. This assumption is tested in two scenario analyses: (1) the rebound in HAQ-DI is less than the initial improvement and (2) HAQ-DI rebounds to the natural history level had the patient not experienced any initial improvement. Rebound to initial gain, rebound less than initial gain and rebound to natural history progression are depicted in Figure 11.

Figure 13 HAQ-DI progression scenarios in BSC



As psoriasis is associated with an unpredictable natural history, no underlying disease progression has been assumed in the model. Instead, patients return to their baseline PASI score.

Health state costs associated with HAQ-DI

The Kobelt et al. (2002) algorithm used in the base case of the current analysis relates to a cohort of people with RA. The Poole et al (2010) study is an alternative source that utilises data from a sample of PsA patients from the BSRBR to develop a multivariate model estimating disease severity from parameters routinely available in primary care data. (124) The relationship between disease severity and costs, based on HAQ-DI, was estimated using a generalised linear model (GLM) that also included age and an interaction term between age and HAQ-DI, which is presented in Equation 4. Since the cost estimated in the Poole equation includes prescription costs (accounting for 38% of the costs), HAQ-DI costs are assumed to account for 62% of the total costs to avoid double counting.

Equation 4 – Poole et al (2010) algorithm for costs associated with HAQ-DI

$$Annual\ costs = \exp(3.537 + 2.048\ x\ HAQ + 0.026\ x\ Age - \ 0.012\ x\ HAQ\ x\ Age)$$

However, a number of limitations have meant that Kobelt et al (2002) has been preferred in the base case of previous appraisals. The Poole algorithm has predicted markedly higher costs for PsA patients with equivalent HAQ-DI scores compared to values predicted for RA patients. While this could be suggestive of a greater economic burden associated with PsA relative to RA, this discrepancy could also be explained by differences in methodology or a consequence of using a separate regression model from the BSRBR to predict HAQ-DI in

the THIN data set. Another limitation is that the predicted HAQ-DI in the Poole et al. (2010) equation does not cover the full range of the HAQ-DI score. Using the GLM model to predict costs for the full range could therefore result in substantial errors in predicting values for more severe disease. Furthermore, despite relating to a PsA cohort, PASI data were not available from the registries informing the equation, therefore the Poole et al (2010) algorithm does not offer an advantage over the Kobelt et al (2002) algorithm in capturing the direct cost impact of skin symptoms. For these reasons, the Poole et al. (2010) algorithm is used only in a sensitivity analysis.

3.7 Base-case results

3.7.1 Base-case incremental cost-effectiveness analysis results

Deterministic base case results using the list price of ixekizumab are presented for the biologic-naïve subpopulation for all psoriasis severity subgroups in Table 52 and for the biologic-experienced subpopulation for all psoriasis severity subgroups in Table 53.

A comparison of clinical outcomes from the trial and model, and disaggregated cost and QALYs results are presented in Appendix J.

In the bDMARD-naive subgroups, the etanercept sequence is the only treatment option that would be considered cost-effective versus the referent (BSC) in a fully incremental analysis according to an ICER threshold of £30,000/QALY. The infliximab sequence also lies on the CE frontier and is associated with an ICER beyond the threshold. All other sequences are dominated or extendedly dominated. When the list price of ixekizumab is used, the ixekizumab sequences are dominated in the fully incremental analyses in all bDMARD-naïve subgroups.

In the bDMARD-experienced subgroup with no psoriasis and mild-to-moderate psoriasis, ustekinumab is the only treatment to lie on the frontier, albeit with an ICER greater than £30,000/QALY versus the referent (BSC) in the no psoriasis subgroup. Both the ixekizumab sequence and ustekinumab sequence lie on the frontier in the moderate-to-severe subgroup but only the ustekinumab sequence is associated with an ICER lower than £30,000/QALY versus BSC.

The QALY difference between the b/tsDMARDs with the most and least QALYs in each subgroup is less than one QALY over a lifetime time horizon. In contrast, the range in costs between the least and most expensive treatments, owing to the confidential price discounts for apremilast and secukinumab, is likely to be wider than predicted by the model. As a confidential price discount PAS is in place for ixekizumab, the results based on the list price overestimate the cost of ixekizumab to the NHS, therefore the results based on the PAS price of ixekizumab are presented in Table 54 and Table 55. While these results may not reflect the true cost to the NHS of apremilast and secukinumab, they are more representative of the cost-effectiveness of the ixekizumab sequences relative to the other bDMARDs that have been recommended by NICE without a confidential price discount.

When the PAS price of ixekizumab is used, ixekizumab is associated with the second lowest cost of the active treatments in the bDMARD-naïve subgroup with no psoriasis and mild-to-

moderate psoriasis and is associated with a lower cost than ustekinumab in the bDMARD-experienced subgroups. The ixekizumab Q4W sequence is associated with an ICER of less than £30,000/QALY versus BSC in the no psoriasis and mild-to-moderate psoriasis subgroups in both the bDMARD-naïve and bDMARD-experienced populations and the ixekizumab Q2W sequence has an ICER of less than £20,000/QALY versus BSC in the moderate-to-severe psoriasis subgroups. In the bDMARD-experienced subgroup, ixekizumab Q2W dominates ustekinumab.

Table 52 Base case results for bDMARD-naïve subpopulation; list price

1st line	2nd line	3rd line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis								
BSC			£54,046	8.09	Referent	Referent	Referent	£38,750
Apremilast	Ustekinumab	BSC	£93,347	9.49	£39,301	1.39	Extendedly dominated	£109,534
Certolizumab pegol	Ustekinumab	BSC	£99,866	9.67	£45,819	1.57	Extendedly dominated	£636,928
Secukinumab 150 mg	Ustekinumab	BSC	£100,241	9.78	£46,195	1.68	Extendedly dominated	IXE sequence dominated
Adalimumab	Ustekinumab	BSC	£101,322	9.71	£47,276	1.61	Dominated	IXE sequence dominated
Biosimilar etanercept	Ustekinumab	BSC	£103,692	10.02	£49,646	1.92	£25,810	IXE sequence dominated
Golimumab	Ustekinumab	BSC	£108,195	9.90	£54,149	1.80	Dominated	IXE sequence dominated
Ixekizumab Q4W	Ustekinumab	BSC	£116,010	9.69	£61,963	1.60	Dominated	Referent
Infliximab	Ustekinumab	BSC	£127,297	10.12	£73,251	2.02	£236,122	£26,593
Mild-to-moderate psoriasis								
BSC			£70,006	7.74	Referent	Referent	Referent	£35,316
Apremilast	Ustekinumab	BSC	£105,446	9.16	£35,440	1.41	Extendedly dominated	£99,733
Certolizumab pegol	Ustekinumab	BSC	£111,375	9.34	£41,369	1.60	Extendedly dominated	£431,727
Secukinumab 150 mg	Ustekinumab	BSC	£111,743	9.47	£41,738	1.72	Extendedly dominated	IXE sequence dominated
Adalimumab	Ustekinumab	BSC	£112,849	9.39	£42,843	1.64	Dominated	IXE sequence dominated
Etanercept 50 mg QW	Ustekinumab	BSC	£114,657	9.69	£44,651	1.95	£22,947	IXE sequence dominated
Golimumab	Ustekinumab	BSC	£118,987	9.59	£48,981	1.85	Dominated	IXE sequence dominated
Ixekizumab Q4W	Ustekinumab	BSC	£127,777	9.38	£57,771	1.64	Dominated	Referent

1st line	2nd line	3rd line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
Infliximab	Ustekinumab	BSC	£138,072	9.82	£68,066	2.08	£175,864	£23,230
Moderate-to-severe psoriasis								
BSC			£99,884	6.21	Referent	Referent	Referent	£29,170
Apremilast	Ustekinumab	BSC	£127,576	7.70	£27,692	1.49	Extendedly dominated	£67,096
Certolizumab pegol	Ustekinumab	BSC	£132,373	7.90	£32,489	1.69	Extendedly dominated	£109,062
Adalimumab	Ustekinumab	BSC	£133,882	7.97	£33,998	1.77	Extendedly dominated	£155,110
Etanercept 50 mg QW	Ustekinumab	BSC	£134,567	8.24	£34,683	2.03	£17,055	IXE sequence dominated
Golimumab	Ustekinumab	BSC	£138,550	8.23	£38,666	2.02	Dominated	IXE sequence dominated
Ixekizumab Q2W	Ustekinumab	BSC	£155,459	8.11	£55,575	1.91	Dominated	Referent
Secukinumab 300 mg	Ustekinumab	BSC	£155,532	7.97	£55,648	1.77	Dominated	SEC sequence dominated
Infliximab	Ustekinumab	BSC	£157,603	8.51	£57,719	2.31	£84,228	£5,335

Table 53 Base case results for bDMARD-experienced subpopulation; list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	£45,092
Ustekinumab	£82,143	8.24	£26,201	0.86	£30,311	IXE sequence dominated
Ixekizumab Q4W	£93,369	8.21	£37,427	0.83	Dominated	Referent
Mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	£40,344
Ustekinumab	£94,133	7.97	£23,862	0.91	£26,231	IXE sequence dominated
Ixekizumab Q4W	£105,562	7.93	£35,291	0.87	Dominated	Referent
Moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	£36,197
Ustekinumab	£118,915	3.21	£19,297	0.95	£20,307	£557,092
Ixekizumab Q2W	£135,063	3.24	£35,446	0.98	£557,092	Referent

Table 54 Base case results for bDMARD-naïve subpopulation; PAS price

Treatment sequence	2nd line	3rd line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis								
BSC			£54,046	8.09	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£93,347	9.49	£39,301	1.39	Extendedly dominated	[redacted]
Ixekizumab Q4W	Ustekinumab	BSC	[redacted]	9.69	[redacted]	1.60	[redacted]	Referent
Certolizumab pegol	Ustekinumab	BSC	£99,866	9.67	£45,819	1.57	Dominated	Dominated
Secukinumab 150 mg	Ustekinumab	BSC	£100,241	9.78	£46,195	1.68	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£101,322	9.71	£47,276	1.61	Dominated	[redacted]
Biosimilar etanercept	Ustekinumab	BSC	£103,692	10.02	£49,646	1.92	£25,810	[redacted]
Golimumab	Ustekinumab	BSC	£108,195	9.90	£54,149	1.80	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£127,297	10.12	£73,251	2.02	£236,122	[redacted]
Mild-to-moderate psoriasis								

Treatment sequence	2nd line	3rd line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
BSC			£70,006	7.74	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£105,446	9.16	£35,440	1.41	Extendedly dominated	[redacted]
Ixekizumab Q4W	Ustekinumab	BSC	[redacted]	9.38	[redacted]	1.64	[redacted]	Referent
Certolizumab pegol	Ustekinumab	BSC	£111,375	9.34	£41,369	1.60	Dominated	[redacted]
Secukinumab 150 mg	Ustekinumab	BSC	£111,743	9.47	£41,738	1.72	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£112,849	9.39	£42,843	1.64	Dominated	[redacted]
Biosimilar etanercept	Ustekinumab	BSC	£114,657	9.69	£44,651	1.95	£22,948	[redacted]
Golimumab	Ustekinumab	BSC	£118,987	9.59	£48,981	1.85	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£138,072	9.82	£68,066	2.08	£175,823	[redacted]
Moderate-to-severe psoriasis								
BSC			£99,884	6.21	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£127,576	7.70	£27,692	1.49	Extendedly dominated	[redacted]
Certolizumab pegol	Ustekinumab	BSC	£132,373	7.90	£32,489	1.69	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£133,882	7.97	£33,998	1.77	Extendedly dominated	[redacted]
Ixekizumab Q2W	Ustekinumab	BSC	[redacted]	8.11	[redacted]	1.91	[redacted]	Referent
Biosimilar etanercept	Ustekinumab	BSC	£134,567	8.24	£34,683	2.03	£17,055	[redacted]
Golimumab	Ustekinumab	BSC	£138,550	8.23	£38,666	2.02	Dominated	[redacted]
Secukinumab 300 mg	Ustekinumab	BSC	£155,532	7.97	£55,648	1.77	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£157,603	8.51	£57,719	2.31	£84,228	[redacted]

Table 55 Base case results for bDMARD-experienced subpopulation; PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	[redacted]
Ixekizumab Q4W	[redacted]	8.21	[redacted]	0.83	[redacted]	Referent
Ustekinumab	£82,143	8.24	£26,201	0.86	£188,339	[redacted]
Mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	[redacted]
Ixekizumab Q4W	[redacted]	7.93	£17,808	0.87	[redacted]	Referent
Ustekinumab	£94,133	7.97	£23,862	0.91	£173,289	[redacted]
Moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	[redacted]
Ixekizumab Q2W	[redacted]	3.24	[redacted]	0.98	[redacted]	Referent
Ustekinumab	£118,915	3.21	£19,297	0.95	Dominated	[redacted]

3.8 Sensitivity analyses

3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken with 2,000 model simulations. A full list of all parameters included in the probabilistic sensitivity analyses is presented in Table 56 below. Mean values and their standard error are also presented, and standard errors are calculated from confidence intervals, where available, and two times the standard normal deviate of 1.96, according to Equation 5, as described in the Cochrane Handbook. (125) In the absence of data on the variability around the sampling distribution of mean values, the standard error is assumed to be equal to the mean value divided by 4.

Equation 5 – Calculation of standard error from confidence interval

$$se = \frac{(upper\ limit - lower\ limit)}{3.92}$$

The utility regression intercept is assumed to be beta distributed, since this is a utility bounded at the upper limit by one, and the expected value is close to one with a small variance. The other utility regression coefficients are assumed to be normally distributed as many variables are reasonably described by this type of distribution. The normal distribution is bell-shaped as it is symmetrical around the mean; the size of the bell depends on the standard deviation, e.g. it is small and narrow for small standard deviations.

Annual discontinuation rate and adverse event rates are assumed to be beta distributed as values range between 0 and 1. Based off the mean ($\bar{x}$) and standard error (SE), each α and β is calculated based on the following set of equations (Equation 6):

Equation 6 – Calculation of alpha and beta for beta distributed parameters

$$\alpha = \bar{x} * \left(\frac{\bar{x} * (1 - \bar{x})}{se^2}\right) - 1$$

$$\beta = (1 - \bar{x}) * \left(\frac{\bar{x} * (1 - \bar{x})}{se^2}\right) - 1$$

A gamma distribution is assumed for all other parameters that can range between zero and infinity. Calculation of each α and β are based on Equation 7:

Equation 7 Calculation of alpha and beta for gamma distributed parameters

$$\alpha = \left(\frac{\bar{x}}{s}\right)^2$$

$$\beta = \frac{s^2}{\bar{x}}$$

Probabilistic sensitivity analysis inputs are listed in Table 56. Probabilistic results are presented in Table 57 for each subgroup using the list price of ixekizumab. As per the deterministic results, the etanercept and infliximab sequences are the only treatments in the bDMARD-naïve subgroups that lie on the CE frontier with all other treatments dominated or extendedly dominated with a similar magnitude of ICERs. The ICERs for ustekinumab in the bDMARD-experienced population are also similar to the deterministic results. CE planes and CEACs are depicted in Figure 14 to Figure 25.

Table 56 Probabilistic sensitivity analysis inputs

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
Utility (bDMARD-naïve)	Intercept	[redacted]	[redacted]	Beta	NA
	HAQ	[redacted]	[redacted]	Normal	NA
	PASI	[redacted]	[redacted]	Normal	NA
Utility (bDMARD-experienced)	Intercept	[redacted]	[redacted]	Beta	NA
	HAQ	[redacted]	[redacted]	Normal	NA
	PASI	[redacted]	[redacted]	Normal	NA
HAQ progression	Annual HAQ progression	0.072	0.007	Gamma	NA
Drop out rate	Annual discontinuation rate	0.165	0.041	Beta	NA
Mean weight	Mean weight	87.02	0.766	Normal	Calculated from mean and SD reported in Nash et al (2017) (69) and Mease et al (2017) (70)
Monitoring costs	Cost of full blood count (£)	3.00	0.8	Gamma	Assumption SE=mean/4
	Cost of liver function test (£)	1	0.3	Gamma	Assumption SE=mean/4
	Cost of ESR (£)	3	0.8	Gamma	Assumption SE=mean/4
	Cost of urea and electrolytes test (£)	1	0.3	Gamma	Assumption SE=mean/4
	Cost of X-Ray (£)	30	7.5	Gamma	Assumption SE=mean/4
	Cost of TB Heaf test (£)	8.91	2.2	Gamma	Assumption SE=mean/4
	Cost of ANA (£)	3	0.8	Gamma	Assumption SE=mean/4
	Cost of dsDNA (£)	3	0.8	Gamma	Assumption SE=mean/4
Monitoring frequency in trial period for	Monitoring: Number of FBC - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of	2.00	0.500	Gamma	Assumption

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
SC-administered bDMARDs	LFT - trial period				SE=mean/4
	Monitoring: Number of ESR - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of U&E - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of X-Ray - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of TB Heaf test - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of ANA - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of dsDNA- trial period	1.00	0.250	Gamma	Assumption SE=mean/4
Monitoring frequency in continued treatment period for SC-administered bDMARDs	Monitoring: Number of FBC - continuous treatment	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of LFT - continuous treatment	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of ESR - continuous treatment	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of U&E - continuous treatment	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of X-Ray - continuous treatment	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of TB Heaf test - continuous treatment	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of ANA - continuous treatment	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of dsDNA - continuous treatment	1.00	0.250	Gamma	Assumption SE=mean/4
Monitoring frequency in trial period for apremilast	Monitoring: Number of FBC - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of LFT - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of ESR - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of U&E - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of X-Ray - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of TB Heaf test - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of ANA - trial period	1.00	0.250	Gamma	Assumption SE=mean/4

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
	Monitoring: Number of dsDNA- trial period	1.00	0.250	Gamma	Assumption SE=mean/4
Monitoring frequency in continued treatment period for apremilast	Monitoring: Number of FBC - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of LFT - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of ESR - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of U&E - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of X-Ray - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of TB Heaf test - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of ANA - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of dsDNA - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
Monitoring frequency in trial period for infliximab	Monitoring: Number of FBC - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of LFT - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of ESR - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of U&E - trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of X-Ray - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of TB Heaf test - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of ANA - trial period	1.00	0.250	Gamma	Assumption SE=mean/4
	Monitoring: Number of dsDNA- trial period	1.00	0.250	Gamma	Assumption SE=mean/4
Monitoring frequency in continued treatment period for infliximab	Monitoring: Number of FBC - continuous treatment	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of LFT - continuous treatment	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of ESR - continuous treatment	2.00	0.500	Gamma	Assumption SE=mean/4
	Monitoring: Number of U&E - continuous	2.00	0.500	Gamma	Assumption SE=mean/4

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
	treatment				
	Monitoring: Number of X-Ray - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of TB Heaf test - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of ANA - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
	Monitoring: Number of dsDNA - continuous treatment	0.00	0.000	Gamma	Assumption SE=mean/4
Physician Visits	SC administration, trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	SC administration, continued treatment (annual)	0.00	0.000	Gamma	Assumption SE=mean/4
	IV administration, trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	IV administration, continued treatment (annual)	0.00	0.000	Gamma	Assumption SE=mean/4
	Oral administration, trial period	2.00	0.500	Gamma	Assumption SE=mean/4
	Oral administration, continued treatment period	1.00	0.250	Gamma	Assumption SE=mean/4
Admin costs	Cost of nurse training for SC injection (£)	43.00	10.8	Gamma	Assumption SE=mean/4
	Cost of IV infusion (£)	236.19	59.0	Gamma	Assumption SE=mean/4
Physician visit	Cost of Office visit (MD) (£)	142.74	35.7	Gamma	Assumption SE=mean/4
Health state costs	Kobelt HAQ regression constant	565.64	365.0	Normal	Kobelt
	Kobelt HAQ regression intercept	1867.56	657.3	Normal	Kobelt
	Corbett PASI cost uncontrolled psoriasis	0.00	0.0	Gamma	Assumption SE=mean/4
	Corbett PASI cost controlled psoriasis	0.00	0.0	Gamma	Assumption SE=mean/4
	Kobelt cost adjustment factor	0.85	0.2	Beta	Assumption SE=mean/4
BSC efficacy (bDMARD-naïve)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75	[redacted]	NA	CODA	NA
	PsARC and PASI90	[redacted]	NA	CODA	NA
	PsARC and PASI100	[redacted]	NA	CODA	NA
	PASI50 response	[redacted]	NA	CODA	NA
	PASI75 response	[redacted]	NA	CODA	NA
	PASI90 response	[redacted]	NA	CODA	NA
	PASI100 response	[redacted]	NA	CODA	NA
BSC efficacy	PsARC	[redacted]	NA	CODA	NA

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
(bDMARD-experienced)	PsARC and PASI75	[redacted]	NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
BSC HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders		NA	CODA	NA
Ixekizumab Q2W efficacy (bDMARD-naïve)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Ixekizumab Q2W efficacy (bDMARD-experienced)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Ixekizumab Q2W HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders		NA	CODA	NA
Ixekizumab Q4W efficacy (bDMARD-naïve)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Ixekizumab Q4W efficacy (bDMARD-experienced)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Ixekizumab Q4W HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders		NA	CODA	NA
Adalimumab efficacy (bDMARD-	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
naïve)	PsARC and PASI100	[redacted]	NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Adalimumab HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders		NA	CODA	NA
Apremilast efficacy (bDMARD-naïve)	PsARC		NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Adalimumab HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders		NA	CODA	NA
Etanercept 50 mg QW efficacy (bDMARD-naïve)	PsARC		NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Etanercept HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders		NA	CODA	NA
Infliximab efficacy (bDMARD-naïve)	PsARC		NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Infliximab HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders		NA	CODA	NA
Ustekinumab efficacy (bDMARD-experienced)	PsARC		NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Ustekinumab	HAQ reduction		NA	CODA	NA

Category	Parameter	Mean	SE (95% LCI, 95% LCI)	Distribution	Comment
HAQ-DI reduction from baseline	responders				
	HAQ reduction non-responders	[redacted]	NA	CODA	NA
Secukinumab 150 mg efficacy (bDMARD-naïve)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Secukinumab 300 mg efficacy (bDMARD-naive)	PsARC		NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Secukinumab 150mg and 300mg HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders	[redacted]	NA	CODA	NA
Golimumab efficacy (bDMARD-naive)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Golimumab HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders	[redacted]	NA	CODA	NA
Certolizumab pegol efficacy (bDMARD-naive)	PsARC	[redacted]	NA	CODA	NA
	PsARC and PASI75		NA	CODA	NA
	PsARC and PASI90		NA	CODA	NA
	PsARC and PASI100		NA	CODA	NA
	PASI50 response		NA	CODA	NA
	PASI75 response		NA	CODA	NA
	PASI90 response		NA	CODA	NA
	PASI100 response		NA	CODA	NA
Certolizumab pegol HAQ-DI reduction from baseline	HAQ reduction responders		NA	CODA	NA
	HAQ reduction non-responders	[redacted]	NA	CODA	NA

ADA = adalimumab; BSC = best supportive care;CI = confidence interval; CODA = Convergence Diagnostic and Output Analysis; CrI = credible interval; ETN = etanercept; FBC = full blood count; INF = infliximab; IXE = ixekizumab; IV = intravenous; LFT = liver function test; N/A = not applicable; NMSC = non-melanoma skin cancer; NR = not reported; PASI = Psoriasis Area and Severity Index; QW = once weekly; Q2W = every 2 weeks; SC = subcutaneous; SE = standard error; SEC = secukinumab; UST = ustekinumab

Table 57 Probabilistic sensitivity analyses

Treatment sequence	Total costs (£)	Total QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis				
BSC	£54,046	8.09	Referent	Referent
APR-UST-BSC	£93,347	9.49	Extendedly dominated	£28,231
CZP-UST-BSC	£99,866	9.67	Extendedly dominated	£29,116
SEC150-UST-BSC	£100,241	9.78	Extendedly dominated	£27,470
ADA-UST-BSC	£101,322	9.71	Dominated	£29,328
ETN-UST-BSC	£103,692	10.02	£25,810	£25,810
GOL-UST-BSC	£108,195	9.90	Dominated	£30,042
IXEQ4W-UST-BSC	£116,010	9.69	Dominated	£38,750
INF-UST-BSC	£127,297	10.12	£236,122	£36,200
bDMARD-naïve; mild-to-moderate psoriasis				
BSC	£70,006	7.74	Referent	Referent
APR-UST-BSC	£105,446	9.16	Extendedly dominated	£25,102
CZP-UST-BSC	£111,375	9.34	Extendedly dominated	£25,892
SEC150-UST-BSC	£111,743	9.47	Extendedly dominated	£24,241
ADA-UST-BSC	£112,849	9.39	Dominated	£26,083
ETN-UST-BSC	£114,657	9.69	£22,948	£22,948
GOL-UST-BSC	£118,987	9.59	Dominated	£26,531
IXEQ4W-UST-BSC	£127,777	9.38	Dominated	£35,317
INF-UST-BSC	£138,072	9.82	£175,823	£32,741
bDMARD-naïve; moderate-to-severe psoriasis				
BSC	£99,884	6.21	Referent	Referent
APR-UST-BSC	£127,576	7.70	Extendedly dominated	£18,589
CZP-UST-BSC	£132,373	7.90	Extendedly dominated	£19,184
ADA-UST-BSC	£133,882	7.97	Extendedly dominated	£19,250
ETN-UST-BSC	£134,567	8.24	£17,055	£17,055
GOL-UST-BSC	£138,550	8.23	Dominated	£19,098
IXEQ2W-UST-BSC	£155,459	8.11	Dominated	£29,170
SEC300-UST-BSC	£155,532	7.97	Dominated	£31,486
INF-UST-BSC	£157,603	8.51	£84,228	£25,018
bDMARD-experienced; no psoriasis				
BSC	£55,942	7.38	Referent	Referent
Ustekinumab	£82,143	8.24	£30,311	£30,311
Ixekizumab Q4W	£93,369	8.21	Dominated	£45,028

Treatment sequence	Total costs (£)	Total QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-experienced; mild-to-moderate psoriasis				
BSC	£70,271	7.06	Referent	Referent
Ustekinumab	£94,133	7.97	£26,231	£26,231
Ixekizumab Q4W	£105,562	7.93	Dominated	£40,344
bDMARD-experienced; moderate-to-severe psoriasis				
BSC	£99,618	2.26	Referent	Referent
Ustekinumab	£118,915	3.21	£20,307	£20,307
Ixekizumab Q2W	£135,063	3.24	£557,092	£36,197

Figure 14 Probabilistic CE plane for biologic-naïve patient population with no psoriasis

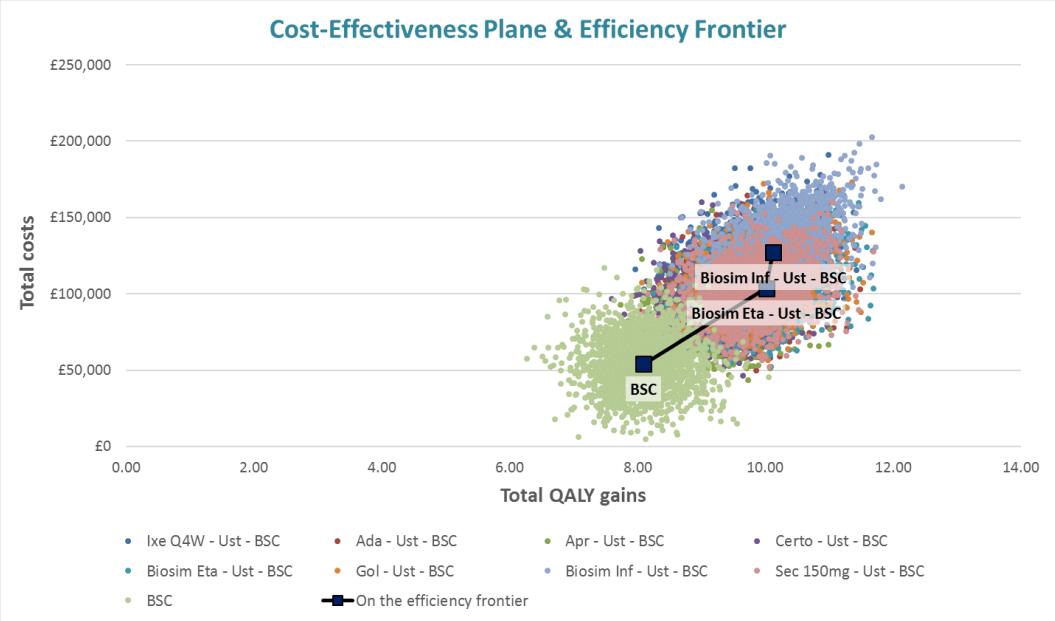


Figure 15 Probabilistic CE plane for biologic-naïve patient population with mild-to-moderate psoriasis

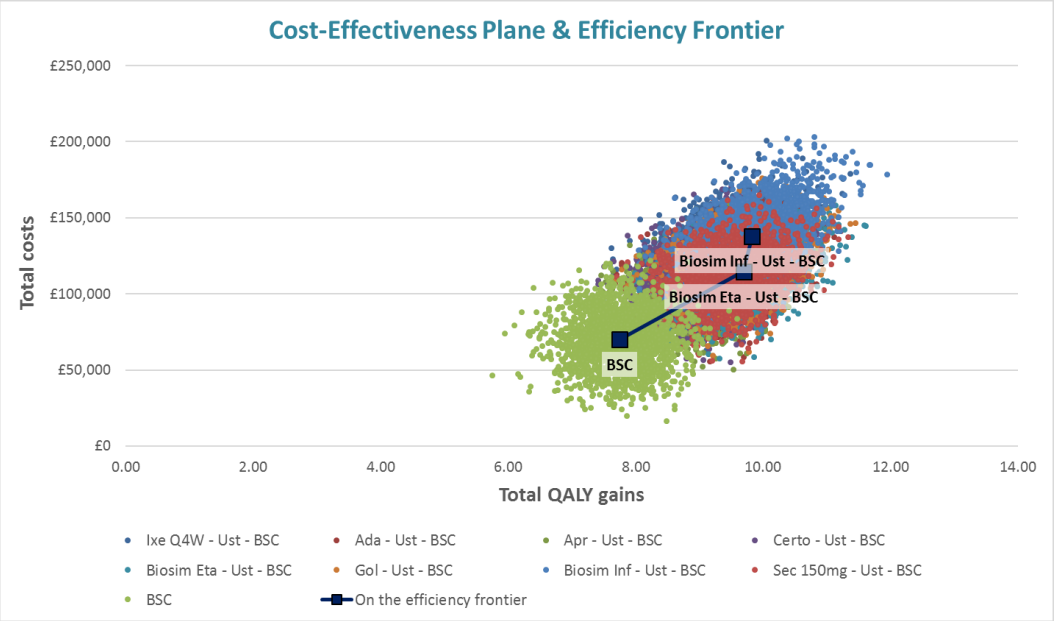


Figure 16 Probabilistic CE plane for biologic-naïve patient population with moderate-to-severe psoriasis

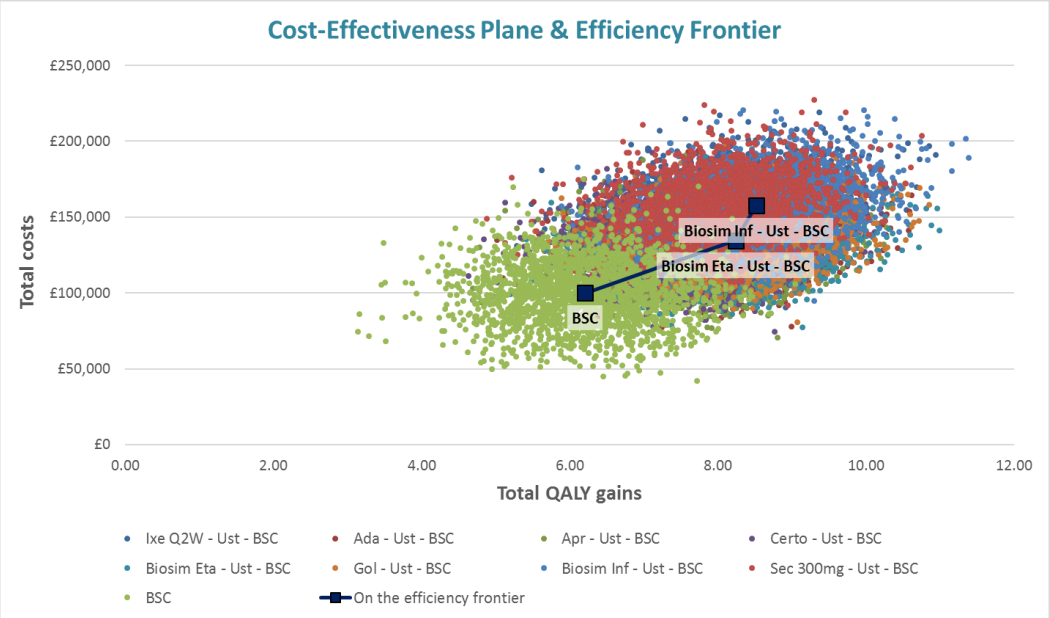


Figure 17 Probabilistic CE plane for biologic-experienced patient population with no psoriasis

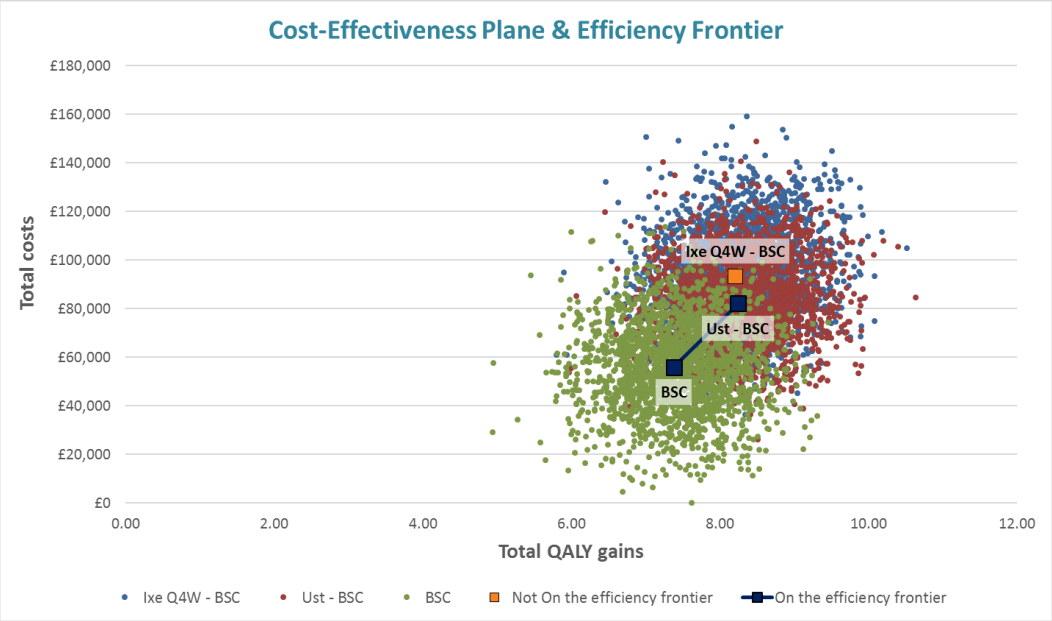


Figure 18 Probabilistic CE plane for biologic-experienced patient population with mild-to-moderate psoriasis

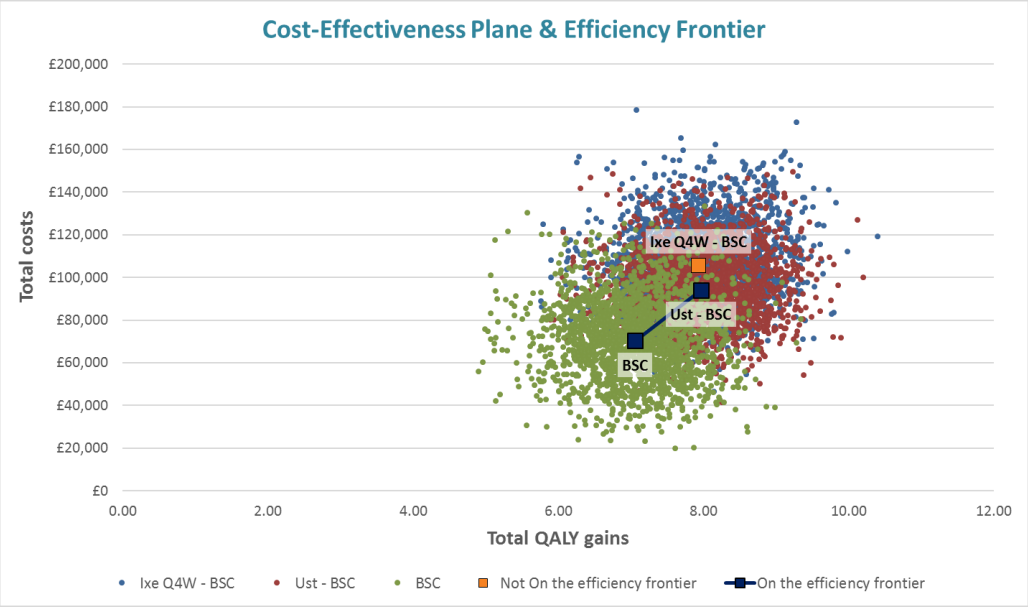


Figure 19 Probabilistic CE plane for biologic-experienced patient population with moderate-to-severe psoriasis

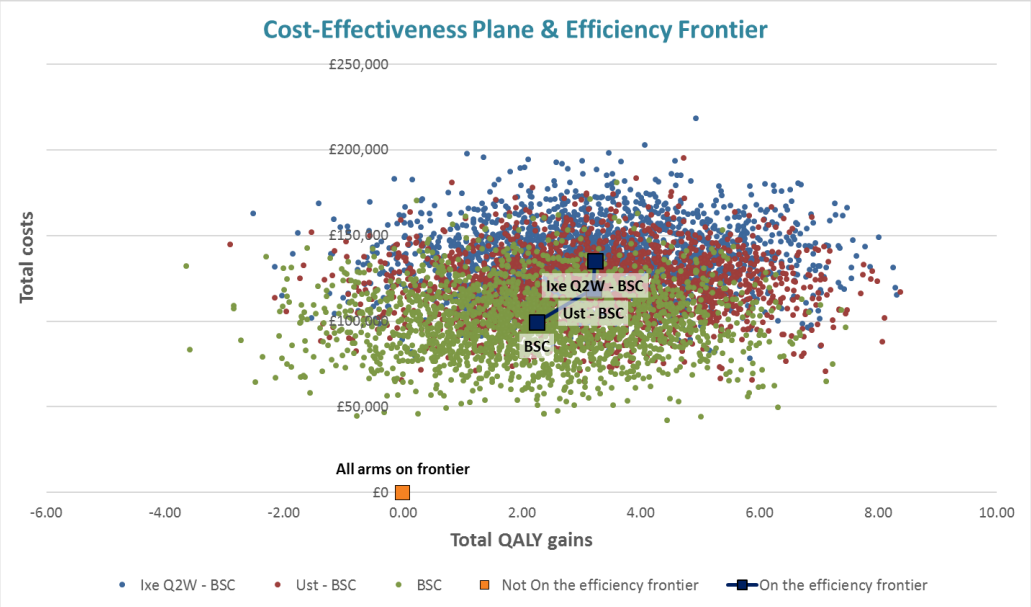


Figure 20 CEAC for biologic-naïve patient population with no psoriasis

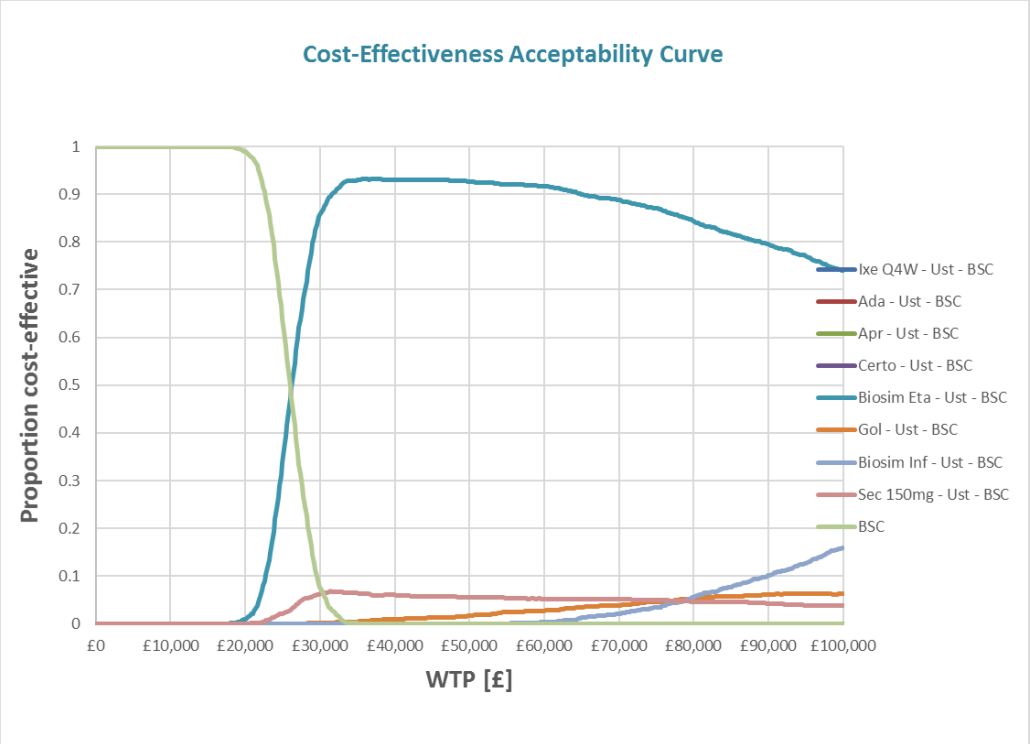


Figure 21 CEAC for biologic-naïve patient population with mild-to-moderate psoriasis

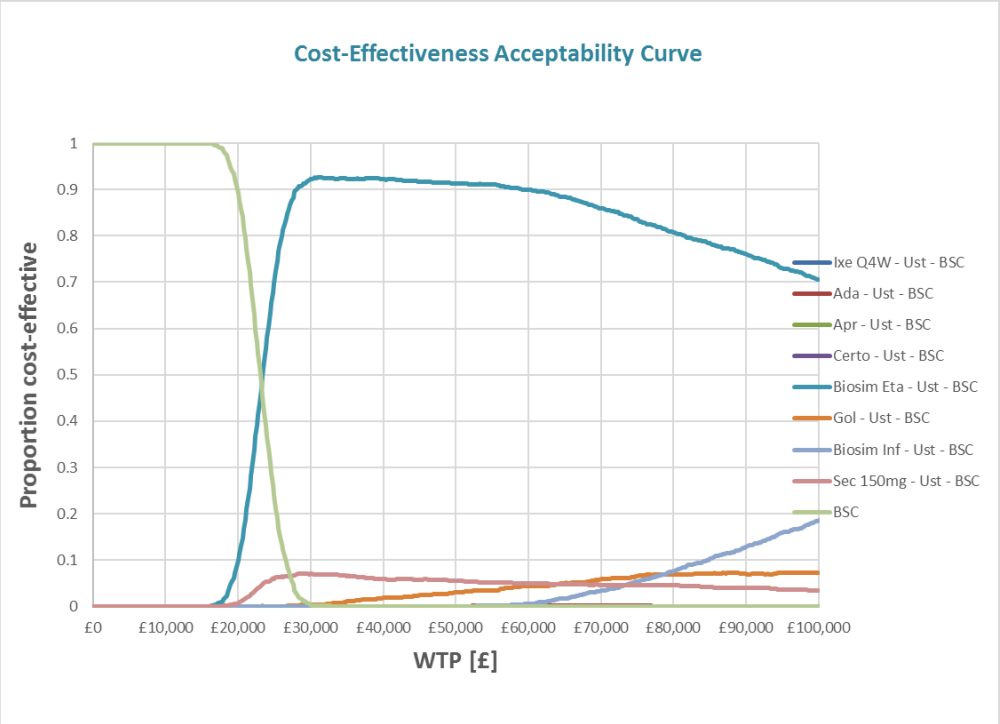


Figure 22 CEAC for biologic-naïve patient population with moderate-to-severe psoriasis

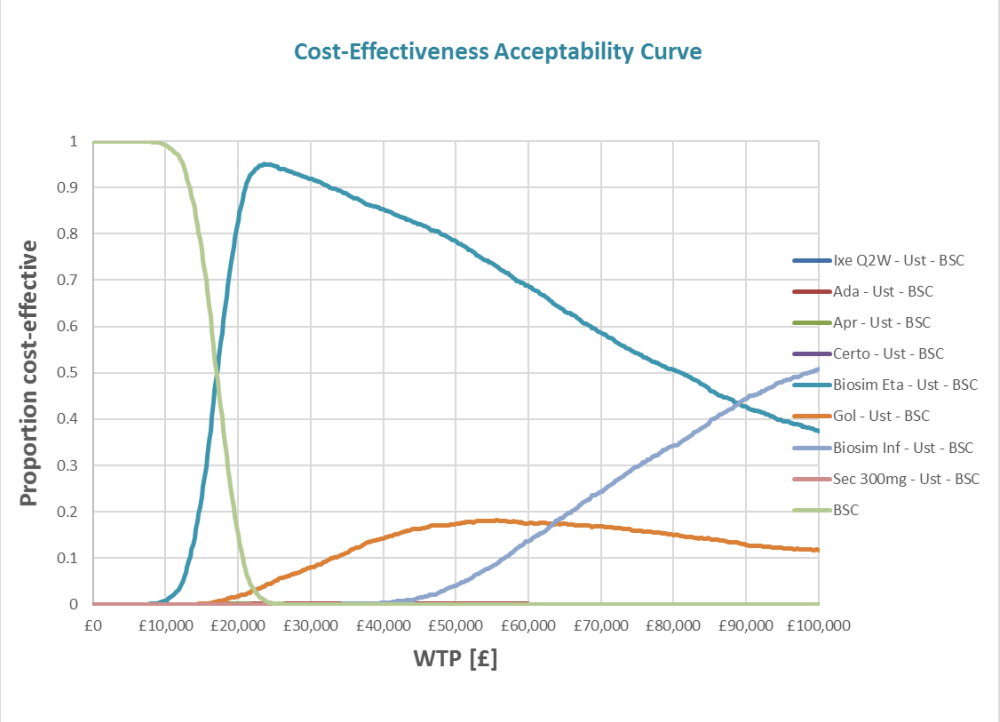


Figure 23 CEAC for biologic-experienced patient population with no psoriasis

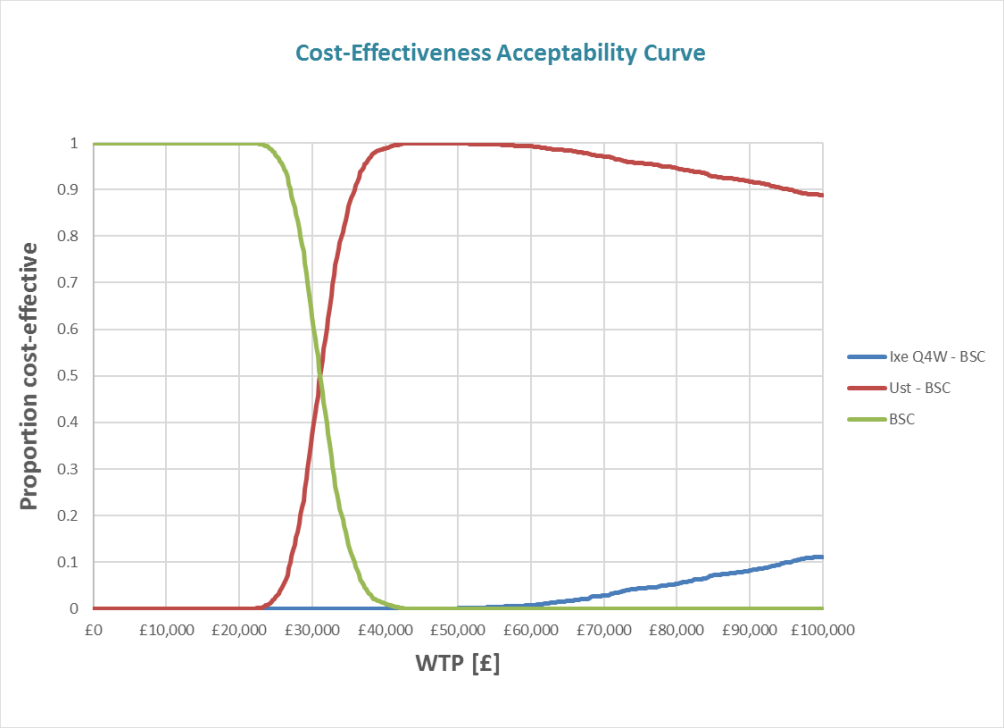


Figure 24 CEAC for biologic-experienced patient population with mild-to-moderate psoriasis

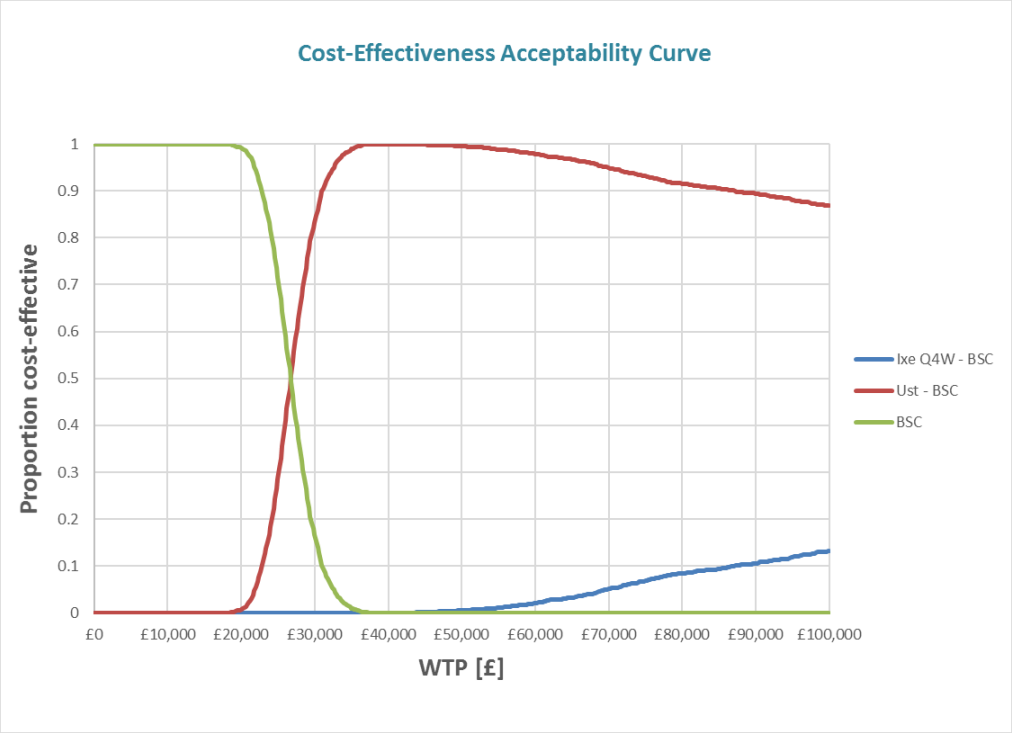
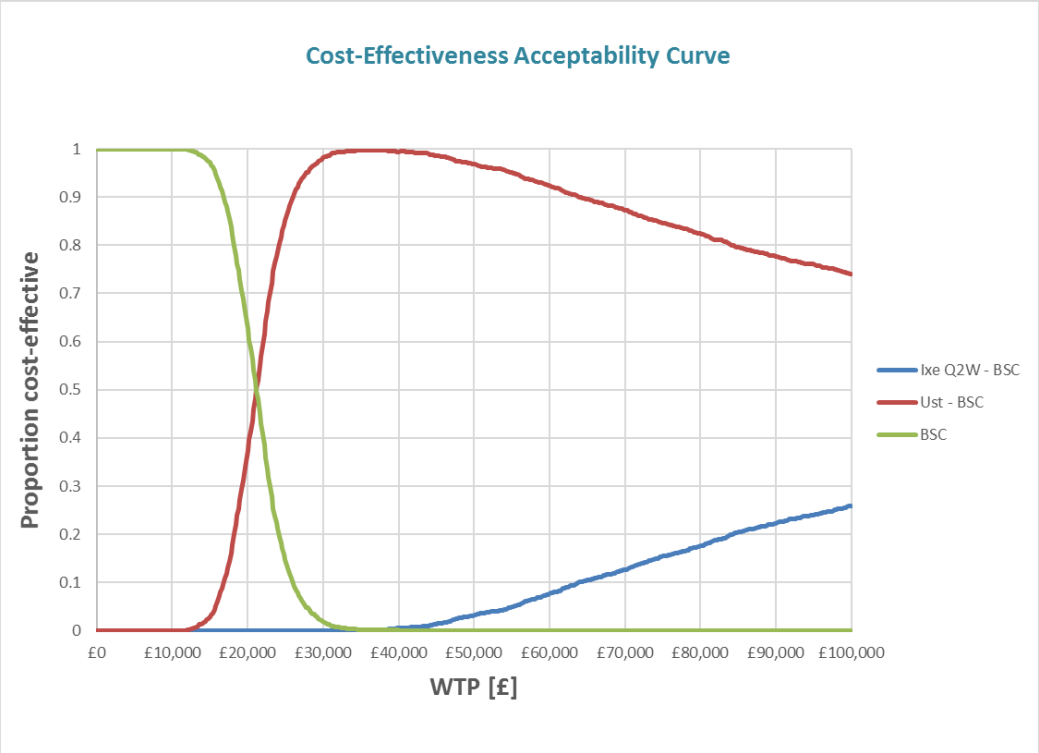


Figure 25 CEAC for biologic-experienced patient population with moderate-to-severe psoriasis



3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were undertaken to assess the impact of key variables on the model outcomes. The annual discontinuation rate is varied between the upper and lower limits of the 95% confidence interval and for other parameters, values were varied by either plus or minus 20% from the base-case value or by plus or minus one unit.

The parameters varied in the DSA are presented in Table 58. Tornado diagrams depicting the one-way sensitivity analyses results for the ixekizumab sequence versus secukinumab are presented in Figure 26, Figure 27 and Figure 28 in the bDMARD-naïve subgroups. The results for ixekizumab versus ustekinumab are presented in Figure 29, Figure 30 and Figure 31 in the bDMARD-experienced subgroups.

Table 58 DSA inputs

Category	Parameter	Mean	Upper bound	Lower bound	Comment
Model settings	Discount rate QALYS	3.5%	0%	6%	Assumption
	Discount rate costs	3.5%	0%	6%	Assumption
	Mean weight	87.02	69.6	104.4	± 20% of mean value
	Annual discontinuation rate	16.5%	4.7%	42.8%	Rodgers et al 2011 (96)

Category	Parameter	Mean	Upper bound	Lower bound	Comment
	Annual HAQ progression	0.072	0.065	0.079	± 0.007, Corbett
Utility model coefficients – bDMARD-naive	Utility regression intercept	[redacted]	[redacted]	[redacted]	± SE
	Utility HAQ coefficient	[redacted]	[redacted]	[redacted]	± SE
	Utility PASI coefficient	[redacted]	[redacted]	[redacted]	± SE
Utility model coefficients – bDMARD-experienced	Utility regression intercept	[redacted]	[redacted]	[redacted]	± SE
	Utility HAQ coefficient	[redacted]	[redacted]	[redacted]	± SE
	Utility PASI coefficient	[redacted]	[redacted]	[redacted]	± SE
	PsARC-PASI75 correlation coefficient	0.400	0.000	0.787	Lower = 0, upper calculated from trt in seq, min of upper bounds
Drug costs (pack)	Ixekizumab Q2W	1125.00	900.0	1350.00	± 20% of mean value
	Ixekizumab Q2W	1125.00	900.0	1350.00	± 20% of mean value
	Adalimumab	704.28	563.4	845.1	± 20% of mean value
	Apremilast	550.00	440.0	660.0	± 20% of mean value
	Certolizumab pegol	715.00	572.0	858.0	± 20% of mean value
	Etanercept 50 mg (biosimilar)	656.00	524.8	787.2	± 20% of mean value
	Golimumab	762.97	610.4	915.6	± 20% of mean value
	Infliximab (biosimilar)	377.00	301.6	452.4	± 20% of mean value
	Ustekinumab	2147.00	1717.6	2576.4	± 20% of mean value
	Secukinumab 150mg	1218.78	975.0	1462.5	± 20% of mean value
	Secukinumab 300mg	1218.78	975.0	1462.5	± 20% of mean value
	Cost of self-admin training	43.00	34.4	51.6	± 20% of mean value
	Cost of physician visit for IV	236.19	189.0	283.4	± 20% of mean value
	Cost of Office visit (MD)	142.74	114.2	171.3	± 20% of mean value
	Kobelt HAQ regression constant	565.64	452.5	678.8	± 20% of mean value
	Kobelt HAQ regression intercept	1867.56	1494.0	2241.1	± 20% of mean value
	Corbett PASI cost uncontrolled psoriasis	892.00	713.6	1070.4	± 20% of mean value
	Corbett PASI cost controlled psoriasis	72.00	57.6	86.4	± 20% of mean value
	Kobelt cost adjustment factor	0.85	0.8	0.9	± 10% of mean value
Monitoring costs	Cost of full blood count	3.00	2.4	3.6	± 20% of mean value

Category	Parameter	Mean	Upper bound	Lower bound	Comment
	Cost of liver function test	1.00	0.8	1.2	± 20% of mean value
	Cost of ESR	3.00	2.4	3.6	± 20% of mean value
	Cost of urea and electrolytes test	1.00	0.8	1.2	± 20% of mean value
	Cost of X-Ray	30.00	24.0	36.0	± 20% of mean value
	Cost of ANA	3.00	2.4	3.6	± 20% of mean value
	Cost of dsDNA	3.00	2.4	3.6	± 20% of mean value
SC administration monitoring frequency	Monitoring: Number of FBC - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of LFT - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of ESR - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of U&E - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of X-Ray - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of TB Heaf test - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of ANA - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of dsDNA- trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of FBC - continuous treatment	2	1	3	± 1 test - assumption
	Monitoring: Number of LFT - continuous treatment	2	1	3	± 1 test - assumption
	Monitoring: Number of ESR - continuous treatment	2	1	3	± 1 test - assumption
	Monitoring: Number of U&E - continuous treatment	2	1	3	± 1 test - assumption
Oral administration monitoring frequency	Monitoring: Number of FBC - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of LFT - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of ESR - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of U&E - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of X-Ray - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of TB Heaf test - trial period	1	0	2	± 1 test - assumption

Category	Parameter	Mean	Upper bound	Lower bound	Comment
	Monitoring: Number of ANA - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of dsDNA- trial period	1	0	2	± 1 test - assumption
IV administration monitoring frequency	Monitoring: Number of FBC - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of LFT - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of ESR - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of U&E - trial period	2	1	3	± 1 test - assumption
	Monitoring: Number of X-Ray - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of TB Heaf test - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of ANA - trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of dsDNA- trial period	1	0	2	± 1 test - assumption
	Monitoring: Number of FBC - continuous treatment	2	1	3	± 1 test - assumption
	Monitoring: Number of LFT - continuous treatment	2	1	3	± 1 test - assumption
	Monitoring: Number of ESR - continuous treatment	2	1	3	± 1 test - assumption
	Monitoring: Number of U&E - continuous treatment	2	1	3	± 1 test - assumption
Physician Visits	SC administration, trial period	2	1	3	± 1 visit - assumption
	IV administration, trial period	2	1	3	± 1 visit - assumption
Ixekizumab Q2W (bDMARD-naïve)	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Ixekizumab Q4W(bDMARD-naïve)	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value

Category	Parameter	Mean	Upper bound	Lower bound	Comment
Ixekizumab Q2W (bDMARD-experienced)	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Ixekizumab Q4W (bDMARD-experienced)	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Adalimumab	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Etanercept 50 mg QW	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Infliximab	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Secukinumab 150 mg	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Secukinumab 300 mg	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value

Category	Parameter	Mean	Upper bound	Lower bound	Comment
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Golimumab	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Apremilast	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Certolizumab pegol	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
BSC	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value
Ustekinumab	PsARC	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI75	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI90	[redacted]	[redacted]	[redacted]	± 10% of mean value
	PsARC and PASI100	[redacted]	[redacted]	[redacted]	± 10% of mean value

Figure 26 Tornado diagram: bDMARD-naïve subgroup with no psoriasis; ixekizumab Q4W sequence versus secukinumab 150 mg sequence

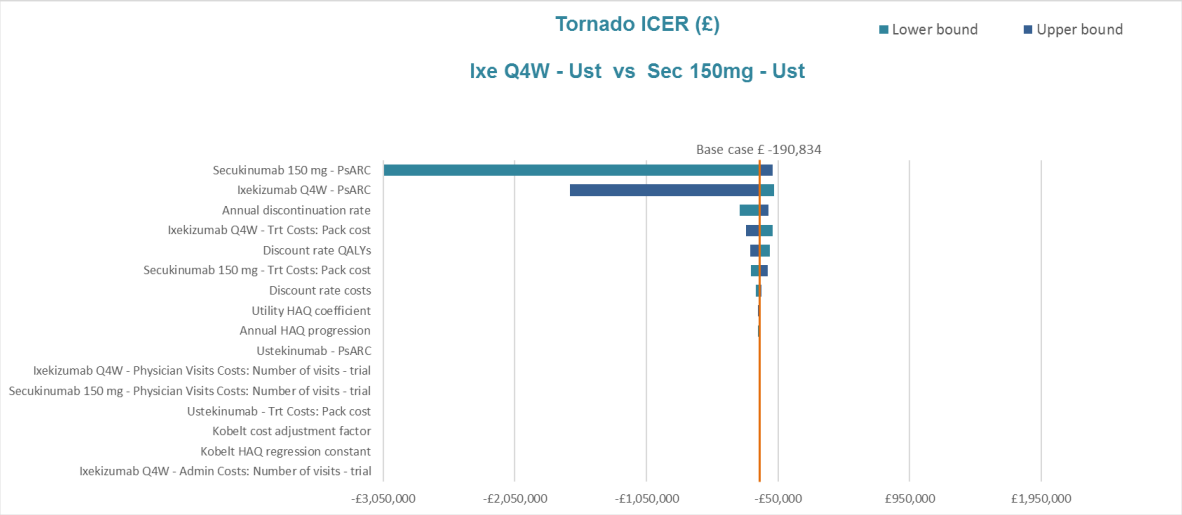


Figure 27 Tornado diagram: bDMARD-naïve subgroup with mild-to-moderate psoriasis; ixekizumab Q4W sequence versus secukinumab 150 mg sequence

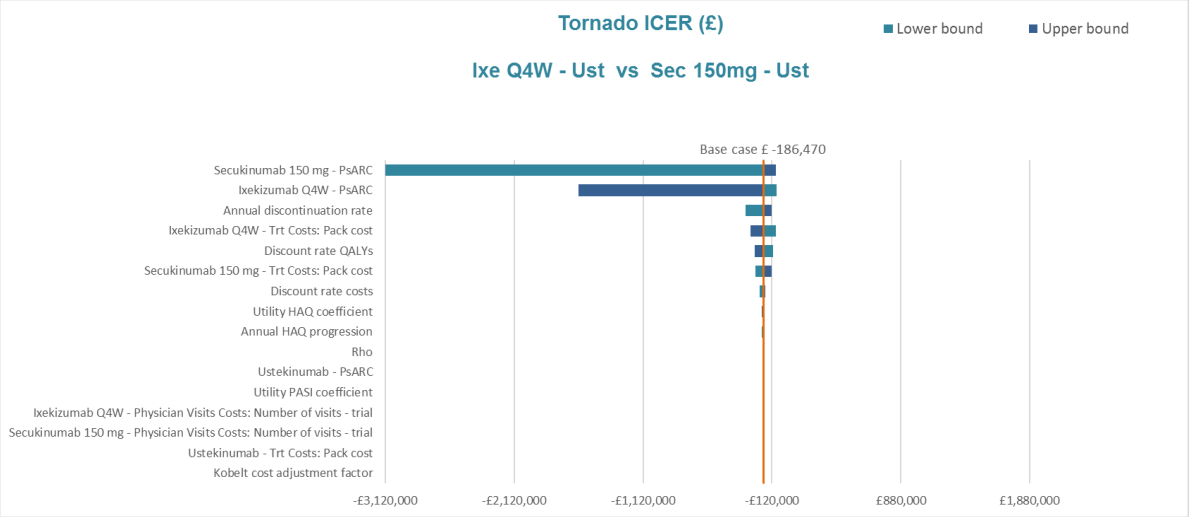


Figure 28 **Tornado diagram: bDMARD-naïve subgroup with moderate-to-severe psoriasis; ixekizumab Q2W sequence versus secukinumab 300 mg sequence**

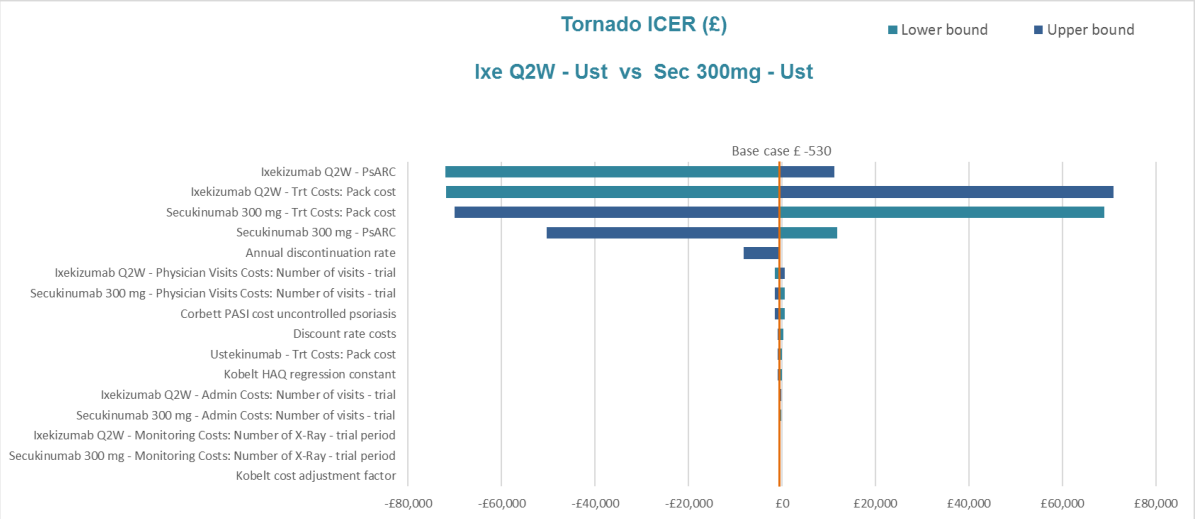


Figure 29 **Tornado diagram: bDMARD-experienced subgroup with no psoriasis; ixekizumab Q4W sequence versus ustekinumab sequence**

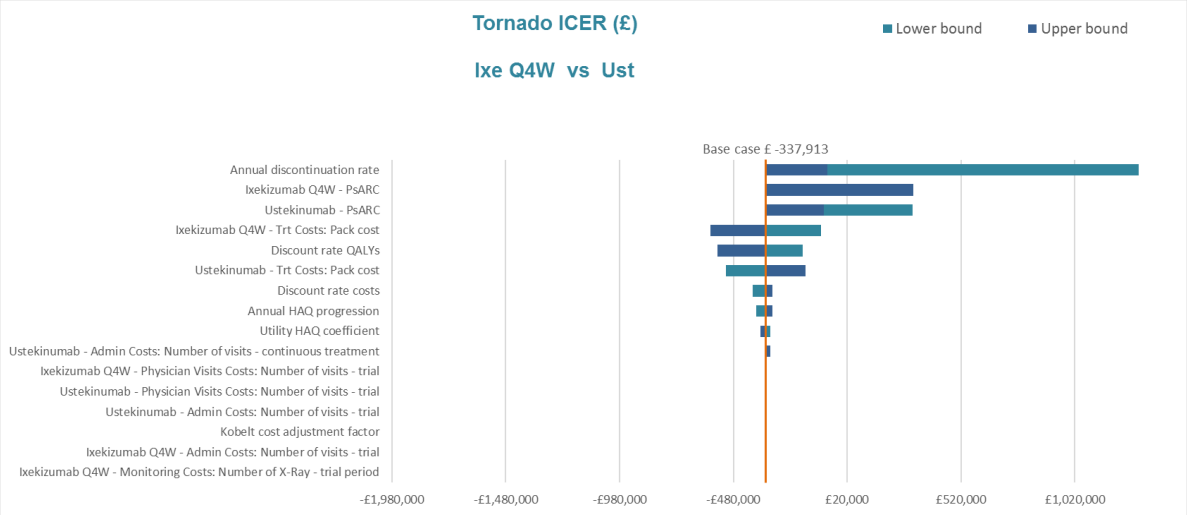


Figure 30 Tornado diagram: bDMARD-experienced subgroup with mild-to-moderate psoriasis; ixekizumab Q4W sequence versus ustekinumab sequence

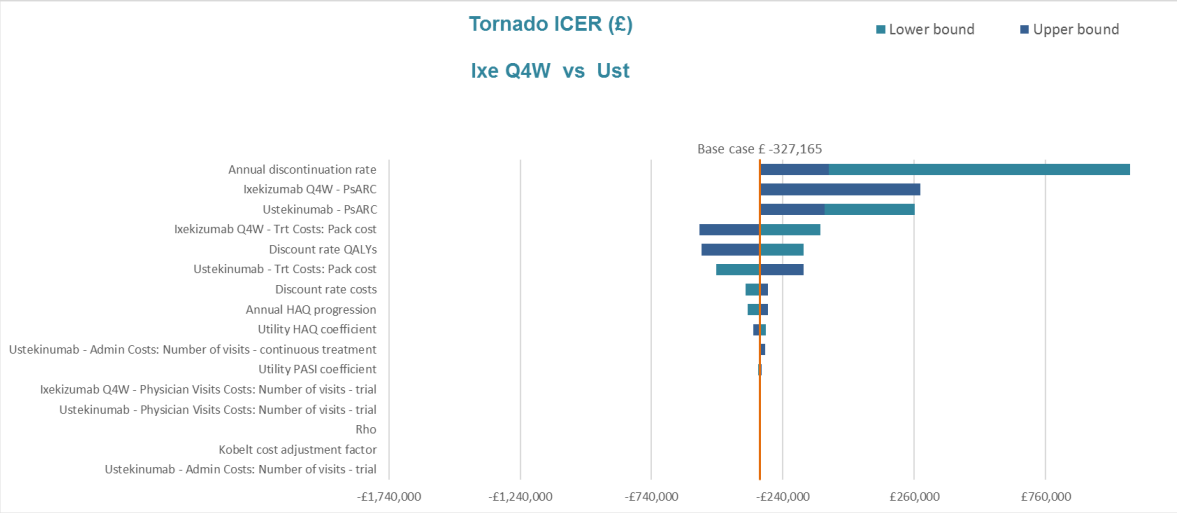
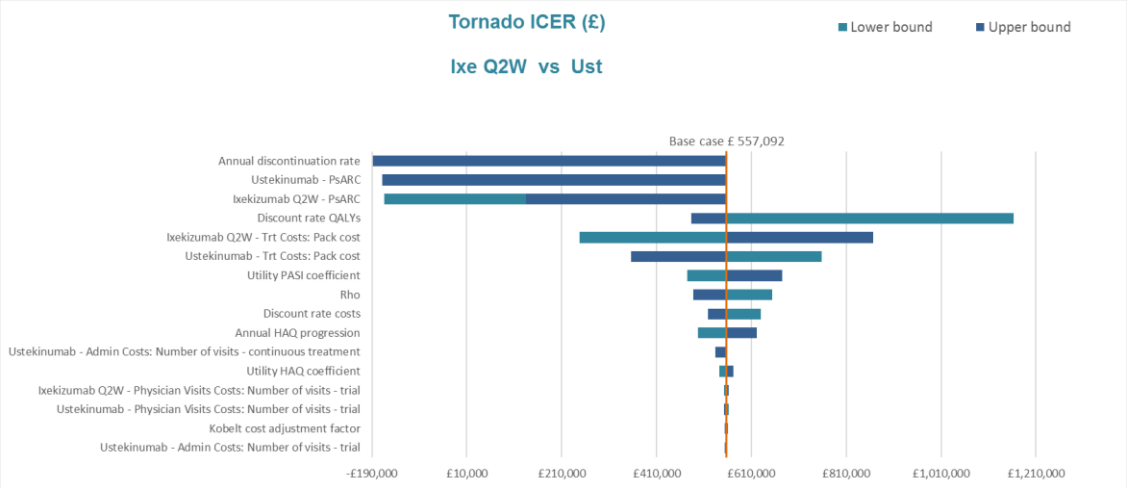


Figure 31 Tornado diagram: bDMARD-experienced subgroup with moderate-to-severe psoriasis; ixekizumab Q2W sequence versus ustekinumab sequence



3.8.3 Scenario analysis

The structural uncertainty was explored by assessing the change in results using alternative assumptions or sources for key input parameters. Each scenario is described in further detail below. As confidential price discounts are in place for ixekizumab, apremilast and secukinumab, list prices are used to inform the results, therefore the results presented below are informative insofar as they describe the directional impact of the scenarios relative to the base case.

Single treatment comparators in the bDMARD-naïve population

A fully incremental analysis was undertaken using single treatment comparators followed by BSC using the list price of ixekizumab and base case model settings. Ixekizumab is associated with the second highest cost of the comparator set when the list price is used and is dominated in the fully incremental analysis in all subgroups. In all subgroups, there is less than a difference of one QALY between the active treatments associated with the least and most QALYs. Consequently, the use of the list price of ixekizumab, which overestimates the cost to the NHS, and the small denominators in the ICER calculations between treatments drive the large pairwise ICERs between ixekizumab and other treatments and the dominance of some treatments over ixekizumab.

Table 59 Single treatment comparators in bDMARD-naïve population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) IXE vs comparator
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	£45,498
Apremilast	£69,794	8.73	£15,748	0.63	Extendedly dominated	£104,700
Certolizumab pegol	£77,054	8.93	£23,008	0.84	Extendedly dominated	£1,370,314
Secukinumab 150 mg	£77,468	9.04	£23,422	0.95	Extendedly dominated	IXE dominated
Adalimumab	£78,485	8.97	£24,439	0.88	Dominated	IXE dominated
Etanercept 50 mg QW	£81,662	9.31	£27,616	1.22	£22,629	IXE dominated
Golimumab	£86,414	9.20	£32,368	1.11	Dominated	IXE dominated
Ixekizumab Q4W	£92,827	8.95	£38,781	0.85	Dominated	Referent
Infliximab	£105,554	9.43	£51,508	1.33	£214,711	£26,554 vs IXE
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	£41,175
Apremilast	£83,942	8.40	£13,936	0.65	Extendedly dominated	£95,650
Certolizumab pegol	£90,547	8.61	£20,541	0.86	Extendedly dominated	£665,033
Secukinumab 150 mg	£90,950	8.74	£20,944	0.99	Extendedly dominated	IXE dominated
Adalimumab	£91,998	8.65	£21,992	0.91	Dominated	IXE dominated
Etanercept 50 mg QW	£94,541	8.99	£24,535	1.24	£19,745	IXE dominated
Golimumab	£99,097	8.90	£29,091	1.15	Dominated	IXE dominated
Ixekizumab Q4W	£106,611	8.63	£36,605	0.89	Dominated	Referent
Infliximab	£118,217	9.13	£48,212	1.39	£163,909	£23,304 vs IXE
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	£32,985
Apremilast	£110,161	6.94	£10,277	0.73	Extendedly	£64,488

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) IXE vs comparator
					dominated	
Certolizumab pegol	£115,503	7.17	£15,619	0.96	Extendedly dominated	£109,947
Adalimumab	£116,994	7.24	£17,110	1.03	Extendedly dominated	£156,219
Etanercept 50 mg QW	£118,270	7.54	£18,386	1.33	£13,802	IXE dominated
Golimumab	£122,435	7.54	£22,551	1.33	Extendedly dominated	IXE dominated
Secukinumab 300 mg	£138,401	7.23	£38,517	1.02	Dominated	£991
Ixekizumab Q2W	£138,548	7.38	£38,664	1.17	Dominated	Referent
Infliximab	£141,516	7.82	£41,632	1.62	£81,647	£6,675 vs IXE

Meta-regression in bDMARD-naïve population: placebo response adjustment

Table 60 Single treatment comparators in bDMARD-naïve population; placebo-adjusted response rate

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs ixekizumab
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	£45,364
Apremilast	£70,479	8.75	£16,433	0.66	Extendedly dominated	£108,327
Adalimumab	£77,716	8.94	£23,670	0.85	Extendedly dominated	£589,061
Certolizumab pegol	£80,571	9.06	£26,525	0.96	Extendedly dominated	IXE dominated
Biosimilar etanercept	£81,362	9.30	£27,316	1.21	£22,642	IXE dominated
Secukinumab 150 mg	£82,824	9.30	£28,778	1.21	Extendedly dominated	IXE dominated
Golimumab	£83,070	9.08	£29,024	0.99	Dominated	IXE dominated
Ixekizumab Q4W	£93,809	8.97	£39,763	0.88	Dominated	Referent
Biosimilar infliximab	£102,862	9.35	£48,816	1.26	£435,678	£23,870 vs IXE
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	£41,041
Apremilast	£84,535	8.43	£14,529	0.68	Extendedly dominated	£98,895
Adalimumab	£91,313	8.63	£21,307	0.88	Extendedly dominated	£504,018
Certolizumab pegol	£93,689	8.74	£23,683	1.00	Extendedly dominated	IXE dominated
Biosimilar etanercept	£94,277	8.97	£24,271	1.23	£19,775	IXE dominated
Secukinumab 150 mg	£95,600	9.00	£25,595	1.25	£50,281	IXE dominated
Golimumab	£96,116	8.77	£26,110	1.02	Dominated	IXE dominated
Ixekizumab Q4W	£107,530	8.66	£37,524	0.91	Dominated	Referent
Biosimilar infliximab	£115,719	9.05	£45,713	1.30	£413,267	£21,104 vs IXE
bDMARD-naïve; moderate-to-severe						

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs ixekizumab
psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	£32,819
Apremilast	£110,566	6.97	£10,682	0.77	Extendedly dominated	£66,092
Adalimumab	£116,477	7.22	£16,593	1.02	Extendedly dominated	£124,873
Certolizumab pegol	£117,896	7.35	£18,012	1.14	Extendedly dominated	£351,040
Biosimilar etanercept	£118,078	7.52	£18,194	1.31	£13,871	IXE dominated
Golimumab	£120,180	7.36	£20,296	1.16	Dominated	£423,479
Ixekizumab Q2W	£139,290	7.41	£39,406	1.20	Dominated	Referent
Biosimilar infliximab	£139,405	7.70	£39,521	1.50	£116,262	£393 vs IXE
Secukinumab 300 mg	£149,029	7.56	£49,145	1.35	Dominated	£64,468 vs IXE

Response assessment for ixekizumab at 16 weeks

The SmPC for ixekizumab in psoriasis states that if response is not achieved by 16-20 weeks, discontinuation should be considered. (1) In the main analysis, a 12 week stopping rule is implemented for ixekizumab. This aligns with the main time point for PsARC assessment in the SPIRIT trials and the stopping rule for TNF-alpha inhibitors recommended by NICE in PsA (Table 38). Similarly, Novartis' model submitted to the MTA used a 12 week stopping rule for secukinumab, which contrasts with the 16 week stopping rule in the SmPC. (115)

In this scenario analysis, efficacy data at week 16 are used for ixekizumab and time points for other treatments are kept the same. A response assessment timepoint of 16 weeks is associated with greater costs and QALYs for the ixekizumab sequence relative to the base case. When the list price is used, this scenario does not affect the positioning of the ixekizumab sequence with respect to the cost-effectiveness frontier in all model subgroups.

Table 61 Scenario analysis: week 16 response assessment for ixekizumab

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs ixekizumab sequence
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	£38,790
APR-UST-BSC	£93,826	9.50	£39,780	1.41	Extendedly dominated	£99,524
CZP-UST-BSC	£100,314	9.68	£46,268	1.59	Extendedly dominated	£273,093
SEC 150-UST-BSC	£100,708	9.79	£46,662	1.70	Extendedly dominated	IXE dominated

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs ixekizumab sequence
ADA-UST-BSC	£101,236	9.70	£47,190	1.61	Dominated	£358,403
ETN-UST-BSC	£104,122	10.03	£50,076	1.94	£25,817	IXE dominated
GOL-UST-BSC	£108,624	9.91	£54,578	1.82	Dominated	IXE dominated
IXE Q4W-UST-BSC	£118,286	9.75	£64,240	1.66	Dominated	Referent
INF-UST-BSC	£127,744	10.13	£73,698	2.04	£236,798	£24,673 vs IXE sequence
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	£35,342
APR-UST-BSC	£105,869	9.18	£35,864	1.43	Extendedly dominated	£90,867
CZP-UST-BSC	£111,773	9.36	£41,767	1.61	Extendedly dominated	£225,329
SEC 150-UST-BSC	£112,156	9.48	£42,150	1.74	Extendedly dominated	IXE dominated
ADA-UST-BSC	£112,773	9.38	£42,767	1.64	Dominated	£305,347
ETN-UST-BSC	£115,038	9.71	£45,033	1.96	£22,947	IXE dominated
GOL-UST-BSC	£119,368	9.61	£49,362	1.86	Dominated	IXE dominated
IXE Q4W-UST-BSC	£129,913	9.44	£59,907	1.70	Dominated	Referent
INF-UST-BSC	£138,471	9.84	£68,465	2.10	£176,607	£21,391 vs IXE sequence
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	£29,008
APR-UST-BSC	£127,889	7.72	£28,005	1.51	Extendedly dominated	£58,770
CZP-UST-BSC	£132,671	7.92	£32,787	1.71	Extendedly dominated	£80,108
ADA-UST-BSC	£133,825	7.97	£33,941	1.76	Extendedly dominated	£90,421
ETN-UST-BSC	£134,851	8.26	£34,967	2.05	£17,037	IXE dominated
GOL-UST-BSC	£138,835	8.25	£38,951	2.04	Dominated	IXE dominated
SEC 300-UST-BSC	£155,966	8.00	£56,082	1.79	Dominated	£12,392
INF-UST-BSC	£157,907	8.53	£58,023	2.32	£84,811	IXE dominated
IXE Q2W-UST-BSC	£159,095	8.25	£59,211	2.04	Dominated	Referent
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	£44,892
Ustekinumab	£82,623	8.26	£26,681	0.88	£30,220	IXE dominated
Ixekizumab Q4W	£95,031	8.25	£39,088	0.87	Dominated	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs ixekizumab sequence
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	£40,192
Ustekinumab	£94,559	7.99	£24,287	0.93	£26,143	IXE dominated
Ixekizumab Q4W	£107,139	7.98	£36,867	0.92	Dominated	Referent
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	£37,157
Ustekinumab	£119,233	3.23	£19,615	0.97	£20,214	IXE dominated
Ixekizumab Q2W	£133,666	3.17	£34,048	0.92	Dominated	Referent

Inclusion of secukinumab and certolizumab pegol in biologic-experienced in patient population

Secukinumab and certolizumab pegol are both recommended for use in the treatment of PsA in patients whose disease has not responded to a prior TNF-alpha inhibitor. The recommendation for certolizumab pegol specifies that in order to receive treatment with certolizumab pegol following inadequate response on a prior TNF-alpha inhibitor, patients' disease must have responded within the first 12 weeks of prior treatment and subsequently failed to respond after 12 weeks (i.e. secondary non-response). This reflects the exclusion of patients with primary non-response on a prior TNF-alpha inhibitor from the RAPID-PsA trial. In contrast, in order to receive secukinumab, inadequate response on a prior TNF-alpha inhibitor could have occurred within the first 12 weeks or after the first 12 weeks.

Biologic-experienced subgroup data at week 12 and 16 for certolizumab pegol and secukinumab, respectively, were not published at the time of the NMA being conducted. To facilitate a comparison with ixekizumab, overall population data for certolizumab pegol and secukinumab have been used to inform the biologic-experienced network. As the overall population for both the RAPID-PsA trial and FUTURE-2 trials comprised mainly biologic-naïve patients, these treatment are considered only in a scenario analysis and not in the base case biologic-experienced network.

When these treatment sequences are considered, only the certolizumab pegol and ustekinumab sequences lie on the CE frontier when list prices are used for both IL-17s. The ixekizumab sequence dominates the secukinumab sequence and is also associated with more QALYs than the certolizumab pegol sequence; however, as per the base case, when

using the list price of ixekizumab, the ixekizumab sequence is dominated by the ustekinumab sequence.

Table 62 Scenario analysis: inclusion of secukinumab and certolizumab pegol in bDMARD-experienced

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs ixekizumab
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	£44,182
Certolizumab pegol	£80,329	8.27	£24,387	0.90	£27,197	£211,521
Ustekinumab	£85,799	8.38	£29,857	1.01	£50,168	IXE dominated
Ixekizumab Q4W	£99,580	8.37	£43,638	0.99	Dominated	Referent
Secukinumab 300 mg	£103,621	8.29	£47,679	0.91	Dominated	Dominated by IXE
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	£36,508
Certolizumab pegol	£91,990	8.10	£21,719	1.05	£20,778	£241,378
Ustekinumab	£97,374	8.23	£27,103	1.17	£43,069	IXE dominated
Ixekizumab Q4W	£111,363	8.18	£41,091	1.13	Dominated	Referent
Secukinumab 300 mg	£115,570	8.11	£45,298	1.05	Dominated	Dominated by IXE
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	£23,258
Certolizumab pegol	£116,121	3.88	£16,503	1.62	£10,195	£199,670
Ustekinumab	£121,338	4.08	£21,720	1.82	£26,082	IXE dominated
Ixekizumab Q2W	£140,053	3.99	£40,435	1.74	Dominated	Referent
Secukinumab 300 mg	£140,265	3.87	£40,648	1.62	Dominated	Dominated by IXE

Excess mortality due to PsA

As mortality risk is assumed to be independent of treatment, applying a different source of excess mortality due to PsA or excluding the multiplier affects the costs and benefits of sequences differently due to the differences in the timing of events such as treatment discontinuation. The use of the higher mortality multiplier from Wong et al (1997) reduces both the costs and benefits associated with each treatment as patients proceed to the death state faster relative to the base case analysis. The exclusion of the excess mortality risk due to PsA results in only general UK population background mortality and patients remain on treatment for longer. These scenarios do not affect the position of the ixekizumab sequence

with respect to the CE frontier, i.e. the ixekizumab sequence is dominated in all subgroups when the list price is used.

Table 63 Scenario analysis: Wong et al (1997)

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£51,980	7.90	Referent	Referent	Referent	Referent
APR-UST-BSC	£91,077	9.26	£39,097	1.36	Extendedly dominated	£28,725
CZP-UST-BSC	£97,533	9.44	£45,552	1.54	Extendedly dominated	£29,623
SEC150-UST-BSC	£97,930	9.55	£45,950	1.64	Extendedly dominated	£27,934
ADA-UST-BSC	£98,993	9.48	£47,013	1.58	Dominated	£29,831
ETN-UST-BSC	£101,333	9.78	£49,353	1.88	£26,232	£26,232
GOL-UST-BSC	£105,808	9.66	£53,828	1.76	Dominated	£30,592
IXEQ4W-UST-BSC	£113,625	9.47	£61,644	1.56	Dominated	£39,391
INF-UST-BSC	£124,817	9.88	£72,837	1.98	£240,194	£36,802
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£67,400	7.57	Referent	Referent	Referent	Referent
APR-UST-BSC	£102,663	8.95	£35,263	1.38	Extendedly dominated	£25,541
CZP-UST-BSC	£108,535	9.13	£41,135	1.56	Extendedly dominated	£26,340
SEC150-UST-BSC	£108,925	9.25	£41,525	1.68	Extendedly dominated	£24,647
ADA-UST-BSC	£110,013	9.17	£42,613	1.61	Dominated	£26,527
ETN-UST-BSC	£111,796	9.47	£44,396	1.90	£23,323	£23,323
GOL-UST-BSC	£116,099	9.37	£48,699	1.80	Dominated	£27,010
IXEQ4W-UST-BSC	£124,882	9.17	£57,482	1.60	Dominated	£35,893
INF-UST-BSC	£135,093	9.60	£67,693	2.03	£178,104	£33,275
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£96,270	6.08	Referent	Referent	Referent	Referent
APR-UST-BSC	£123,840	7.54	£27,570	1.46	Extendedly dominated	£18,901
CZP-UST-BSC	£128,589	7.74	£32,319	1.66	Extendedly dominated	£19,497
ADA-UST-BSC	£130,102	7.81	£33,833	1.73	Extendedly dominated	£19,557
ETN-UST-BSC	£130,772	8.07	£34,502	1.99	£17,324	£17,324
GOL-UST-BSC	£134,732	8.06	£38,462	1.98	Dominated	£19,413
IXEQ2W-UST-BSC	£151,596	7.95	£55,326	1.87	Dominated	£29,610
SEC300-UST-BSC	£151,672	7.81	£55,402	1.73	Dominated	£31,971
INF-UST-BSC	£153,694	8.34	£57,424	2.26	£84,763	£25,386
bDMARD-experienced; no psoriasis						
BSC	£53,846	7.20	Referent	Referent	Referent	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
Ustekinumab	£79,953	8.05	£26,106	0.85	£30,683	£30,683
Ixekizumab Q4W	£91,116	8.02	£37,269	0.82	Dominated	£45,511
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£67,661	6.91	Referent	Referent	Referent	Referent
Ustekinumab	£91,448	7.80	£23,787	0.89	£26,631	£26,631
Ixekizumab Q4W	£102,812	7.77	£35,151	0.86	Dominated	£40,881
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£96,008	2.27	Referent	Referent	Referent	Referent
Ustekinumab	£115,256	3.20	£19,248	0.93	£20,629	£20,629
Ixekizumab Q2W	£131,333	3.23	£35,325	0.96	£539,418	£36,687

Table 64 Scenario analysis: no excess mortality due to PsA

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£57,427	8.40	Referent	Referent	Referent	Referent
APR-UST-BSC	£97,010	9.83	£39,583	1.44	Extendedly dominated	£27,553
CZP-UST-BSC	£103,616	10.02	£46,189	1.63	Extendedly dominated	£28,419
SEC150-UST-BSC	£103,962	10.13	£46,534	1.73	Extendedly dominated	£26,831
ADA-UST-BSC	£105,067	10.06	£47,640	1.66	Dominated	£28,636
ETN-UST-BSC	£107,479	10.38	£50,052	1.98	£25,227	£25,227
GOL-UST-BSC	£112,021	10.26	£54,594	1.86	Dominated	£29,284
IXEQ4W-UST-BSC	£119,832	10.04	£62,405	1.65	Dominated	£37,870
INF-UST-BSC	£131,250	10.48	£73,822	2.09	£230,383	£35,368
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£74,265	8.03	Referent	Referent	Referent	Referent
APR-UST-BSC	£109,948	9.48	£35,683	1.46	Extendedly dominated	£24,500
CZP-UST-BSC	£115,957	9.68	£41,692	1.65	Extendedly dominated	£25,276
SEC150-UST-BSC	£116,295	9.80	£42,030	1.77	Extendedly dominated	£23,683
ADA-UST-BSC	£117,426	9.72	£43,161	1.69	Dominated	£25,472
ETN-UST-BSC	£119,268	10.03	£45,003	2.01	£22,429	£22,429
GOL-UST-BSC	£123,635	9.94	£49,370	1.91	Dominated	£25,871
IXEQ4W-UST-BSC	£132,434	9.71	£58,169	1.68	Dominated	£34,525
INF-UST-BSC	£142,847	10.17	£68,581	2.14	£172,576	£32,001
bDMARD-naïve; moderate-to-severe psoriasis						

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
BSC	£105,782	6.41	Referent	Referent	Referent	Referent
APR-UST-BSC	£133,641	7.94	£27,859	1.53	Extendedly dominated	£18,161
CZP-UST-BSC	£138,503	8.15	£32,722	1.75	Extendedly dominated	£18,752
ADA-UST-BSC	£140,008	8.23	£34,227	1.82	Extendedly dominated	£18,827
ETN-UST-BSC	£140,712	8.50	£34,931	2.09	£16,682	£16,682
GOL-UST-BSC	£144,728	8.49	£38,946	2.09	Dominated	£18,662
IXEQ2W-UST-BSC	£161,699	8.37	£55,918	1.96	Dominated	£28,562
SEC300-UST-BSC	£161,768	8.22	£55,986	1.82	Dominated	£30,819
INF-UST-BSC	£163,907	8.78	£58,125	2.37	£83,455	£24,507
bDMARD-experienced; no psoriasis						
BSC	£59,365	7.65	Referent	Referent	Referent	Referent
Ustekinumab	£85,696	8.54	£26,331	0.88	£29,806	£29,806
Ixekizumab Q4W	£97,009	8.50	£37,644	0.85	Dominated	£44,371
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£74,537	7.30	Referent	Referent	Referent	Referent
Ustekinumab	£98,501	8.23	£23,964	0.93	£25,685	£25,685
Ixekizumab Q4W	£110,020	8.19	£35,483	0.90	Dominated	£39,611
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£105,509	2.23	Referent	Referent	Referent	Referent
Ustekinumab	£124,872	3.20	£19,363	0.97	£19,867	£19,867
Ixekizumab Q2W	£141,120	3.23	£35,611	1.00	£584,547	£35,525

Poole et al (2010) algorithm for healthcare resource use cost

The Poole et al (2010) algorithm reduces the incremental costs of all active treatment sequences versus BSC in all subgroups with the exception of the moderate-to-severe subgroups.

Table 65 Scenario analysis: Poole et al (2010) algorithm

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£33,708	8.09	Referent	Referent	Referent	Referent
APR-UST-BSC	£67,188	9.49	£33,480	1.39	Extendedly dominated	£24,049

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
CZP-UST-BSC	£74,047	9.67	£40,339	1.57	Extendedly dominated	£25,633
SEC150-UST-BSC	£74,460	9.78	£40,752	1.68	Extendedly dominated	£24,233
ADA-UST-BSC	£75,550	9.71	£41,842	1.61	Dominated	£25,957
ETN-UST-BSC	£77,490	10.02	£43,782	1.92	£22,762	£22,762
GOL-UST-BSC	£81,677	9.90	£47,969	1.80	Dominated	£26,613
IXEQ4W-UST-BSC	£90,540	9.69	£56,832	1.60	Dominated	£35,541
INF-UST-BSC	£100,936	10.12	£67,228	2.02	£234,537	£33,224
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£33,708	7.74	Referent	Referent	Referent	Referent
APR-UST-BSC	£67,188	9.16	£33,480	1.41	Extendedly dominated	£23,714
CZP-UST-BSC	£74,047	9.34	£40,339	1.60	Extendedly dominated	£25,247
SEC150-UST-BSC	£74,460	9.47	£40,752	1.72	Extendedly dominated	£23,669
ADA-UST-BSC	£75,550	9.39	£41,842	1.64	Dominated	£25,474
ETN-UST-BSC	£77,490	9.69	£43,782	1.95	£22,501	£22,501
GOL-UST-BSC	£81,677	9.59	£47,969	1.85	Dominated	£25,983
IXEQ4W-UST-BSC	£90,540	9.38	£56,832	1.64	Dominated	£34,744
INF-UST-BSC	£100,936	9.82	£67,228	2.08	£176,057	£32,338
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£34,320	6.21	Referent	Referent	Referent	Referent
APR-UST-BSC	£67,667	7.70	£33,347	1.49	Extendedly dominated	£22,386
CZP-UST-BSC	£74,508	7.90	£40,188	1.69	Extendedly dominated	£23,730
ADA-UST-BSC	£76,010	7.97	£41,690	1.77	Extendedly dominated	£23,605
ETN-UST-BSC	£77,924	8.24	£43,604	2.03	£21,442	£21,442
GOL-UST-BSC	£82,112	8.23	£47,793	2.02	Dominated	£23,606
SEC300-UST-BSC	£97,165	7.97	£62,846	1.77	Dominated	£35,559
IXEQ2W-UST-BSC	£97,626	8.11	£63,307	1.91	Dominated	£33,228
INF-UST-BSC	£101,361	8.51	£67,041	2.31	£85,693	£29,059
bDMARD-experienced; no psoriasis						
BSC	£40,819	7.38	Referent	Referent	Referent	Referent
Ustekinumab	£62,957	8.24	£22,138	0.86	£25,611	£25,611
Ixekizumab Q4W	£74,656	8.21	£33,837	0.83	Dominated	£40,709
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£34,629	7.06	Referent	Referent	Referent	Referent
Ustekinumab	£57,490	7.97	£22,862	0.91	£25,132	£25,132
Ixekizumab Q4W	£69,123	7.93	£34,494	0.87	Dominated	£39,434
bDMARD-						

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
experienced; moderate-to-severe psoriasis						
BSC	£33,404	2.26	Referent	Referent	Referent	Referent
Ustekinumab	£56,423	3.21	£23,019	0.95	£24,224	£24,224
Ixekizumab Q2W	£72,530	3.24	£39,125	0.98	£555,640	£39,955

HAQ-DI rebound scenario assumption in BSC

Assuming a scenario of HAQ-DI rebound to natural history in BSC increases the cost and decreases the QALYs of all active treatments versus BSC whereas the converse is true of a rebound in HAQ-DI of less than the initial gain.

In the bDMARD-naïve population, when HAQ-DI rebounds to natural history, the fully incremental sequences on the frontier are associated with higher ICERs relative to the base case: etanercept and infliximab were associated with the greatest improvements in HAQ-DI in the trial period and are accordingly affected to a greater extent by the rebound to natural history. Similarly, ixekizumab was associated with the third greatest improvement from baseline HAQ-DI for PsARC responders, therefore in the bDMARD-naïve population, pairwise ICERs versus the adalimumab, apremilast, certolizumab pegol and BSC sequences are higher versus the base case. In the bDMARD-experienced population, the rebound of HAQ-DI to natural history results in a slight QALY increase for ixekizumab versus ustekinumab, which contrasts with the base case results in which ustekinumab dominates ixekizumab. Although ixekizumab is associated with a greater improvement in HAQ-DI in PsARC responders in the trial period, the higher PsARC response rate of ustekinumab may account for the positive incremental QALY of ixekizumab relative to ustekinumab.

When HAQ-DI is assumed to rebound to less than the initial gain, the ixekizumab sequence continues to be dominated in the fully incremental analysis for all subgroups (except bDMARD-experience with moderate-to-severe psoriasis) and in pairwise analyses by the same treatment sequences in each subgroup as per the base case. The pairwise ICERs for the ixekizumab sequence when not dominated by other sequences and the ICERs all treatment sequences on the CE frontier are lower than the base case.

Table 66 Scenario analysis: HAQ-DI rebound to natural history

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	Referent
APR-UST-BSC	£95,152	8.85	£41,106	0.76	Extendedly dominated	£54,065
CZP-UST-BSC	£101,819	8.98	£47,773	0.89	Extendedly dominated	£53,677
SEC150-UST-BSC	£102,212	9.09	£48,166	0.99	Extendedly dominated	£48,558
ADA-UST-BSC	£103,270	9.02	£49,224	0.93	Dominated	£52,915
ETN-UST-BSC	£105,819	9.27	£51,773	1.18	£43,911	£43,911
GOL-UST-BSC	£110,378	9.13	£56,332	1.04	Dominated	£54,251
IXEQ4W-UST-BSC	£117,882	9.04	£63,836	0.94	Dominated	£67,644
INF-UST-BSC	£129,493	9.35	£75,446	1.25	£312,389	£60,126
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	Referent
APR-UST-BSC	£107,251	8.52	£37,245	0.78	Extendedly dominated	£47,750
CZP-UST-BSC	£113,328	8.66	£43,322	0.91	Extendedly dominated	£47,395
SEC150-UST-BSC	£113,714	8.78	£43,708	1.03	Extendedly dominated	£42,353
ADA-UST-BSC	£114,797	8.71	£44,791	0.96	Dominated	£46,616
ETN-UST-BSC	£116,784	8.95	£46,778	1.20	£38,939	£38,939
GOL-UST-BSC	£121,169	8.83	£51,164	1.08	Dominated	£47,282
IXEQ4W-UST-BSC	£129,649	8.73	£59,643	0.98	Dominated	£60,834
INF-UST-BSC	£140,268	9.06	£70,262	1.31	£215,473	£53,623
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	Referent
APR-UST-BSC	£129,366	7.07	£29,482	0.86	Extendedly dominated	£34,156
CZP-UST-BSC	£134,309	7.22	£34,425	1.02	Extendedly dominated	£33,895
ADA-UST-BSC	£135,814	7.30	£35,930	1.09	Extendedly dominated	£32,958
ETN-UST-BSC	£136,676	7.50	£36,792	1.30	£28,403	£28,403
GOL-UST-BSC	£140,715	7.47	£40,831	1.27	Dominated	£32,229
IXEQ2W-UST-BSC	£157,383	7.44	£57,499	1.23	Dominated	£46,687
SEC300-UST-BSC	£157,403	7.32	£57,519	1.11	Dominated	£51,702
INF-UST-BSC	£159,781	7.75	£59,897	1.54	£92,618	£38,773
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	Referent
Ustekinumab	£83,220	7.84	£27,278	0.46	£58,944	£58,944
Ixekizumab Q4W	£94,300	7.86	£38,358	0.48	£523,890	£79,265
bDMARD-						

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	Referent
Ustekinumab	£95,313	7.53	£25,042	0.47	£53,345	£53,345
Ixekizumab Q4W	£106,587	7.55	£36,315	0.49	£485,082	£73,711
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	Referent
Ustekinumab	£120,114	2.76	£20,496	0.50	£40,764	£40,764
Ixekizumab Q2W	£136,141	2.83	£36,523	0.58	£215,206	£63,268

Table 67 Scenario analysis: HAQ-DI rebound to 50% of initial gain

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	Referent
APR-UST-BSC	£92,426	9.81	£38,380	1.71	Extendedly dominated	£22,387
CZP-UST-BSC	£98,981	9.98	£44,935	1.88	Extendedly dominated	£23,860
SEC150-UST-BSC	£99,359	10.08	£45,313	1.99	Extendedly dominated	£22,766
ADA-UST-BSC	£100,437	10.02	£46,391	1.92	Dominated	£24,137
ETN-UST-BSC	£102,848	10.31	£48,802	2.22	£21,993	£21,993
GOL-UST-BSC	£107,364	10.19	£53,318	2.09	Dominated	£25,469
IXEQ4W-UST-BSC	£115,107	10.01	£61,060	1.92	Dominated	£31,883
INF-UST-BSC	£126,468	10.41	£72,422	2.31	£249,649	£31,302
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	Referent
APR-UST-BSC	£104,525	9.48	£34,519	1.73	Extendedly dominated	£19,906
CZP-UST-BSC	£110,490	9.65	£40,484	1.91	Extendedly dominated	£21,226
SEC150-UST-BSC	£110,861	9.78	£40,856	2.03	Extendedly dominated	£20,121
ADA-UST-BSC	£111,963	9.70	£41,957	1.95	Dominated	£21,488
ETN-UST-BSC	£113,813	9.99	£43,807	2.24	£19,545	£19,545
GOL-UST-BSC	£118,155	9.88	£48,150	2.14	Dominated	£22,530
IXEQ4W-UST-BSC	£126,874	9.70	£56,868	1.95	Dominated	£29,135
INF-UST-BSC	£137,243	10.11	£67,237	2.37	£183,309	£28,381
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
APR-UST-BSC	£126,659	8.02	£26,775	1.81	Extendedly dominated	£14,786
CZP-UST-BSC	£131,491	8.21	£31,607	2.00	Extendedly dominated	£15,788
ADA-UST-BSC	£133,000	8.28	£33,116	2.08	Extendedly dominated	£15,959
ETN-UST-BSC	£133,725	8.53	£33,841	2.33	£14,535	£14,535
GOL-UST-BSC	£137,721	8.52	£37,837	2.31	Dominated	£16,347
IXEQ4W-UST-BSC	£154,575	8.42	£54,691	2.21	Dominated	£24,694
SEC300-UST-BSC	£154,634	8.29	£54,750	2.08	Dominated	£26,299
INF-UST-BSC	£156,777	8.80	£56,893	2.60	£85,951	£21,912
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	Referent
Ustekinumab	£81,154	8.61	£25,212	1.23	£20,444	£20,444
Ixekizumab Q4W	£92,397	8.57	£36,455	1.19	Dominated	£30,541
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	Referent
Ustekinumab	£93,093	8.36	£22,821	1.30	£17,585	£17,585
Ixekizumab Q4W	£104,536	8.32	£34,264	1.26	Dominated	£27,244
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	Referent
Ustekinumab	£117,865	3.60	£18,247	1.34	£13,599	£13,599
Ixekizumab Q2W	£133,559	3.80	£33,941	1.54	£78,958	£22,031

Alternative utility algorithm

The use of the EQ-5D-5L data from the SPIRIT-P1 trial for the bDMARD-naïve population and SPIRIT-P2 trial for the bDMARD-experienced population are associated with greater total QALYs. However, the ICERs increase slightly for all treatments on the CE frontier and pairwise ICERs for the ixekizumab sequences. The magnitude of the intercepts in these equations is greater than those in the mapped EQ-5D-3L utility models and the coefficients estimated for HAQ-DI and PASI are smaller relative to the base case, resulting in a higher baseline utility value. Moreover, the effect of active treatments on disease activity has less of an impact on utility in the 5L algorithms compared to the mapped 3L equations, which may account for the smaller incremental QALYs of sequences relative to BSC.

When the York utility algorithm is selected, the total QALYs associated with each treatment option are lower relative to the base case and the ICERs of the treatments on the frontier and of the pairwise ICERs for the ixekizumab sequences in all subgroups are lower relative

to the base case. The coefficients for HAQ and PASI are greater than the utility model used in the base case. As the effect of active treatment on disease activity has a greater impact on utility compared to the mapped 3L equations, the incremental QALYs of sequences relative to BSC are greater.

Table 68 Coefficients of linear regression of utility versus HAQ-DI and PASI

	Intercept	HAQ-DI	PASI
Source	**Mean**	**Mean**	**Mean**
EQ-5D-5L (bDMARD-naïve: SPIRIT-P1)	[redacted]	[redacted]	[redacted]
EQ-5D-5L (bDMARD-experienced: SPIRIT-P2)	[redacted]	[redacted]	[redacted]
York model	0.897	-0.298	-0.004

Table 69 Scenario analysis: York model coefficients

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£54,046	5.18	Referent	Referent	Referent	Referent
APR-UST-BSC	£93,347	7.28	£39,301	2.10	Extendedly dominated	£18,757
CZP-UST-BSC	£99,866	7.55	£45,819	2.37	Extendedly dominated	£19,345
SEC150-UST-BSC	£100,241	7.71	£46,195	2.53	Extendedly dominated	£18,252
ADA-UST-BSC	£101,322	7.61	£47,276	2.43	Dominated	£19,486
ETN-UST-BSC	£103,692	8.07	£49,646	2.89	£17,149	£17,149
GOL-UST-BSC	£108,195	7.89	£54,149	2.71	Dominated	£19,961
IXEQ4W-UST-BSC	£116,010	7.59	£61,963	2.41	Dominated	£25,747
INF-UST-BSC	£127,297	8.23	£73,251	3.05	£156,887	£24,053
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	4.90	Referent	Referent	Referent	Referent
APR-UST-BSC	£105,446	7.01	£35,440	2.11	Extendedly dominated	£16,788
CZP-UST-BSC	£111,375	7.29	£41,369	2.39	Extendedly dominated	£17,326
SEC150-UST-BSC	£111,743	7.46	£41,738	2.56	Extendedly dominated	£16,284
ADA-UST-BSC	£112,849	7.35	£42,843	2.45	Dominated	£17,483
ETN-UST-BSC	£114,657	7.81	£44,651	2.91	£15,329	£15,329
GOL-UST-BSC	£118,987	7.65	£48,981	2.75	Dominated	£17,826
IXEQ4W-UST-BSC	£127,777	7.34	£57,771	2.44	Dominated	£23,715
INF-UST-BSC	£138,072	7.99	£68,066	3.09	£132,273	£22,029
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	3.63	Referent	Referent	Referent	Referent
APR-UST-BSC	£127,576	5.80	£27,692	2.17	Extendedly	£12,765

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
					dominated	
CZP-UST-BSC	£132,373	6.09	£32,489	2.46	Extendedly dominated	£13,206
ADA-UST-BSC	£133,882	6.17	£33,998	2.55	Extendedly dominated	£13,357
ETN-UST-BSC	£134,567	6.60	£34,683	2.98	£11,644	£11,644
GOL-UST-BSC	£138,550	6.51	£38,666	2.89	Dominated	£13,398
IXEQ2W-UST-BSC	£155,459	6.34	£55,575	2.72	Dominated	£20,454
SEC300-UST-BSC	£155,532	6.15	£55,648	2.53	Dominated	£22,027
INF-UST-BSC	£157,603	6.89	£57,719	3.27	£79,663	£17,663
bDMARD-experienced; no psoriasis						
BSC	£55,942	4.18	Referent	Referent	Referent	Referent
Ustekinumab	£82,143	5.40	£26,201	1.22	£21,462	£21,462
Ixekizumab Q4W	£93,369	5.35	£37,427	1.17	Dominated	£31,882
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	4.78	Referent	Referent	Referent	Referent
Ustekinumab	£94,133	6.05	£23,862	1.28	£18,675	£18,675
Ixekizumab Q4W	£105,562	6.00	£35,291	1.23	Dominated	£28,786
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	3.55	Referent	Referent	Referent	Referent
Ustekinumab	£118,915	4.85	£19,297	1.30	£14,873	£14,873
Ixekizumab Q2W	£135,063	4.87	£35,446	1.32	£769,896	£26,884

Table 70 Scenario analysis: EQ-5D-5L utilities from SPIRIT trials

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£54,046	10.00	Referent	Referent	Referent	Referent
APR-UST-BSC	£93,347	11.31	£39,301	1.31	Extendedly dominated	£29,891
CZP-UST-BSC	£99,866	11.48	£45,819	1.49	Extendedly dominated	£30,829
SEC150-UST-BSC	£100,241	11.59	£46,195	1.59	Extendedly dominated	£29,086
ADA-UST-BSC	£101,322	11.52	£47,276	1.52	Dominated	£31,053
ETN-UST-BSC	£103,692	11.81	£49,646	1.82	£27,328	£27,328
GOL-UST-BSC	£108,195	11.70	£54,149	1.70	Dominated	£31,809
IXEQ4W-UST-BSC	£116,010	11.51	£61,963	1.51	Dominated	£41,030
INF-UST-BSC	£127,297	11.91	£73,251	1.91	£250,012	£38,330
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	9.51	Referent	Referent	Referent	Referent
APR-UST-BSC	£105,446	10.85	£35,440	1.34	Extendedly	£26,401

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
					dominated	
CZP-UST-BSC	£111,375	11.03	£41,369	1.52	Extendedly dominated	£27,218
SEC150-UST-BSC	£111,743	11.15	£41,738	1.64	Extendedly dominated	£25,382
ADA-UST-BSC	£112,849	11.07	£42,843	1.57	Dominated	£27,371
ETN-UST-BSC	£114,657	11.36	£44,651	1.85	£24,164	£24,164
GOL-UST-BSC	£118,987	11.27	£48,981	1.76	Dominated	£27,774
IXEQ4W-UST-BSC	£127,777	11.07	£57,771	1.56	Dominated	£36,994
INF-UST-BSC	£138,072	11.50	£68,066	1.99	£166,179	£34,226
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	7.38	Referent	Referent	Referent	Referent
APR-UST-BSC	£127,576	8.84	£27,692	1.45	Extendedly dominated	£19,048
CZP-UST-BSC	£132,373	9.04	£32,489	1.66	Extendedly dominated	£19,610
ADA-UST-BSC	£133,882	9.13	£33,998	1.74	Extendedly dominated	£19,529
ETN-UST-BSC	£134,567	9.36	£34,683	1.97	£17,573	£17,573
GOL-UST-BSC	£138,550	9.40	£38,666	2.02	Extendedly dominated	£19,176
IXEQ2W-UST-BSC	£155,459	9.28	£55,575	1.90	Dominated	£29,303
SEC300-UST-BSC	£155,532	9.14	£55,648	1.76	Dominated	£31,698
INF-UST-BSC	£157,603	9.70	£57,719	2.31	£68,269	£24,975
bDMARD-experienced; no psoriasis						
BSC	£55,942	9.48	Referent	Referent	Referent	Referent
Ustekinumab	£82,143	10.28	£26,201	0.80	£32,798	£32,798
Ixekizumab Q4W	£93,369	10.25	£37,427	0.77	Dominated	£48,723
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	9.12	Referent	Referent	Referent	Referent
Ustekinumab	£94,133	9.96	£23,862	0.84	£28,367	£28,367
Ixekizumab Q4W	£105,562	9.93	£35,291	0.81	Dominated	£43,620
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	4.30	Referent	Referent	Referent	Referent
Ustekinumab	£118,915	5.19	£19,297	0.88	£21,898	£21,898
Ixekizumab Q2W	£135,063	5.21	£35,446	0.91	£574,009	£38,980

Treatment continuation rule based on PsARC and PASI response rates

Table 71 Scenario analysis: PsARC and PASI 75

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	Referent
APR-UST-BSC	£82,978	9.06	£28,932	0.97	Extendedly dominated	£29,932
ETN-UST-BSC	£83,943	9.12	£29,896	1.02	Extendedly dominated	£29,197
CZP-UST-BSC	£84,119	9.12	£30,073	1.02	Dominated	£29,381
ADA-UST-BSC	£88,657	9.23	£34,611	1.14	Extendedly dominated	£30,404
SEC150-UST-BSC	£93,443	9.48	£39,396	1.38	£28,497	£28,497
GOL-UST-BSC	£95,014	9.42	£40,968	1.33	Dominated	£30,811
IXEQ4W-UST-BSC	£108,754	9.48	£54,708	1.39	Extendedly dominated	£39,487
INF-UST-BSC	£119,009	9.86	£64,962	1.77	£66,028	£36,709
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	Referent
APR-UST-BSC	£96,466	8.75	£26,460	1.01	Extendedly dominated	£26,315
ETN-UST-BSC	£97,331	8.81	£27,325	1.06	Extendedly dominated	£25,686
CZP-UST-BSC	£97,357	8.81	£27,351	1.07	Extendedly dominated	£25,653
ADA-UST-BSC	£101,602	8.93	£31,596	1.19	Extendedly dominated	£26,633
SEC150-UST-BSC	£105,809	9.19	£35,803	1.44	£24,845	£24,845
GOL-UST-BSC	£107,277	9.13	£37,271	1.39	Dominated	£26,816
IXEQ4W-UST-BSC	£121,131	9.19	£51,125	1.44	Extendedly dominated	£35,410
INF-UST-BSC	£130,489	9.59	£60,484	1.84	£61,250	£32,800
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	Referent
APR-UST-BSC	£121,400	7.37	£21,516	1.17	Extendedly dominated	£18,450
CZP-UST-BSC	£121,810	7.45	£21,926	1.24	£17,649	£17,649
ETN-UST-BSC	£122,085	7.44	£22,201	1.23	Dominated	£18,072
ADA-UST-BSC	£125,471	7.59	£25,587	1.38	Extendedly dominated	£18,476
GOL-UST-BSC	£129,782	7.85	£29,898	1.64	£20,066	£18,234
SEC300-UST-BSC	£148,777	7.85	£48,893	1.64	Extendedly dominated	£29,755
IXEQ2W-UST-BSC	£149,656	8.00	£49,772	1.79	Extendedly dominated	£27,797
INF-UST-BSC	£151,432	8.36	£51,548	2.15	£42,203	£23,946
bDMARD-experienced;						

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
no psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	Referent
Ustekinumab	£78,624	8.11	£22,682	0.73	£31,085	£31,085
Ixekizumab Q4W	£79,274	7.86	£23,332	0.48	Dominated	£48,492
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	Referent
Ustekinumab	£91,014	7.90	£20,743	0.84	£24,788	£24,788
Ixekizumab Q4W	£92,400	7.61	£22,129	0.55	Dominated	£39,968
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	Referent
Ustekinumab	£116,582	3.49	£16,965	1.23	£13,744	£13,744
Ixekizumab Q2W	£124,478	3.19	£24,860	0.94	Dominated	£26,537

Table 72 Scenario analysis: PsARC and PASI 90

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	Referent
CZP-UST-BSC	£75,373	8.81	£21,327	0.71	£29,944	£29,944
APR-UST-BSC	£75,981	8.79	£21,935	0.69	Dominated	£31,599
ETN-UST-BSC	£76,120	8.80	£22,074	0.70	Dominated	£31,372
ADA-UST-BSC	£79,242	8.88	£25,196	0.79	Extendedly dominated	£31,926
GOL-UST-BSC	£84,021	9.03	£29,975	0.94	Extendedly dominated	£32,053
SEC150-UST-BSC	£84,743	9.10	£30,697	1.01	£31,805	£30,489
IXEQ4W-UST-BSC	£96,325	9.13	£42,279	1.03	Extendedly dominated	£40,884
INF-UST-BSC	£106,175	9.47	£52,129	1.38	£57,302	£37,751
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	Referent
CZP-UST-BSC	£89,578	8.49	£19,572	0.75	£26,219	£26,219
APR-UST-BSC	£90,329	8.47	£20,323	0.73	Dominated	£27,983
ETN-UST-BSC	£90,424	8.48	£20,418	0.74	Dominated	£27,757
ADA-UST-BSC	£93,240	8.57	£23,234	0.83	Extendedly dominated	£28,058
GOL-UST-BSC	£97,510	8.73	£27,504	0.99	Extendedly dominated	£27,922
SEC150-UST-BSC	£98,202	8.80	£28,196	1.06	£27,696	£26,654
IXEQ4W-UST-BSC	£109,700	8.83	£39,694	1.09	Extendedly dominated	£36,527
INF-UST-BSC	£118,733	9.20	£48,728	1.45	£52,238	£33,585
bDMARD-naïve;						

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
moderate-to-severe psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	Referent
CZP-UST-BSC	£115,963	7.09	£16,079	0.89	£18,102	£18,102
APR-UST-BSC	£116,991	7.07	£17,107	0.86	Dominated	£19,912
ETN-UST-BSC	£117,008	7.07	£17,124	0.87	Dominated	£19,730
ADA-UST-BSC	£119,214	7.20	£19,330	0.99	Extendedly dominated	£19,538
GOL-UST-BSC	£122,467	7.40	£22,583	1.19	£21,392	£18,941
SEC300-UST-BSC	£138,369	7.47	£38,485	1.26	Extendedly dominated	£30,506
IXEQ2W-UST-BSC	£139,861	7.60	£39,977	1.40	Extendedly dominated	£28,589
INF-UST-BSC	£141,830	7.95	£41,946	1.74	£35,207	£24,075
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	Referent
Ixekizumab Q4W	£71,690	7.67	£15,748	0.30	ED	£53,230
Ustekinumab	£73,935	7.93	£17,992	0.55	£32,592	£32,592
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	Referent
Ixekizumab Q4W	£85,319	7.40	£15,047	0.35	ED	£43,573
Ustekinumab	£86,858	7.71	£16,587	0.65	£25,666	£25,666
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	Referent
Ustekinumab	£113,474	3.27	£13,856	1.01	£13,680	£13,680
Ixekizumab Q2W	£118,024	2.89	£18,407	0.63	Dominated	£29,173

Table 73 Scenario analysis: PsARC and PASI 100

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	Referent	Referent	Referent	Referent
CZP-UST-BSC	£68,964	8.58	£14,918	0.48	£30,971	£30,971
ETN-UST-BSC	£70,321	8.57	£16,275	0.48	Dominated	£34,001
APR-UST-BSC	£70,400	8.58	£16,354	0.48	Extendedly dominated	£33,845
ADA-UST-BSC	£72,163	8.62	£18,117	0.53	Extendedly dominated	£34,284
GOL-UST-BSC	£75,443	8.72	£21,397	0.63	Extendedly dominated	£34,101
SEC150-UST-BSC	£77,224	8.79	£23,178	0.69	£39,010	£33,426
IXEQ4W-UST-BSC	£85,472	8.81	£31,426	0.72	Extendedly dominated	£43,669

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY) vs BSC
INF-UST-BSC	£94,069	9.10	£40,023	1.01	£53,007	£39,580
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	Referent	Referent	Referent	Referent
CZP-UST-BSC	£83,879	8.25	£13,873	0.51	£27,463	£27,463
ETN-UST-BSC	£85,288	8.25	£15,282	0.50	Dominated	£30,516
APR-UST-BSC	£85,404	8.25	£15,398	0.51	Extendedly dominated	£30,451
ADA-UST-BSC	£86,952	8.30	£16,946	0.56	Extendedly dominated	£30,522
GOL-UST-BSC	£89,889	8.41	£19,883	0.66	Extendedly dominated	£30,014
SEC150-UST-BSC	£91,606	8.48	£21,600	0.73	£34,324	£29,578
IXEQ4W-UST-BSC	£99,752	8.50	£29,746	0.76	Extendedly dominated	£39,212
INF-UST-BSC	£107,662	8.81	£37,656	1.07	£47,798	£35,318
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	Referent	Referent	Referent	Referent
CZP-UST-BSC	£111,686	6.81	£11,802	0.60	£19,586	£19,586
ETN-UST-BSC	£113,197	6.80	£13,313	0.59	Dominated	£22,474
APR-UST-BSC	£113,379	6.81	£13,495	0.60	Dominated	£22,546
ADA-UST-BSC	£114,507	6.87	£14,623	0.67	Extendedly dominated	£21,948
GOL-UST-BSC	£116,758	7.01	£16,874	0.81	£24,701	£20,886
SEC300-UST-BSC	£129,822	7.09	£29,938	0.89	Extendedly dominated	£33,754
IXEQ2W-UST-BSC	£131,252	7.20	£31,368	1.00	Extendedly dominated	£31,503
INF-UST-BSC	£132,826	7.50	£32,942	1.30	£32,984	£25,437
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	Referent
Ixekizumab Q4W	£66,386	7.54	£10,444	0.17	ED	£62,334
Ustekinumab	£69,298	7.76	£13,356	0.38	£35,267	£35,267
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	Referent
Ixekizumab Q4W	£80,367	7.25	£10,095	0.20	ED	£51,701
Ustekinumab	£82,749	7.51	£12,478	0.45	£27,949	£27,949
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	Referent
Ustekinumab	£110,399	2.97	£10,781	0.71	£15,150	£15,150
Ixekizumab Q2W	£113,220	2.62	£13,602	0.36	Dominated	£37,469

3.8.4 Summary of sensitivity analyses results

The sensitivity analyses were conducted to indicate which key parameters and assumptions had the greatest impact on the results. The deterministic sensitivity analyses demonstrated that there were some common factors across the pairwise comparisons that had the greatest impact on the implications for cost-effectiveness: treatment acquisition costs, discontinuation rate, discounting of costs and QALYs, PsARC response rates and utility model coefficients. With the exception of these parameters, ICERs were generally robust to variation in parameters.

Scenario analyses were conducted to test key assumptions and assess the directional impact on the cost-effectiveness of ixekizumab. Ixekizumab sequence was either extendedly dominated or dominated in all scenario analyses based on the list price of ixekizumab. Assumptions that had the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base case were HAQ-DI rebound to natural history in the BSC treatment state, the York utility model coefficients, Poole et al (2010) algorithm for costs associated with HAQ-DI, and combining PsARC and PASI rates as the treatment continuation rule. When a time point of 16 weeks was used for response assessment, ixekizumab was associated with an increase in both total costs and total QALYs with little impact on the ICER versus BSC relative to the base case.

3.9 Subgroup analysis

The subgroups considered in the economic analysis were prior treatment experience stratified by the extent of concomitant psoriasis.

Presenting economic analyses for bDMARD-naïve and –experienced patient populations separately was appropriate as the SPIRIT-P1 and SPIRIT-P2 trials relate separately to these patient populations. PsARC response and utility valuation were estimated for each subgroup from the respective trials. Furthermore, the pathway recommendations by NICE for ustekinumab and secukinumab 300 mg necessitate the evaluation of these subgroups as separate decision problems. The outcome of TA340 established the precedent of using a particular therapy specifically in patients who had a prior inadequate response to TNF-alpha inhibitor therapy. The licence wording for secukinumab states that the recommended dose for patients with concomitant moderate to severe plaque psoriasis or who are anti-TNF-alpha inadequate responders is 300 mg.

The presence and/or severity of concomitant psoriasis was assumed not to affect joint response but was used to determine health state resource use costs and utilities. The subgroups relating to presence and/or severity of concomitant psoriasis aligned with the

approach taken by the Assessment Group in the 2016 York model and the licence wording for secukinumab. The expected licence wording for ixekizumab recommends a dosing regimen of 80 mg Q2W for 12 weeks followed by 80 mg Q4W thereafter for patients with concomitant moderate-to-severe psoriasis. This dosing regimen was based on the PsA subgroup data from the UNCOVER trial programme in psoriasis and aligns with the dosing regimen in TA442 for ixekizumab in the treatment of moderate-to-severe psoriasis. It was not possible to conduct a subgroup analysis by psoriasis severity in the SPIRIT-P1 and SPIRIT-P2 trials separately as the sample sizes were not large enough to provide meaningful results.

Lastly, the key point of note with respect to sub-groups is that the data provided in Section 2.7 presented various sub-groups where ixekizumab efficacy was consistent regardless of baseline patient characteristics, therefore exploration of cost-effectiveness by clinically defined sub-groups was not warranted.

3.10 Validation

3.10.1 Validation of the de novo cost-effectiveness analysis

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision-Making (SMDM) Joint Task Force for Modelling Good Research Practices describes model validity simply, as “how well the model reproduces reality”. (126) The guidelines define the following five elements of model validation.

Face validity

Face validity of the conceptual model was checked in an advisory board with clinical and health economic experts. Revisions to the conceptual model were made on the basis of feedback from the advisory board and the recent York 2016 model, and subsequently incorporated in the model development.

Verification or internal validity

The model was developed by an external consultancy and internal validation was undertaken by another external consultancy. The model was checked by the second consultancy from an overall health economics and outcomes research (HEOR) perspective and to quality control the programming of the model to identify errors or omissions. A cell-by-cell technical validation was carried out and the VBA code was checked.

Cross validity: comparison of results with other models analysing the same problem

Replicating comparisons from previous submissions may be one way of checking cross-validity. However, the confidential PAS price for secukinumab and apremilast makes the cross-validation of base case ICERs between previous submissions difficult. In the bDMARD-naïve subgroups in the current analysis, the etanercept and infliximab sequences are the only options that lie on the CE frontier that can be compared to previous economic evaluations as they are not associated with a PAS. The ICERs for these treatments are broadly in line with the ICERs reported in the Assessment Group report for TA445. In the bDMARD-experienced subgroups, the ICERs for ustekinumab versus BSC align with those reported in the TA445 Assessment Group report.

External validity: comparing model results with real-world results

Long term observational studies have not been carried out for ixekizumab, therefore external validity of real world clinical effectiveness is difficult to assess.

Predictive validity: comparing model results with prospectively observed events

Adalimumab is included as a reference arm in the SPIRIT-P1 trial and is included in a powered head-to-head study versus ixekizumab that is currently underway (NCT03151551). Although data from the head-to-head trial are not currently available, predictive validity could be assessed by comparing the ICER for ixekizumab versus adalimumab from the model, as and when it can be updated with the powered head-to-head trial data, to the ICER as it is with currently available indirect evidence.

3.10.2 Validation of input data

A hierarchy of evidence in the estimation of parameters is outlined in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 13. (127) The five data elements described in the TSD are clinical effect sizes, baseline clinical data, resource use, unit costs and health utilities. The sources of evidence used to inform the economic model are therefore ranked highly in each category of the hierarchy with scores of 1+ to 2. The model uses clinical effect sizes from a Bayesian NMA and baseline clinical data from the SPIRIT-P1 and-P2 trials. Resource use estimates are sourced from previously published economic evaluations and unit costs from recently published UK sources. Health utilities were assessed from patients in the SPIRIT trials using the EQ-5D-5L and were mapped to the EQ-5D-3L. The utility data subsequently informed a utility algorithm with a functional form that aligned with recent economic evaluations in PsA. (2)

3.11 Interpretation and conclusions of economic evidence

The de novo economic analysis uses the modelling approach of the York PsA models as a foundation to assess the effect of treatment on both the joint and skin components of PsA. The second revision of the York model was developed in 2016. As this model structure was accepted by the Committee for TA445, the current analysis follows this model approach. In modelling the time spent on each active treatment as two discrete time periods, i.e. a trial period and continued treatment period, the model structure reflects the clinical pathway in PsA in England and Wales. Joint response assessment in the model, i.e. achievement of PsARC at the end of 12-24 weeks, aligns with the treatment continuation rule for NICE.

The 2016 York model considered six patient subgroups, each characterised by both their prior bDMARD exposure and presence or severity of concomitant psoriasis. This approach was considered important to use in the current model to generate economic results that are relevant for all patients who are eligible for b/tsDMARD therapy for two reasons. First, the recommended licensed dosing regimen of both IL-17 DMARDs are specific to the presence of concomitant moderate-to-severe psoriasis and, in the case of secukinumab, whether the patient has receive a prior TNF-alpha inhibitor. The two dosing regimens are associated with different levels of clinical response and as such, capturing the differences in transition probabilities in the model is paramount. Moreover, the cost implications render the two doses of secukinumab (150 mg and 300 mg) and the trial period dosing regimens of ixekizumab Q2W and ixekizumab Q4W important to consider in the economic evaluation separately, rather than as a blended average of the two dosing regimens. Second, the STA for ustekinumab and the MTA for certolizumab pegol and secukinumab established a precedent of recommending treatments following inadequate response or contraindication to a TNF-alpha inhibitor. Considering a population with prior exposure to a bDMARD was therefore also necessary from a national reimbursement perspective.

A strength of the model is its flexibility to incorporate b/tsDMARD treatment sequences using data from the relevant Bayesian analysis networks specific to the line of therapy. Ustekinumab, certolizumab pegol and secukinumab were recommended by NICE for patients with prior TNF-exposure. In clinical practice, patients may receive a TNF-alpha inhibitor following failure on a prior TNF-alpha inhibitor. While the model has the flexibility to capture different combinations and orderings of treatments, ustekinumab was selected in the base case as a common second-line bDMARD across treatment sequences, in alignment with the approach in TA445. The recommendation of certolizumab pegol in bDMARD-experienced patients is restricted only to those with secondary non-response to a prior TNF-

alpha inhibitor and market research data indicates that Stelara is associated with a larger market share in second-line use of bDMARDs than secukinumab (Company budget impact template). (128)

HRQoL data were directly elicited from patients in SPIRIT-P1 and SPIRIT-P2 using the EQ-5D-5L instrument and mapped to the EQ-5D-3L dataset in accordance with NICE's position statement. The EQ-5D-3L data were estimated for the bDMARD-naïve and bDMARD-experienced populations, separately, to reflect the inherent differences in terms of functional disability and skin involvement between these two populations.

A further strength of the model is the incorporation of additional PASI health states. IL-17 therapies in psoriasis have been associated with higher rates of skin response and clearance. To better capture the effect of these treatments on concomitant psoriasis in patients with PsA, the effect of PASI 50 and 75 response on costs and utilities is captured in the base case analyses, and PASI 75, PASI 90 and PASI 100 are tested in sensitivity analyses as part of the treatment continuation rule in conjunction with PsARC.

A limitation of the model is the availability of subgroup-specific data on relevant clinical outcomes. The 2016 York model was informed by clinical outcomes specific to the bDMARD-naïve and bDMARD-experienced subgroups at the relevant assessment timepoints for each treatment of interest. However, these data are not publicly available for all comparators. A systematic literature review identified gaps in the availability of bDMARD-naïve and bDMARD-experienced data for certolizumab pegol and secukinumab at the relevant timepoints for response assessment. In the absence of these data, overall population data have been used in the bDMARD-naïve network in the base case. As the majority of patients in these trials were bDMARD-naïve, these studies have only been incorporated in the bDMARD-experienced network in a sensitivity analysis. Furthermore, given the small patient numbers in the bDMARD-experienced network, it was not possible to conduct a meta-regression adjusting for placebo response in this population, therefore placebo-adjusted response rates are considered only for the bDMARD-naïve population in a sensitivity analysis.

The presence of confidential PAS price discounts for apremilast, secukinumab and ixekizumab hinders the comparison of the predicted results with previously published economic evaluations. Using the list price of ixekizumab in the base case analyses results in both ixekizumab Q2W in the bDMARD-naïve subgroup with moderate-to-severe psoriasis and ixekizumab Q4W in the no psoriasis and mild-to-moderate psoriasis subgroups being dominated or extendedly dominated by other treatments. When the PAS price of ixekizumab

is included in the analyses, the ixekizumab sequences are extendedly dominated in the bDMARD-naïve subpopulation and lie on the frontier in the bDMARD-experienced population. In the no psoriasis and mild-to-moderate psoriasis subgroups, the ixekizumab Q4W sequences are associated with an ICER of less than £30,000/QALY versus BSC and in the moderate-to-severe psoriasis subgroup, the ICER for ixekizumab Q2W versus BSC is lower than £20,000/QALY.

Assumptions that had the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base case were HAQ-DI rebound to natural history in the BSC treatment state, use of the York utility model coefficients, Poole et al (2010) algorithm to estimate HAQ-DI-related costs, and combining PsARC and PASI 100 rates as the treatment continuation rule. An assessment time point of 16 weeks for ixekizumab was associated with an increase in total QALYs and a small non-directional impact on the ICER versus BSC relative to the base case.

The QALYs predicted by the model for each active treatment or treatment sequence lie within the range of one QALY over a lifetime horizon; notably, the difference between ixekizumab and ustekinumab in the bDMARD population is 0.03 QALYs in the no psoriasis and moderate-to-severe psoriasis subgroups and 0.04 QALYs in the mild-to-moderate subgroup. The small denominators in the ICER calculation in each model subgroup are indicative of the similarity in efficacy between treatments. When the PAS price of ixekizumab is taken into account, ixekizumab is associated with a total cost that is lower than the alternative treatment options that do not have confidential PAS discounts.

4 References

1. European Medicines Agency. Taltz - Summary of product characteristics 2016.

2. National Institute for Health and Care Excellence. Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs [TA445] 2017 [Available from: https://www.nice.org.uk/guidance/ta445.

3. Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. P & T : a peer-reviewed journal for formulary management. 2010;35(12):680-9.

4. Psoriasis Association. Psoriatic Arthritis 2016 [Available from: https://www.psoriasis-association.org.uk/media/InformationSheets/PSA_2016.pdf.

5. Dewing KA. Management of patients with psoriatic arthritis. The Nurse practitioner. 2015;40(4):40-6; quiz 6-7.

6. Eder L, Haddad A, Rosen CF, Lee KA, Chandran V, Cook R, et al. The Incidence and Risk Factors for Psoriatic Arthritis in Patients With Psoriasis: A Prospective Cohort Study. Arthritis & rheumatology (Hoboken, NJ). 2016;68(4):915-23.

7. Siannis F, Farewell VT, Cook RJ, Schentag CT, Gladman DD. Clinical and radiological damage in psoriatic arthritis. Annals of the rheumatic diseases. 2006;65(4):478-81.

8. Haroon M, FitzGerald O. Psoriatic arthritis: complexities, comorbidities and implications for the clinic. Expert review of clinical immunology. 2016;12(4):405-16.

9. Liu JT, Yeh HM, Liu SY, Chen KT. Psoriatic arthritis: Epidemiology, diagnosis, and treatment. World journal of orthopedics. 2014;5(4):537-43.

10. Butt AQ, McArdle A, Gibson DS, FitzGerald O, Pennington SR. Psoriatic arthritis under a proteomic spotlight: application of novel technologies to advance diagnosis and management. Current rheumatology reports. 2015;17(5):35.

11. Huynh D, Kavanaugh A. Psoriatic arthritis: current therapy and future directions. Expert opinion on pharmacotherapy. 2013;14(13):1755-64.

12. Boehncke WH, Menter A. Burden of disease: psoriasis and psoriatic arthritis. American journal of clinical dermatology. 2013;14(5):377-88.

13. McLaughlin M, Ostor A. Early treatment of psoriatic arthritis improves prognosis. The Practitioner. 2014;258(1777):21-4, 3.

14. Tintle SJ, Gottlieb AB. Psoriatic arthritis for the dermatologist. Dermatologic clinics. 2015;33(1):127-48.

15. Mease PJ. Biologic Therapy for Psoriatic Arthritis. Rheumatic diseases clinics of North America. 2015;41(4):723-38.

16. Novelli LC, MS;Chiricozzi, A; Perricone, R. The new era for the treatment of psoriasis and psoriatic arthritis: perspectives and validated strategies. Autoimm Rev. 2014;13(1):64-9.

17. Ogdie A, Langan S, Love T, Haynes K, Shin D, Seminara N, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. Rheumatology (Oxford, England). 2013;52(3):568-75.

18. Lories RJ, de Vlam K. Tumour necrosis factor inhibitors in the treatment of psoriatic arthritis: a view on effectiveness, clinical practice and toxicity. Expert opinion on biological therapy. 2014;14(12):1825-36.

19. Koolaee RM TJ, Ogdie A. Epidemiology and natural history of psoriatic arthritis: an update what dermatologists need to know. Curr Dermatol Rep 2013;2(1):66-76.

20. Husni ME. Comorbidities in Psoriatic Arthritis. Rheumatic diseases clinics of North America. 2015;41(4):677-98.

21. Ali Y TB, Schentag CT et al. Improved survival in psoriatic arthritis with calendar time. Arthritis and rheumatism. 2007;Aug;56((8)):2708-14.

22. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Time trends in epidemiology and characteristics of psoriatic arthritis over 3 decades: a population-based study. The Journal of rheumatology. 2009;36(2):361-7.

23. Buckley C, Cavill C, Taylor G, Kay H, Waldron N, Korendowych E, et al. Mortality in psoriatic arthritis - a single-center study from the UK. The Journal of rheumatology. 2010;37(10):2141-4.

24. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis and rheumatism. 2011;63(5):1182-9.

25. Alten R SV, Conaghan P G, Huneault L, Sullivan E, Blackburn S, Tian H, et al Psoriatic Arthritis Limits Patients' Abilities to Undertake Activities Crucial for

Normal Daily Life and Impacts Happiness, Results from a Multinational Real-World

Sample. American College of Rheumatology. 2016.

26. National Institute for Health and Care Excellence. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis [TA199] 2010 [Available from: https://www.nice.org.uk/guidance/ta199.

27. National Institute for Health and Care Excellence. Golimumab for the treatment of psoriatic arthritis [TA220] 2011 [Available from: https://www.nice.org.uk/guidance/ta220.

28. National Institute for Health and Care Excellence. Ustekinumab for treating active psoriatic arthritis [TA340] 2015 [Available from: https://www.nice.org.uk/guidance/ta340.

29. National Institute for Health and Care Excellence. Apremilast for treating active psoriatic arthritis [TA433] 2017 [Available from: https://www.nice.org.uk/guidance/ta433.

30. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis & rheumatology (Hoboken, NJ). 2016;68(5):1060-71.

31. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Annals of the rheumatic diseases. 2016;75(3):499-510.

32. Coates LC, Tillett W, Chandler D, Helliwell PS, Korendowych E, Kyle S, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. Rheumatology (Oxford, England). 2013;52(10):1754-7.

33. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2013;9(1):30.

34. Nash P, Clegg DO. Psoriatic arthritis therapy: NSAIDs and traditional DMARDs. Annals of the rheumatic diseases. 2005;64 Suppl 2:ii74-7.

35. van de Kerkhof PC, Reich K, Kavanaugh A, Bachelez H, Barker J, Girolomoni G, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the

population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. Journal of the European Academy of Dermatology and Venereology : JEADV. 2015;29(10):2002-10.

36. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic Arthritis and Burden of Disease: Patient Perspectives from the Population-Based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) Survey. Rheumatology and therapy. 2016;3(1):91-102.

37. Salvarani C, Macchioni P, Olivieri I, Marchesoni A, Cutolo M, Ferraccioli G, et al. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. The Journal of rheumatology. 2001;28(10):2274-82.

38. Schett G, Coates LC, Ash ZR, Finzel S, Conaghan PG. Structural damage in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: traditional views, novel insights gained from TNF blockade, and concepts for the future. Arthritis research & therapy. 2011;13 Suppl 1:S4.

39. Kavanaugh AC MM, P.Gladman, D.Adebajo, A.Gomez-Reino, J.Wollenhaupt et al. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-WEEK) improvement in measures of disease activity in patients with psoriatic arthritis: Results from 3 phase 3, randomized, controlled trials. . Annals of the rheumatic diseases. 2014;73: .

40. Kaltwasser JP, Nash P, Gladman D, Rosen CF, Behrens F, Jones P, et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. Arthritis and rheumatism. 2004;50(6):1939-50.

41. Abu-Shakra M, Gladman DD, Thorne JC, Long J, Gough J, Farewell VT. Longterm methotrexate therapy in psoriatic arthritis: clinical and radiological outcome. The Journal of rheumatology. 1995;22(2):241-5.

42. Rahman P, Gladman DD, Cook RJ, Zhou Y, Young G. The use of sulfasalazine in psoriatic arthritis: a clinic experience. The Journal of rheumatology. 1998;25(10):1957-61.

43. Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, FitzGerald O, Winthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Annals of the rheumatic diseases. 2012;71(3):319-26.

44. Mease P, Deodhar A, Fleischmann R, Wollenhaupt J, Gladman D, Leszczynski P, et al. Effect of certolizumab pegol over 96 weeks in patients with psoriatic arthritis with and without prior antitumour necrosis factor exposure. RMD open. 2015;1(1):e000119.

45. Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis research & therapy. 2009;11(2):R52.

46. Soubrier AS, Bele-Philippe P, Cortet B, Ramdane-Sebbane N, Bacle-Boutry MA, Lemeunier L, et al. Treatment response, drug survival and safety of anti-tumour necrosis factor alpha therapy in 193 patients with psoriatic arthritis: a twelve-year "real life" experience. Joint, bone, spine : revue du rhumatisme. 2015;82(1):31-7.

47. Menter A, Papp KA, Gooderham M, Pariser DM, Augustin M, Kerdel FA, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). Journal of the European Academy of Dermatology and Venereology : JEADV. 2016;30(7):1148-58.

48. Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor alpha inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis and rheumatism. 2013;65(5):1213-23.

49. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet (London, England). 2000;356(9227):385-90.

50. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Annals of the rheumatic diseases. 2005;64(8):1150-7.

51. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis and rheumatism. 2005;52(10):3279-89.

52. Genovese MM, PJ; Thomson, GTD; et al. . Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. Journal of Rheumatology. 2007;34(5):1040-50.

53. Gladman DD, Sampalis JS, Illouz O, Guerette B. Responses to adalimumab in patients with active psoriatic arthritis who have not adequately responded to prior therapy: effectiveness and safety results from an open-label study. The Journal of rheumatology. 2010;37(9):1898-906.

54. Van den Bosch F, Manger B, Goupille P, McHugh N, Rodevand E, Holck P, et al. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. Annals of the rheumatic diseases. 2010;69(2):394-9.

55. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Annals of the rheumatic diseases. 2014;73(1):48-55.

56. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet (London, England). 2013;382(9894):780-9.

57. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Annals of the rheumatic diseases. 2014;73(6):990-9.

58. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Annals of the rheumatic diseases. 2007;66(4):498-505.

59. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis and rheumatism. 2009;60(4):976-86.

60. Mease P. A short history of biological therapy for psoriatic arthritis. Clinical and experimental rheumatology. 2015;33(5 Suppl 93):S104-8.

61. Frleta M, Siebert S, McInnes IB. The interleukin-17 pathway in psoriasis and psoriatic arthritis: disease pathogenesis and possibilities of treatment. Current rheumatology reports. 2014;16(4):414.

62. Behrens F, Canete JD, Olivieri I, van Kuijk AW, McHugh N, Combe B. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. Rheumatology (Oxford, England). 2015;54(5):915-26.

63. National Institute for Health and Care Excellence. DMARDs - Scenario: Methotrexate 2017 [Available from: https://cks.nice.org.uk/dmards#!scenario:10.

64. Liu L, Lu J, Allan BW, Tang Y, Tetreault J, Chow CK, et al. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. Journal of inflammation research. 2016;9:39-50.

65. National Institute for Health and Care Excellence. Spondyloarthritis in over 16s: diagnosis and management. NICE guideline [NG65] 2017 [Available from: https://www.nice.org.uk/guidance/ng65.

66. National Institute for Health and Care Excellence. Psoriasis. NICE quality standard [QS40] 2013 [Available from: https://www.nice.org.uk/guidance/qs40.

67. National Institute for Health and Care Excellence. Psoriasis: assessment and management NICE clinical guideline [CG153] 2012 [Available from: https://www.nice.org.uk/guidance/cg153.

68. National Institute for Health and Care Excellence. Musculoskeletal conditions. NICE Pathway 2013 [Available from: https://pathways.nice.org.uk/pathways/musculoskeletal-conditions.

69. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Annals of the rheumatic diseases. 2017;76(1):79-87.

70. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet (London, England). 2017;389(10086):2317-27.

71. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. 2006 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf.

72. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Online Supplement for Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet (London, England). 2017;389(10086):2317-27.

73. Eli Lilly and Company Limited. SPIRIT-P1 (NCT01695239) - Clinical Study Report (CSR), Data on file. 2016.

74. Eli Lilly and Company Limited. SPIRIT-P2 (NCT02349295) - Clinical Study Report (CSR), Data on file. 2016.

75. Eli Lilly and Company Limited. SPIRIT-P1 (NCT01695239), w52 - Clinical Study Report (CSR), Data on file. 2016.

76. Eli Lilly and Company Limited. SPIRIT-P2 (NCT02349295), w52 - Clinical Study Report (CSR), Data on file. 2016.

77. Thom HJ, SM; McInnes, IB; Nash, P; Ritchlin, C; Kanters, S; Palaka, E; Gandhi, K; Mpofu, S. Psoriatic Arthritis Response Criteria scores: results of a placebo-adjusted network meta-analysis with secukinumab Washington, DC, USA2016 [updated 21-25 May 2016. Available from: https://www.ispor.org/research_pdfs/52/pdffiles/PMS10.pdf.

78. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis and rheumatism. 2005;52(4):1227-36.

79. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis and rheumatism. 2004;50(7):2264-72.

80. Mease P HS, FitzGerald O, et al. . Efficacy and Safety of Tofacitinib, an Oral Janus Kinase Inhibitor, or Adalimumab in Patients with Active Psoriatic Arthritis and an Inadequate Response to Conventional Synthetic Dmards: A Randomized, Placebo-Controlled, Phase 3 Trial [abstract]. 2016. Arthritis Rheumatol. 2016;68((suppl 10).).

81. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Annals of the rheumatic diseases. 2014;73(6):1020-6.

82. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van den Bosch F, et al. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. The Journal of rheumatology. 2016;43(9):1724-34.

83. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Annals of the rheumatic diseases. 2016;75(6):1065-73.

84. Helliwell. Ixekizumab Provides Sustained Improvement in Signs and Symptoms in Patients with Active Psoriatic Arthritis: Two Year Results from a Phase 3 Trial [abstract]. Arthritis Rheumatol. 2017.

85. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: Results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. Journal of the American Academy of Dermatology. 2014;70(5):871-81.e30.

86. Parisi R GC, Ashcroft DM. Systematic review of the incidence and prevalence of psoriasis. British Journal of Dermatology. 2011;165(6):e5.

87. National Institute for Health and Care Excellence. Ixekizumab for treating moderate to severe plaque psoriasis. Final scope [TA442] 2016 [Available from: https://www.nice.org.uk/guidance/ta442/documents/final-scope.

88. Bansback NJ, Ara R, Barkham N, Brennan A, Fraser AD, Conway P, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology (Oxford, England). 2006;45(8):1029-38.

89. Bojke L, Epstein D, Craig D, Rodgers M, Woolacott N, Yang H, et al. Modelling the cost-effectiveness of biologic treatments for psoriatic arthritis. Rheumatology (Oxford, England). 2011;50 Suppl 4:iv39-iv47.

90. Bravo Vergel Y, Hawkins NS, Claxton K, Asseburg C, Palmer S, Woolacott N, et al. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford, England). 2007;46(11):1729-35.

91. Cawson MR, Mitchell SA, Knight C, Wildey H, Spurden D, Bird A, et al. Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic arthritis. BMC musculoskeletal disorders. 2014;15:26.

92. Cummins E, Asseburg C, Punekar YS, Shore E, Morris J, Briggs A, et al. Cost-effectiveness of infliximab for the treatment of active and progressive psoriatic arthritis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(1):15-23.

93. Cummins E, Asseburg C, Prasad M, Buchanan J, Punekar YS. Cost effectiveness of golimumab for the treatment of active psoriatic arthritis. The European journal of health economics : HEPAC : health economics in prevention and care. 2012;13(6):801-9.

94. Mughal FC, H; Cure, S; Morris, J; Tencer, T; Zhang, F. COST-EFFECTIVENESS OF APREMILAST IN PSORIATIC ARTHRITIS IN SCOTLAND Value in Health. 2015;18:A644.

95. Rencz F BV, Pentek M, Gulacsi L, Baji P. A cost-effectiveness analysis of biosimilar infliximab (inflectra) for the treatment of psoriatic arthritis in nine European countries. Value in Health. 2016;19 ((7)):A540-A1.

96. Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2011;15(10):i-xxi, 1-329.

97. Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M, et al. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation 2017 [updated OctPMC5641819]. 1-326]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28976302.

98. British National Formulary [Internet]. Available from: https://www.bnf.org/.

99. Monthly Index of Medical Specialities [Internet]. 2018. Available from: http://www.mims.co.uk/.

100. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2016 2016 [Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/.

101. NHS reference costs 2015 to 2016. National schedule of reference costs: the main schedule [Internet]. 2016. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.

102. Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. Arthritis and rheumatism. 2002;46(9):2310-9.

103. Hartman M, Prins M, Swinkels OQ, Severens JL, De Boo T, Van Der Wilt GJ, et al. Cost-effectiveness analysis of a psoriasis care instruction programme with dithranol compared with UVB phototherapy and inpatient dithranol treatment. Br J Dermatol. 2002;147(3):538-44.

104. Poyner W, Adnitt, Menday. . Economic impact of psoriasis treatment on the patient and on the National Health Service. Journal of Dermatological Treatment. 1999;Volume 10(1).

105. Merola JF, Lockshin B, Mody EA. Switching biologics in the treatment of psoriatic arthritis. Semin Arthritis Rheum. 2017;47(1):29-37.

106. Pan Mersey Area Prescribing Committee. Mersey Biologics Pathway for Psoriatic Arthritis and patients with Spondyloarthritis (SpA) 2017 [Available from: http://www.panmerseyapc.nhs.uk/guidelines/documents/G14.pdf.

107. Greater Manchester Medicines Management Group. Harmonised biologics pathway for ankylosing spondylitis (including non-radiographic axial spondyloarthritis - AS) and

psoriatic arthritis (PsA) 2018 [Available from: http://gmmmg.nhs.uk/docs/guidance/GMMMG-AS-PsA-pathway-v4-2a.pdf.

108. Electronic Medicines Compendium. Summary of Product Characteristics: Humira 40 mg/0.8 ml pre-filled syringe and pre-filled pen 2017 [Available from: https://www.medicines.org.uk/emc/medicine/21201.

109. Electronic Medicines Compendium. Summary of Product Characteristics: Otezla 30mg tablets 2018 [Available from: https://www.medicines.org.uk/emc/medicine/29792.

110. Electronic Medicines Compendium. Summary of Product Characteristics: Cimzia 200mg solution for injection in pre-filled pen 2018 [Available from: https://www.medicines.org.uk/emc/product/7387.

111. Electronic Medicines Compendium. Summary of Product Characteristics: Enbrel 25 mg powder and solvent for solution for injection 2017 [Available from: https://www.medicines.org.uk/emc/medicine/3343.

112. Electronic Medicines Compendium. Summary of Product Characteristics: Simponi 50mg solution for injection in pre-filled pen 2017 [Available from: https://www.medicines.org.uk/emc/product/8122.

113. Electronic Medicines Compendium. Summary of Product Characteristics: Remicade 100mg for concentrate for solution for infusion 2017 [Available from: https://www.medicines.org.uk/emc/medicine/3236/SPC/Remicade+100mg+powder+for+concentrate+for+solution+for+infusion/.

114. Electronic Medicines Compendium. Summary of Product Characteristics: Stelara 45 mg solution for injection 2017 [Available from: https://www.medicines.org.uk/emc/medicine/21425.

115. Electronic Medicines Compendium. Summary of Product Characteristics: Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen 2017 [Available from: https://www.medicines.org.uk/emc/medicine/29848.

116. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. Arthritis and rheumatism. 1997;40(10):1868-72.

117. EuroQoL Research Foundation. What is EQ-5D 2016 [Available from: http://www.euroqol.org/.

118. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(5):708-15.

119. Curtis JR, Wright GC, Strand V, Davis CS, Hitraya E, Sasso EH. Reanalysis of the Multi-Biomarker Disease Activity Score for Assessing Disease Activity in the Abatacept Versus Adalimumab Comparison in Biologic-Naive Rheumatoid Arthritis Subjects with Background Methotrexate Study: Comment on the Article by Fleischmann et al. Arthritis & rheumatology (Hoboken, NJ). 2017;69(4):863-5.

120. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2008 2008 [Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/.

121. Department of Health. A simple guide to Payment by Results 2012 [Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477919/2014-15_Reference_costs_publication.pdf.

122. Infliximab biosimilar [Internet]. 2015. Available from: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=5794.

123. Etanercept biosimilar [Internet]. 2016. Available from: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=6049.

124. Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. Rheumatology (Oxford, England). 2010;49(10):1949-56.

125. Cochrane Collaboration. Handbook for Systematic Reviews of Interventions 2011 [Available from: http://handbook.cochrane.org/.

126. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(6):843-50.

127. NICE Decision Support Unit. Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models 2011 [Available from: http://www.nicedsu.org.uk/TSD%2013%20model%20parameters.pdf.

128. Ipsos Healthcare EU5 Psoriatic Arthritis Therapy Monitor (Pulse Report) – Study period: Q3 2017, 50 physicians reporting on 95 patients, all data collected online © Ipsos 2018, all rights reserved. [Data on file].

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Single technology appraisal

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]

Dear James,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 2 February 2018 from Eli Lilly. In general, they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **13 March 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (Ross.Dent@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
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Section A: Clarification on effectiveness data

Literature searching

A1. **Priority question:** The company noted systematic errors and mistakes in the search strategies conducted for the initial review. To ensure relevant studies included in previous systematic reviews (SRs) and network meta-analyses (NMAs) were picked up by the incorrect initial review searches, the company reported conducting cross-checks (appendices, page 7).[1]
In order for the ERG to conduct independent verification:
   a) Please provide full and specific details of how you identified the SRs and NMA which were screened as part of the 'cross-checking' (for example, search strategies and date spans).
   b) Please provide date of searches, date spans, full strategies reported in sufficient detail that they can be reproduced, including names of databases and hosts.
   c) Please report the number of SR/NMA references retrieved from each individual source.

A2. **Priority question:** Please provide a list of full references as well as the PDFs for the 41 SRs and NMAs described in the PRISMA flowchart for the initial review (appendices, page 21).[1]

A3. The PRISMA flowchart for the study flow for the Updated Review shows 101 records excluded before screening "as previously captured in ELLPHC162159 SLR" (appendices, page 22).[1]
Please provide a full reference and the PDF for ELLPHC162159 as well as a detailed rationale justifying this decision.

A4. Please explain why the clinical effectiveness searches were limited to English language publications only.

Patient population

A5. **Priority question:** A proportion of patients in SPIRIT-P1 were bDMARDs-naïve and SPIRIT-P2 included patients who were previously treated with one or more bDMARDs. The pre-treatment of these patients may be different from the pre-treatment of UK patients who would be eligible for biologic treatment.
   a) Please clarify whether patients included in those trials are representative of UK clinical practice.
   b) Please explain the potential effect of including less/more heavily pre-treated patients on the clinical and cost effectiveness of ixekizumab.
   c) Please provide 12 and 16 weeks results for all reported outcomes in the subgroup of patients eligible for treatment with biologics (referred to as the “NICE ITT population” in the company submission).

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d) Please provide 12 and 16 week results for the NMA outcomes listed in Tables 15 and 16 of the company submission (CS) appendices.[1] Please only include results of trials conducted in patients eligible for biologic treatment for psoriatic arthritis (PsA) in the UK, according to the final scope issued by NICE.[2]
e) Please provide the footnote for the asterisk used in Table 15 of the CS appendices.[1]

A6. The number of patients and percentages by region reported for SPIRIT-P2 does not add up. Please provide a corrected breakdown of regions and countries of participants in the SPIRIT-P1 and SPIRIT-P2 trials (cf. Table 9 of the CS[3]).

A7. Please discuss the differences in outcomes (e.g. Tender Joint Count (TJC), Swollen Joint Count (SJC), DAS-28, HAQ-DI) when comparing the British Society for Rheumatology Biologics Registry (BSRBR), SPIRIT-P1, and SPIRIT-P2 trials. Please discuss the potential impact on the study generalisability (cf. Table 32 of the CS[3]).

Network meta-analysis

A8. **Priority question:** Some of the outcomes defined in company's decision problem (Table 1 of the CS) were not included in either the NMA or the economic model, namely ACR 20/ 50/ 70, minimal disease activity (MDA), Leeds Enthesitis Index (LEI), nail psoriasis severity index (NAPSI), Leeds Dactylitis Index (LDI), modified total Sharp score (mTSS), adverse events, and mortality. Please provide all relevant results, including NMA results, for at least ACR 20 and adverse events (e.g. any adverse events (AE), any serious adverse events (SAE), ≥ 1 treatment emergent adverse events (TEAE), treatment discontinuation, malignancies).

A9. **Priority question:** Please provide a discussion of the clinical similarity of the trials included in each NMA, e.g. disease severity, previous treatments and length of follow-up. This should expand on the information presented in Tables 13, 17, and 18 of the appendices.[1]

A10. The NMA results have been reported as percentages or means for each treatment without statistical comparisons between treatments in the NMA, especially between ixekizumab and other treatments. Please provide odds ratios with 95% credible intervals (CrI) for the treatment comparisons of interest for binary outcomes or mean differences with CrI for continuous outcomes.

A11. **Priority question:** Please provide the data used in each NMA model in a format suitable for entering directly into R and/or WinBUGs.

A12. **Priority question:** Please provide the results of all random effects NMA models.

A13. **Priority question:** Please present and discuss the main conclusion from the NMA regarding the clinical effectiveness of ixekizumab compared to other treatments.

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A14. Please discuss which of the reported NMAs you consider to be the most clinically relevant.

Section B: Clarification on cost effectiveness data

Literature searching

B1. Please explain why the cost-effectiveness model input searches were limited to English, French, German, Italian or Spanish language publications only.

B2. For all cost-effectiveness and model input searches documented in pages 154-174 of the appendices,[1] please provide the following information for each individual search strategy:
   a) Date parameters of search
   b) Database host/interface (e.g. Ovid, ProQuest etc.)
   c) Number of results retrieved by each search line and the overall number retrieved from each database.

B3. HEED and the HTA database were searched for this submission. Please explain why NHS EED (NHS Economic Evaluation Database) was not searched.

Model structure

B4. **Priority question:** Response to treatment is a crucial element of the model structure, and informs the transition to the treatment continuation state. Response to treatment, assessed using the Psoriatic Arthritis Response Criteria (PsARC), is a function of change in disease state and not absolute disease severity. As a result, patients in the treatment continuation health state with response may be heterogeneous with regard to quality of life and costs.
   a) Please provide the PsARC response rates for each comparator in each subgroup.
   b) Please justify the use of PsARC response to determine response. The ERG acknowledges that this measure is commonly used to assess treatment response in PsA patients. However, because it is based on relative reductions, patients in the continuous treatment health states may be heterogeneous in terms of absolute disease severity. .This presents challenges for the accurate estimation of health-related quality of life and costs and resource use associated with these health states.
   c) Please show that patients achieving response are homogeneous with regards to disease severity (in terms of Psoriasis Area and Severity Index (PASI) and HAQ-DI scores), utility gain from response, and with regards to costs and resource use.

B5. It is assumed that patients in the 'no psoriasis' subgroup at the beginning of the cost effectiveness model will not develop psoriasis later on. Additionally, it is assumed that PASI scores of patients with psoriasis return to their baseline score in case of non-response to treatment or treatment discontinuation, i.e. the severity of psoriasis does not change over time.

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a) Please provide a definition of 'no psoriasis' given that these patients have active psoriatic arthritis.
b) Please also provide definitions for 'mild to moderate psoriasis' and 'moderate to severe psoriasis'.
c) Please justify the assumptions of no change in baseline psoriasis over time and elaborate on the potential impact of this assumption on the estimated cost effectiveness.

B6. Assumptions around changes in PASI and HAQ-DI scores in the model are unclear.
a) Patients in the 'trial period' health states experience instantaneous PASI and HAQ-DI improvements. Please justify why this improvement takes place at treatment initiation.
b) Please provide a scenario analysis in which the improvement in PASI and HAQ-DI scores for responders and non-responders is modelled as a gradual improvement until response assessment.
c) Please explain why patients who transition to best supportive care (BSC) experience an instant rebound to the baseline PASI, and implement a more gradual rebound if necessary.
d) Please provide explanation for the HAQ-DI calculations over time for patients receiving BSC.

Patient population

B7. **Priority question:** The baseline PASI scores used for the different subgroups in this submission differ from previous appraisals (i.e. the adaptation of the York model for TA 445[4]) and it is not clear how these scores were obtained.
a) Please describe how baseline PASI scores have been determined for the 'no psoriasis', 'mild-to-moderate psoriasis', and 'moderate-to-severe psoriasis' subgroups.
b) Please discuss the differences in these PASI scores compared with TA 445, and the potential impact on cost effectiveness of these differences.
c) Please explain what is meant by "TA 445 naive baseline" in relation to baseline HAQ and PASI scores (cells J20:K20, 'Main'-tab, cost effectiveness model).

Intervention and comparators

B8. **Priority question:** CS Tables 39 and 40 provide an overview of treatment sequences used in the cost effectiveness model.[3]
a) Please provide further justifcation for the selection of treatment sequences (besides the selection in the York model).
b) Please justify why treatment sequences are composed of two biologics followed by BSC in the bDMARD-naïve subgroup and of one biologic followed by BSC in the bDMARD-experienced subgroup (i.e. assuming patients would receive a maximum of two biologics).

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c) Please clarify whether the overview of treatment sequences in Tables 39 and 40 of the CS is exhaustive for the UK context.[3]

B9. Please describe the treatments incorporated in BSC, which, according to the CS[3], is a mix of cDMARDs and palliative care, and discuss whether this reflects UK clinical practice.

B10. The present submission differs from the scope in the selection of comparators and concomitant treatments. In the scope, ustekinumab, certolizumab pegol, secukinumab and BSC are listed as comparators for ixekizumab in bDMARD-experienced patients.[2] However, these comparisons are not provided in the company base-case analyses. The scope furthermore states that bDMARDS may be administered with or without methotrexate (and in SPIRIT-P1 54.2% of patients received methotrexate at baseline).[5]

a) Please include all comparators listed in the scope for all subgroups in the base-case cost effectiveness analyses.
b) Please include methotrexate in all base-case cost effectiveness analyses. More specifically, please provide an estimate of the proportion of patients who would receive concomitant methotrexate with each comparator and incorporate resource use and costs associated with methotrexate treatment in the cost effectiveness model.

Treatment effectiveness

B11. **Priority question:** The file "ID1194 ixekizumab PsA model parameters and state trace (AIC).xlsx" provided in advance of the final submission is helpful to understand the economic model. Please provide an updated version of this file, corresponding to the economic model file submitted with an updated trace and transition matrix.

B12. **Priority question:** Section 3.3 "Clinical parameters and variables" of the CS does not provide an overview of the clinical parameters and variables used in the model.[3]

a) Please provide an overview of all transition probabilities used in the model with sources.
b) Please justify the sources and calculations used to inform the transition probabilities in the model (including why the calculations in Tables 41 and 42 of the CS are appropriate).[3]
c) According to the calculations in Table 41 and the text below this Table, responders are subdivided into PASI 75 and PASI 50-74.[3] Please justify why the other PASI categories (e.g. < PASI 50) are not used.

B13. **Priority question:** CS Table 38 specifies the model trial period for each treatment after which treatment response is assessed.[3] However, for some treatments the model trial period is inconsistent with the time points used in the NMA as specified in CS appendix section 1.8 (e.g. for secukinumab data from the 12 week time point from the FUTURE 2 trial is used in the NMA while the model trial period is 16 weeks).[1]

a) Please justify this inconsistency regarding the model trial period and time point used in the NMA.

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b) Please incorporate necessary adjustments to correct this inconsistency in the economic model.
c) The CS states that "the trial period length is dependent on the biologic and can last from 10 to 16 weeks in alignment with the response assessment time points in NICE guidance for each treatment of interest." (pages 106-107).[3] The 10-16 weeks period is inconsistent with CS Table 38 where the model trial period length is reported to be 12-24 weeks.[3] Please clarify this discrepancy.

B14. In absence of alternative data, treatment discontinuation is assumed to be constant and equal for all biological treatments (independent of treatment line).
a) Please clarify whether this assumption is consistent with expert opinion.
b) Please justify why treatment discontinuation was not based on the SPIRIT trials and/or elicited expert opinion.
c) Please provide the NMA results for treatment discontinuation, where and if possible.

Adverse events

B15. **Priority question:** The CS states that adverse events "were thought to be captured only to the extent that they affect the initial response and the long-term withdrawal rates" (page 121).[3] However, long-term withdrawal rates were treatment-independent in the model, and the extent to which these rates capture treatment-associated adverse events is questionable. Furthermore, the scope identified adverse events as relevant outcomes for this appraisal.[2] Please include the impact of health-related quality of life and resource use and costs associated with adverse events in the cost effectiveness model.

Health-related quality of life

B16. Please provide further information and justification for the estimation of health-related quality of life.
a) Section 3.4 of the CS stated that "no imputation method was applied in case of missing information on EQ-5D as only a small proportion of patients in each trial had a missing EQ-5D score (20/417 in SPIRIT-P1 and 32/331 in SPIRIT-P2)" (page 120).[3] This implicitly assumes that these data were missing at random. Please provide justification for this assumption and provide additional analysis imputing missing data, if necessary.
b) Please provide more explanation and justification for how utility values were estimated using both data points (baseline and at 12 weeks). In particular, please explain whether a mixed effects model was used, and if not, please comment on why this was not used and provide a scenario where utility estimates are based on a mixed effects model (using all available data).

B17. Please provide a scenario analysis in which utility values are adjusted for the general population utility values.

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Resource use and cost

B18. Please justify why costs of BSC are assumed to be zero, given that BSC is a mix of cDMARDs and palliative care according to the CS.[3] Please provide a scenario in which the appropriate costs for BSC are included.

B19. Please provide justification for why the mean weight from SPIRIT-P1 and -P2 was deemed appropriate (i.e. representative of UK clinical practice) to calculate the drug acquisition costs for infliximab.

B20. Please provide justification for estimating resource use associated with the HAQ-DI score.
   a) Neither the Kobelt et al (2002) nor the Poole et al (2010) studies were considered ideal for estimating resource use and costs associated with the HAQ-DI score given that a) Kobelt et al is a study in rheumatoid arthritis patients, b) resource use associated with rheumatoid arthritis may have changed since the publication of this study, and c) Poole et al (2010) was associated with limitations in the calculation of the estimates.[6, 7] Please explain whether alternative data sources, such as the SPIRIT trials or studies included in the recent review by D'Angiolella et al (2018),, were considered for this submission, and explain why they were not used.[8]
   b) Please explain how the estimate of 15% for the reduction in resource use estimates to avoid double-counting of drug acquisition costs was obtained.

Validation

B21. **Priority question:** Please provide a cross-validation of all cost effectiveness analyses identified in the SR, including a Table that considers for each study:
   a) Model structure and major assumptions
   b) Intervention and comparators
   c) Response rates and other (influential) transition probabilities
   d) HRQoL data used
   e) Results
   f) If applicable, possible explanation(s) for discrepant results compared with the present assessment.

B22. The CS states that "the second revision of the York model (2016) served as the foundation of the current de novo analysis" (page 103).[4] However, the economic model submitted by the company deviated from the York model in several aspects (e.g. incorporating additional PASI response thresholds: PASI 50, PASI 90 and PASI 100).
   a) Please specify all deviations from the York model with regards to model structure as well as model assumptions.
   b) Please justify the abovementioned deviations from the York model.

<u>Section C: Textual clarifications and additional points</u>

C1. **Priority question:** Please provide all references used in the CS appendices.[1]

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References

[1] Eli Lilly and Company Limited. *Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194]: Appendices*: Eli Lilly and Company Limited., Feb 2018 [accessed 8.2.18]. 283p.

[2] National Institute for Health and Care Excellence. *Single Technology Appraisal Appendix B. Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs: Final scope* London: NICE, Nov 2017 [accessed 8.2.18]. 5p.

[3] Eli Lilly and Company Limited. *Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194]. Document B: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*: Eli Lilly and Company Limited., 2018 [accessed 8.2.18]. 205p.

[4] National Institute for Health and Care Excellence. *Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (Technology Appraisal TA445) [Internet]*. London: NICE, 2017 [accessed 20.2.18]. 36p. Available from: https://www.nice.org.uk/guidance/ta445

[5] Eli Lilly and Company. *1. RHAP Clinical Study Report: a multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis. LY2439821 (Ixekizumab) - Psoriatic Arthritis. Protocol I1F-MC-RHAP [PDF provided with the company's submission]*: Eli Lilly and Company, 3 Aug 2016 [accessed 8.2.18]. 5360p.

[6] Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. *Arthritis Rheum* 2002;46(9):2310-9.

[7] Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. *Rheumatology (Oxford)* 2010;49(10):1949-56.

[8] D'Angiolella LS, Cortesi PA, Lafranconi A, Micale M, Mangano S, Cesana G, et al. Cost and cost effectiveness of treatments for psoriatic arthritis: a systematic literature review. *PharmacoEcon* 2018.

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Single technology appraisal

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]

Dear James,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 2 February 2018 from Eli Lilly. In general, they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **13 March 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (Ross.Dent@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
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Section A: Clarification on effectiveness data

Literature searching

A1. **Priority question:** The company noted systematic errors and mistakes in the search strategies conducted for the initial review. To ensure relevant studies included in previous systematic reviews (SRs) and network meta-analyses (NMAs) were picked up by the incorrect initial review searches, the company reported conducting cross-checks (appendices, page 7).(1)
In order for the ERG to conduct independent verification:
   a) Please provide full and specific details of how you identified the SRs and NMA which were screened as part of the 'cross-checking' (for example, search strategies and date spans).
   b) Please provide date of searches, date spans, full strategies reported in sufficient detail that they can be reproduced, including names of databases and hosts.
   c) Please report the number of SR/NMA references retrieved from each individual source.

The SLR and NMA publications identified in the updated systematic review and the Assessment Group report for TA445 were used to identify any key publications or outcomes that were missing as a results of the errors in the initial SLR search strategy. The search strategies and date spans of the updated systematic review are presented in Tables 4-8 of Appendix D. The publications identified through these searches and used to cross-check the current SLR are:

- ***Ramiro S, Smolen JS, Landewe R, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2016;75(3):490-498.***

- ***McInnes IB, Nash P, Ritchlin C, et al. THU0437 Secukinumab for The Treatment of Psoriatic Arthritis: Comparative Effectiveness Results versus Licensed Biologics and Apremilast from A Network Meta-Analysis. Annals of the Rheumatic Diseases. 2016;75(Suppl 2):348-349.***

- ***Druyts E, Palmer JB, Balijepalli C, et al. Treatment modifying factors of biologics for psoriatic arthritis: a systematic review and Bayesian meta-regression. Clin Exp Rheumatol. 2017;35(4):681-688.***

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- ***Cawson MR, Mitchell SA, Knight C, et al. Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic arthritis. BMC Musculoskelet Disord. 2014;15:26.***

- ***Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis. 2014;73(2):414-419.***

- ***Lemos LL, de Oliveira Costa J, Almeida AM, et al. Treatment of psoriatic arthritis with anti-TNF agents: a systematic review and meta-analysis of efficacy, effectiveness and safety. Rheumatol Int. 2014;34(10):1345-1360.***

- ***Craig D, O'Connor J, Rodgers M, Rodriguez-Lopez R, Smith A, N W. Ustekinumab for treating active and progressive psoriatic arthritis: A single techology appraisal. Centre for Reviews and Dissemination. 2013.***

- ***Fenix-Caballero S, Alegre-del Rey EJ, Castano-Lara R, Puigventos-Latorre F, Borrero-Rubio JM, Lopez-Vallejo JF. Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis. J Clin Pharm Ther. 2013;38(4):286-293.***

- ***Thorlund K, Druyts E, Avina-Zubieta JA, Mills EJ. Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis. Biologics. 2012;6:417-427.***

- ***Migliore A, Bizzi E, Broccoli S, Lagana B. Indirect comparison of etanercept, infliximab, and adalimumab for psoriatic arthritis: mixed treatment comparison using placebo as common comparator. Clinical rheumatology. 2012;31(1):133-137***

A2. **Priority question:** Please provide a list of full references as well as the PDFs for the 41 SRs and NMAs described in the PRISMA flowchart for the initial review (appendices, page 21).(1)

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A full list of references is provided below and the PDFs can be found in the folder 'A2. SLR references'.

i. ***Acosta Felquer ML, Coates LC, Soriano ER, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. The Journal of rheumatology. 2014;41(11):2277-2285.***

ii. ***Armstrong AW, Tuong W, Love TJ, et al. Treatments for nail psoriasis: a systematic review by the GRAPPA Nail Psoriasis Work Group. The Journal of rheumatology. 2014;41(11):2306-2314.***

iii. ***Barnabe C, Bessette L, Flanagan C, et al. Sex differences in pain scores and localization in inflammatory arthritis: a systematic review and metaanalysis. The Journal of rheumatology. 2012;39(6):1221-1230.***

iv. ***Behrens F, Canete JD, Olivieri I, van Kuijk AW, McHugh N, Combe B. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. Rheumatology (Oxford, England). 2015;54(5):915-926.***

v. ***Betts KA, Griffith J, Friedman A, Zhou ZY, Signorovitch JE, Ganguli A. An indirect comparison and cost per responder analysis of adalimumab, methotrexate and apremilast in the treatment of methotrexate-naive patients with psoriatic arthritis. Current medical research and opinion. 2016;32(4):721-729.***

vi. ***Boehncke WH, Alvarez Martinez D, Solomon JA, Gottlieb AB. Safety and efficacy of therapies for skin symptoms of psoriasis in patients with psoriatic arthritis: a systematic review. The Journal of rheumatology. 2014;41(11):2301-2305.***

vii. ***Bravo Vergel Y, Hawkins NS, Claxton K, et al. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford, England). 2007;46(11):1729-1735.***

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viii. ***Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Annals of the rheumatic diseases. 2013;72(4):517-524.***

ix. ***Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. The Journal of rheumatology. 2006;33(7):1452-1456.***

x. ***Cawson MR, Mitchell SA, Knight C, et al. Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic arthritis. BMC musculoskeletal disorders. 2014;15:26.***

xi. ***Coates LC, Kavanaugh A, Ritchlin CT. Systematic review of treatments for psoriatic arthritis: 2014 update for the GRAPPA. The Journal of rheumatology. 2014;41(11):2273-2276.***

xii. ***Coto-Segura P, Eiris-Salvado N, Gonzalez-Lara L, et al. Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: a systematic review and meta-analysis. The British journal of dermatology. 2013;169(4):783-793.***

xiii. ***Desai RJ, Thaler KJ, Mahlknecht P, et al. Comparative Risk of Harm Associated With the Use of Targeted Immunomodulators: A Systematic Review. Arthritis care & research. 2016;68(8):1078-1088.***

xiv. ***Fang N, Jiang M, Fan Y. Association Between Psoriasis and Subclinical Atherosclerosis: A Meta-Analysis. Medicine. 2016;95(20):e3576.***

xv. ***Gladman DD. Traditional and newer therapeutic options for psoriatic arthritis: an evidence-based review. Drugs. 2005;65(9):1223-1238.***

xvi. ***Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Annals of the rheumatic diseases. 2014;73(2):414-419.***

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xvii. *Lamel SA, Myer KA, Younes N, Zhou JA, Maibach H, Maibach HI. Placebo response in relation to clinical trial design: a systematic review and meta-analysis of randomized controlled trials for determining biologic efficacy in psoriasis treatment. Archives of dermatological research. 2012;304(9):707-717.*

xviii. *Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. RMD open. 2015;1(1):e000017.*

xix. *Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. Journal of the American Academy of Dermatology. 2013;69(6):1014-1024.*

xx. *Nannini C, Cantini F, Niccoli L, et al. Single-center series and systematic review of randomized controlled trials of malignancies in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis receiving anti-tumor necrosis factor alpha therapy: is there a need for more comprehensive screening procedures? Arthritis and rheumatism. 2009;61(6):801-812.*

xxi. *Nash P. Therapies for axial disease in psoriatic arthritis. A systematic review. The Journal of rheumatology. 2006;33(7):1431-1434.*

xxii. *O'Connor J, Rice S, Smith A, et al. The Clinical and Cost Effectiveness of Ustekinumab for the Treatment of Psoriatic Arthritis: A Critique of the Evidence. PharmacoEconomics. 2016;34(4):337-348.*

xxiii. *Orbai AM, Weitz J, Siegel EL, et al. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. The Journal of rheumatology. 2014;41(11):2290-2294.*

xxiv. *Paccou J, Wendling D. Current treatment of psoriatic arthritis: update based on a systematic literature review to establish French Society for Rheumatology (SFR) recommendations for managing spondyloarthritis. Joint, bone, spine : revue du rhumatisme. 2015;82(2):80-85.*

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xxv. *Palazzi C, D'Angelo S, Leccese P, Padula A, Olivieri I. Safety of anti-tumor necrosis factor agents in psoriatic arthritis - an update. Expert opinion on drug safety. 2014;13(2):191-196.*

xxvi. *Pereda CA, Nishishinya MB, Martinez Lopez JA, Carmona L. Efficacy and safety of DMARDs in psoriatic arthritis: a systematic review. Clinical and experimental rheumatology. 2012;30(2):282-289.*

xxvii. *Qu X, Zhang S, Tao L, Song Y. A meta-analysis of apremilast on psoriatic arthritis long-term assessment of clinical efficacy (PALACE). Expert review of clinical pharmacology. 2016;9(6):799-805.*

xxviii. *Ramiro S, Smolen JS, Landewe R, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Annals of the rheumatic diseases. 2016;75(3):490-498.*

xxix. *Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. Annals of the rheumatic diseases. 2008;67(6):855-859.*

xxx. *Ritchlin CT. Therapies for psoriatic enthesopathy. A systematic review. The Journal of rheumatology. 2006;33(7):1435-1438.*

xxxi. *Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Annals of the rheumatic diseases. 2015;74(3):480-489.*

xxxii. *Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. Jama. 2011;306(8):864-871.*

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xxxiii. ***Saad AA, Symmons DP, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. The Journal of rheumatology. 2008;35(5):883-890.***

xxxiv. ***Schoels MM, Braun J, Dougados M, et al. Treating axial and peripheral spondyloarthritis, including psoriatic arthritis, to target: results of a systematic literature search to support an international treat-to-target recommendation in spondyloarthritis. Annals of the rheumatic diseases. 2014;73(1):238-242.***

xxxv. ***Sevrain M, Villani AP, Rouzaud M, et al. Treatment (biotherapy excluded) of psoriatic arthritis: an appraisal of methodological quality of international guidelines. Journal of the European Academy of Dermatology and Venereology : JEADV. 2014;28 Suppl 5:33-39.***

xxxvi. ***Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. The Journal of rheumatology. 2006;33(7):1422-1430.***

xxxvii. ***Steiman AJ, Pope JE, Thiessen-Philbrook H, et al. Non-biologic disease-modifying antirheumatic drugs (DMARDs) improve pain in inflammatory arthritis (IA): a systematic literature review of randomized controlled trials. Rheumatology international. 2013;33(5):1105-1120.***

xxxviii. ***Ungprasert P, Thongprayoon C, Davis JM, 3rd. Indirect comparisons of the efficacy of subsequent biological agents in patients with psoriatic arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta-analysis. Clinical rheumatology. 2016;35(7):1795-1803.***

xxxix. ***Ungprasert P, Thongprayoon C, Davis JM, 3rd. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: A meta-analysis. Seminars in arthritis and rheumatism. 2016;45(4):428-438.***

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xl. Woolacott N, Bravo Vergel Y, Hawkins N, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2006;10(31):iii-iv, xiii-xvi, 1-239.

xli. Woolacott NF, Khadjesari ZC, Bruce IN, Riemsma RP. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. Clinical and experimental rheumatology. 2006;24(5):587-593.

A3. The PRISMA flowchart for the study flow for the Updated Review shows 101 records excluded before screening "as previously captured in ELLPHC162159 SLR" (appendices, page 22).(1)
Please provide a full reference and the PDF for ELLPHC162159 as well as a detailed rationale justifying this decision.

ELLPHC162159 refers to the initial systematic review of clinical efficacy that was commissioned by Eli Lilly from an external vendor. These references were excluded at this stage in the PRISMA flow chart as part of the abstract deduplication process.

A4. Please explain why the clinical effectiveness searches were limited to English language publications only.

Most key clinical publications are typically published in the English languages and all publications identified as relevant in previous appraisals in PsA were in the English language, therefore this restriction was applied in the search strategies to filter out in the early stages of the screening process the studies that were likely not to meet the inclusion criteria.

Patient population

A5. **Priority question:** A proportion of patients in SPIRIT-P1 were bDMARDs-naïve and SPIRIT-P2 included patients who were previously treated with one or more bDMARDs. The pre-treatment of these patients may be different from the pre-treatment of UK patients who would be eligible for biologic treatment.
   a) Please clarify whether patients included in those trials are representative of UK clinical practice.

The NICE criteria for initiating biologic treatment are that the person has peripheral arthritis with three or more tender joints and three or more swollen joints, and the

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psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination. All patients enrolled in the SPIRIT 1 study met the criteria of 3 or more tender swollen joints. It is important to note that SPIRIT P1 recruited patients with prior evidence of joint erosions or, if no evidence of joint erosions, a CRP > 6mg/L. This was to ensure the patients were prone to joint erosion in order to demonstrate that ixe could inhibit joint erosion in this study. At baseline, approximately 90% of patients had evidence of joint erosions. Given the extent of joint erosion, treatment with a bDMARD is more likely in these patients than a cDMARD.

Baseline DAS-28 and HAQ-DI scores were slightly lower in SPIRIT 1 than in the BSRBR cohort, suggesting a slightly lower level of disease activity at baseline in SPIRIT-P1. (2) In the Cambridge cohort of patients described in Stober 2018, the tender and swollen joint counts in patients treated with a first-line bDMARD were very similar to those in SPIRIT-P1 although the Cambridge cohort had lower CRP levels, suggesting that disease activity in SPIRIT-P1 may have been more severe than in the Cambridge cohort. (3)

In SPIRIT P1 15% of patients who entered the study were cDMARD naïve, 85% had received at least 1 cDMARD. The BSR-BR paper does not state how many cDMARDs patients had received at baseline but in order to meet NICE eligibility criteria, patients must have received at least two prior cDMARD. Stober 2018 reports only the proportion of patients (65%) receiving a concomitant cDMARD at the time they initiated TNF-alpha inhibitor therapy, which is a similar percentage as in the SPIRIT-P1 trial (64%).

Lilly believe the treatment pattern in the UK has changed since the publication of the BSRBR study, given the entry of several new biologic agents, therefore real world data were sourced from Adelphi that were collected in Q4 2015 to assess the representativeness of patients in SPIRIT-P1 and -P2 with UK clinical practice. (4) In addition, Lilly compared SPIRIT-P1 and -P2 results with the results reported in the most recent treatment pattern study published in UK PSA patients. (5)

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An analysis of UK PSA patients from the Adelphi Psoriatic Arthritis Disease Specific Programme (DSP), a cross sectional anonymized database was undertaken. In Q4 2015, [redacted] UK Rheumatologists and [redacted] UK dermatologists were recruited by field-based interviewers. UK based rheumatologists and dermatologists prospectively completed Patient Record Forms (PRFs) for their next 10 consulting adult (≥18 years) PsA patients. A total of [redacted] patient record forms were completed for UK PSA Patients: [redacted] bDMARD-naïve PSA patients and [redacted] bDMARD-experienced PSA patients.

Ogdie et al (2013) reported the prevalence and treatment patterns of UK PSA patients based on The Health Improvement Network (THIN), a large population-based medical records database in the UK. (5) Two cohorts were derived from THIN to examine the prevalence of PsA in a cross-sectional study among all patients aged 18 to 90 years and among a sub-cohort of 4900 psoriasis patients aged 45 to 65 years. Prescription codes were used to describe therapies after the diagnosis of PsA. Among 4.8 million patients in THIN between the ages of 18 and 90 years, 9045 patients had at least one medical code for PsA. Of those patients, 45.9% with PsA have been prescribed DMARDs. Among the 4064 confirmed psoriasis patients, the prevalence of PsA was 8.6% (95% CI 7.7%, 9.5%). PsA was more prevalent among patients with severe psoriasis [odds ratio (OR) 3.34; 95% CI 2.40, 4.65].

Patients in the UK Adelphi DSP had a similar age distribution, time since PSA diagnosis, time since PSA symptom onset as in SPIRIT-P1. The UK PSA patients in Adelphi DSP had slightly higher rates of prior csDMARD use: [redacted] % of UK PSA Bio-naive patients in Adelphi DSP versus 58.9% of patients in SPIRIT-P1 who received prior csDMARD use and were randomized to Ixekizumab 80mg Q4W. The THIN database (2013) reports 45.9% (n=4,155) had prior DMARD use (independent of being bio-naïve or bio-experienced). The rate of prior use in SPIRIT-P1 is fairly generalisable to UK practice when comparing rate of prior DMARD use in the THIN database

Whilst, there is slightly higher rates of prior csDMARD use in UK clinical practice as captured by ADELPHI DSP, Lilly believe SPIRIT results are still generalizable to the UK as IXE80MGQ4W is effective independent of the number of prior DMARDs used. Based on integrated data from SPIRIT-P1 & -P2, IXE80MGQ4W was superior to placebo on ACR 20 & ACR 50 response rates [NRI] independent of whether the patient

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had an inadequate response to 1 prior DMARD, 2 prior DMARDs or >=3 DMARDs. Please note the sample size is too small to conduct this analysis just for bDMARD-naïve patients, hence the results are based on integrated data.

Table 1 Primary PsA Placebo-Controlled Integrated Analysis Set: SPIRIT-P1 & SPIRIT-P2

	Placebo (n=224)	**Ixekizumab 80MGQ4W (n=229)**
Inadequate Response to 1 DMARD [N]	[redacted]	[redacted]
ACR 20 Response Rate at week 24 [NRI]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value vs placebo	[redacted]	[redacted]
Inadequate Response to 2 DMARDs [N]	[redacted]	[redacted]
ACR 20 Response Rate at week 24 [NRI]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value vs placebo	[redacted]	[redacted]
Inadequate Response to >=3 DMARDs [NRI]	[redacted]	[redacted]
ACR 20 Response Rate at week 24 [NRI]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value vs placebo	[redacted]	[redacted]
Inadequate Response to 1 DMARD [N]	[redacted]	[redacted]
ACR 50 Response Rate at week 24 [NRI]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value vs placebo	[redacted]	[redacted]
Inadequate Response to 2 DMARDs [N]	[redacted]	[redacted]
ACR 50 Response Rate at week 24 [NRI]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value vs placebo	[redacted]	[redacted]
Inadequate Response to >=3 DMARDs [NRI]	[redacted]	[redacted]
ACR 50 Response Rate at week 24 [NRI]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value vs placebo	[redacted]	[redacted]

Based on baseline severity markers, patients in SPIRIT-P1 had higher baseline CRP, greater number of tender and swollen joints than Adelphi DSP, and despite this, patients achieved consistent or higher rates of ACR 20/50/70 response rates than treatments endorsed by NICE for use in UK clinical practice. Lilly believe as patients

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enrolled into SPIRIT-P1 have more active disease at baseline than reported in UK practice, then at least the same level of ACR response rates would be expected to be achieved in UK practice as was demonstrated by SPIRIT-P1.

UK PSA patients in the Adelphi DSP programme had a higher rate of baseline PASI than those enrolled in SPIRIT-P1. However for the subset of patients in SPIRIT-P1 and SPIRIT-P2 [integrated dataset] who met the criteria for moderate to severe psoriasis (PASI>=12, BSA>=10 and sPGA>=3), very good response rates were achieved. Please note the sample size is too small to run this analysis specific for bio-naïve patients.

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Table 2 - Comparison of baseline characteristics in SPIRIT-P1, Adelphi DSP and Ogdie et al (2013)

	SPIRIT-P1					ADELPHI DSP UK PSA Patients	THIN Database Ogdie et al (2013)
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	Bio-Naïve (N=[redacted])	UK PSA Patients ALL Comers[d] (N=9,045)
Age, mean years (SD)	50.6 (12.3)	48.6 (12.4)	49.1 (10.1)	49.8 (12.6)	49.5 (11.9)	[redacted]	44.8
Male, n(%)	48 (45.3)	51 (50.5)	45 (42.1)	48 (46.6)	192 (46.0)	[redacted]	4,588 (50.7)
Number of patients by region, n (%)						[redacted]	
Europe	76 (71.7)	73 (72.3)	80 (74.8)	77 (74.8)	306 (73.4)	[redacted]	UK - 9,045 Unless stated [n]
Rest of the world	30 (28.3)	28 (27.7)	27 (25.2)	26 (25.2)	111 (26.6)	[redacted]	
Weight category, n (%)						[redacted]	NR
< 80 kg	44 (41.5)	33 (32.7)	43 (40.2)	54 (52.4)	174 (41.7)	[redacted]	
≥ 80 to < 100 kg	45 (42.5)	36 (35.6)	43 (40.2)	34 (33.0)	158 (37.9)	[redacted]	
≥ 100 kg	17 (16.0)	32 (31.7)	21 (19.6)	15 (14.6)	85 (20.4)	[redacted]	
Mean BMI, kg/m^2 (SD)	29.2 (6.3)	32.1 (11.4)	30.2 (8.4)	28.6 (6.6)	30.0 (8.5)	[redacted]	NR
Time since PsA diagnosis, mean years (SD) [n]	6.3 (6.9)	6.9 (7.5)	6.2 (6.4)	7.2 (8.0)	6.7 (7.2)	[redacted]	NR
Time since PsA onset, mean years (SD) [n]	6.3 (6.9)	6.9 (7.6)	6.2 (6.4)	7.2 (8.0)	6.7 (7.2)	[redacted]	NR
Previous non-biologic systemic agent, n (%)	67 (63.2)	64 (63.4)	63 (58.9)	72 (69.9)	266 (63.8)	[redacted]	4155 (45.9)

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	SPIRIT-P1					ADELPHI DSP UK PSA Patients	THIN Database Ogdie et al (2013)
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	Bio-Naïve (N=[redacted])	UK PSA Patients ALL Comers[d] (N=9,045)
Previous methotrexate	45 (42.5)	43 (42.6)	37 (34.6)	45 (43.7)	170 (40.8)	[redacted]	3003 (33.2)
Previous sulfasalazine	20 (18.9)	26 (25.7)	19 (17.8)	30 (29.1)	95 (22.8)	[redacted]	1891 (20.9)
Previous leflunomide	13 (12.3)	15 (14.9)	19 (17.8)	10 (9.7)	57 (13.7)	[redacted]	480 (5.3)
Previous apremilast	-	-	-	-	-	[redacted]	NR
Current methotrexate use, n (%)	59 (55.7)	57 (56.4)	57 (53.3)	53 (51.5)	226 (54.2)	[redacted]	NR
cDMARD use, n(%) Past Current	 24 (22.6) 69 (65.1)	 20 (19.8) 67 (66.3)	 22 (20.6) 68 (63.6)	 23 (22.3) 63 (61.2)	 89 (21.3) 267 (64.0)	[redacted] [redacted] [redacted]	 NR
CRP (mg/L), mean (SD) [n] CRP category >6 mg/L, n (%)	15.1 (23.6) 41 (38.7)	(13.2 (19.1) 39 (38.6)	12.8 (16.4) 38 (35.5)	15.1 (25.9) 49 (47.6)	14.1 (21.5) 167 (40.0)	[redacted] [redacted]	 NR
Tender joint count 68 joints, mean (SD)	19.2 (13.0)	19.3 (13.0)	20.5 (13.7)	21.5 (14.1)	20.1 (13.4)	[redacted]	NR
Swollen joint count 66 joints, mean (SD)	10.6 (7.3)	9.9 (6.5)	11.4 (8.2)	12.1 (7.2)	11.0 (7.4)	[redacted]	NR
Percentage of BSA for patients with baseline psoriasis mean (SD) BSA ≥3, n (%) [n]	14.4 (20.2) 67 (67.7)	14.8 (19.2) 68 (72.3)	15.1 (16.3) 73 (73.0)	12 (15.6) 59 (64.8)	14.1 (17.9) 267 (69.5)	[redacted]	NR 4,305(47.6)

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	SPIRIT-P1					ADELPHI DSP UK PSA Patients	THIN Database Ogdie et al (2013)
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	Bio-Naïve (N=[redacted])	UK PSA Patients ALL Comers[d] (N=9,045)
PASI score in patients ≥3% BSA, mean (SD)	6.2 (7.5)	5.5 (6.5)	6.9 (6.6)	6.0 (7.0)	6.1 (6.9)	[redacted]	NR

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The rate of prior csDMARD use is consistent in SPIRIT-P2 with the Adelphi DSP dataset. 77.5% of bio-experienced patients randomized to IXE80MGQ4W received prior csDMARD use compared to [redacted] % of bio-experienced patients in the Adelphi DSP dataset.

In SPIRIT-P2 more patients had an inadequate response to 2 TNFs than was reported in the Adelphi DSP programme. Approximately 35% of patients in SPIRIT-P2 (33.6% - 37.4% of patients depending on arm randomized to in SPIRIT-P2) had inadequate response to 2 TNFs versus [redacted] % with prior exposure to 2 biologics in Adelphi DSP dataset. Given SPIRIT-P2 included a higher proportion of patients with prior exposure to 2 TNFs and we know the majority of the population had discontinued due to inadequate response to treatment, you would expect these results to be replicated in UK clinical practice in a population with a lower rates of exposure to multiple biologics. Results below indicate consistent response to IXE80MGQ4W in patients with inadequate response to 1 or 2 TNFs, Lilly thus believe the results from SPIRIT-P2 could be generalizable to the UK.

Patients in SPIRIT-P2 generally have more severe disease at baseline than those bio-experienced patients treated in UK clinical practice as captured by Adelphi DSP. SPIRIT-P2 included a population with higher baseline CRP scores, greater proportion of patients with baseline CRP >6mg/dl and a greater number of tender joints at baseline. Usually patients who exhibit markers of greater disease severity are more difficult to treat. Given Ixekizumab 80mgQ4W ACR responses in TNF experienced population is consistent with bio-naïve population, one would again expect the results to be replicated in a UK cohort in clinical practice.

Table 3 - Comparison of baseline characteristics in SPIRIT-P2 and Adelphi DSP

Demographic parameter	SPIRIT-P2				ADELPHI DSP UK PSA Patients
	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)	Bio-experienced (N=[redacted])
Age, mean years (SD)	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)	51.9 (12.0)	[redacted]
Male, n(%)	56 (47.5)	63 (51.6)	50 (40.7)	169 (46.6)	[redacted]

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Demographic parameter	SPIRIT-P2				ADELPHI DSP UK PSA Patients
	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)	Bio-experienced (N=[redacted])
Number of patients by region, n (%)					[redacted]
Europe	50 (42.4)	49 (40.2)	50 (40.7)	149 (41.0)	[redacted]
Rest of the world	8 (6.8)	8 (6.6)	10 (8.1)	26 (7.2)	[redacted]
Weight category, n (%)					[redacted]
< 80 kg	38 (32.2)	45 (36.9)	55 (44.7)	138 (38.0)	[redacted]
≥ 80 to < 100 kg	47 (39.8)	41 (33.6)	43 (35.0)	131 (36.1)	[redacted]
≥ 100 kg	33 (28.0)	36 (29.5)	25 (20.3)	94 (25.9)	[redacted]
Mean BMI, kg/m2 (SD)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)	30.9 (7.2)	[redacted]
Time since PsA diagnosis, mean years (SD) [n]	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)	10.0 (8.2)	[redacted]
Time since PsA onset, mean years (SD) [n]	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)	10.0 (8.2)	[redacted]
Previous non-biologic systemic agent, n (%)	90 (76.3)	95 (77.9)	103 (83.7)	288 (79.3)	[redacted]
Previous methotrexate	69 (58.5)	69 (56.6)	72 (58.5)	210 (57.9)	[redacted]
Previous sulfasalazine	31 (26.3)	38 (31.1)	29 (23.6)	98 (27.0)	[redacted]
Previous leflunomide	25 (21.2)	26 (21.3)	29 (23.6)	80 (22.0)	[redacted]
Previous apremilast	5 (4.2)	8 (6.6)	3 (2.4)	16 (4.4)	[redacted]
Current methotrexate use, n (%)	40 (33.9)	48 (39.3)	61 (49.6)	149 (41.0)	[redacted]
cDMARD use, n(%)					[redacted]
Past	66 (55.9)	62 (50.8)	50 (40.7)	178 (49.0)	[redacted]
Current	52 (44.1)	60 (49.2)	73 (59.3)	185 (51.0)	[redacted]
Previous biologic agent, n (%)	118 (100)	122 (100)	123 (100)	363 (100)	[redacted]
Prior TNFi experience, n (%)					[redacted]
Inadequate responder to 1 TNFi	68 (57.6)	71 (58.2)	65 (52.8)	204 (56.2)	[redacted]
Inadequate responder to 2 TNFi	41 (34.7)	41 (33.6)	46 (37.4)	128 (35.3)	[redacted]
Intolerance to a TNFi	9 (7.6)	10 (8.2)	12 (9.8)	31 (8.5)	[redacted]
CRP (mg/L), mean (SD) [n]	12.1 (19.6)	17.0 (27.5)	13.5 (26.1)	14.2 (24.7)a	[redacted]
CRP category >6 mg/L, n (%)	57 (49.1)	60 (50.4)	53 (43.1)	170 (47.5)a	[redacted]
Tender joint count 68 joints, mean (SD) [n]	23.0 (16.2)	22.0 (14.1)	25.0 (17.3)	23.4 (15.9)	[redacted]
Swollen joint count 66 joints, mean (SD) [n]	10.3 (7.4)	13.1 (11.2)	13.5 (11.5)	12.3 (10.3)	[redacted]
Percentage of BSA for patients who have baseline plaque psoriasis, mean (SD)	9.0 (12.7)	12.5 (17.4)	11.6 (18.6)	11.0 (16.4)	[redacted]
BSA ≥ 3%, n (%)	67 (62.6)	68 (61.8)	68 (63.0)	203 (62.5)	[redacted]

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Demographic parameter	SPIRIT-P2				ADELPHI DSP UK PSA Patients
	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)	Bio-experienced (N=[redacted])
PASI score in patients ≥3% BSA, mean (SD)	7.1 (7.1)	9.3 (9.1)	8.8 (10.3)	8.4 (8.9)	[redacted]

The rate of prior use of cDMARD use (1,2 or ≥3) was higher in the Taltz integrated SPIRIT-p1 and –P2 program (62.1% prior use) versus [redacted] % in Adelphi DSP and 46.4% in the THIN database. NICE criteria indicates patients should be intolerant, contra-indicated or failed at least 2 DMARDs. Given this the subset of patients who are closest to representing the NICE criteria are the subset who have received >=3 cDMARDS. Approximately 10% of patients in the integrated SPIRIT-P1 and –P2 dataset had been exposed to ≥3 cDMARDs, which is consistent with Adelphi DSP program ([redacted] %) and is much higher than reported in the THIN database (3.8%). The patients enrolled into SPIRIT-P1 and –P2 can therefore be regarded as fairly generalisable to the PSA population in UK clinical practice.

Table 4 - Prior cDMARD use in SPIRIT-P1 and SPIRIT-P2, Adelphi DSP and Ogdie et al (2013)

	SPIRIT-P1 and SPIRIT-P2 ITT Population				Adelphi DSP UK PSA Patients	THIN Database
	PBO (N=224)	IXE80MGQ4W (N=229)	IXE80MGQ2W (N=226)	Total (N=679)	N=371 (integrated: bio-naïve & bio-experienced)	N= 9,045 All Comers
Previous DMARD Use n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4836 (53.5)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2819 (31.2)
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1049 (11.6%)
>=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	341 (3.8%)

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Based on baseline demographics (including age, time since diagnosis, rates of prior use of csDMARDs and rates of prior biologic use and markers of disease severity) either being consistent with SPIRIT-P1 and P2 or in favour of the likelihood of a better response in a UK clinical practice cohort on the basis of less severe disease, Lilly believe, SPIRIT-P1 and P2 are expected to be generalizable to a UK PSA cohort.

b) Please explain the potential effect of including less/more heavily pre-treated patients on the clinical and cost effectiveness of ixekizumab.

More heavily pre-treated patients may be likely to have more severe disease, having exhausted more treatment options compared to less heavily pre-treated patients. Due to the small patient numbers meeting the criteria of at least two prior cDMARDs, the analysis results in Table 19 of CS Document B were based on the placebo-controlled integrated data set, which includes bDMARD-naïve patients from SPIRIT-P1 and bDMARD-experienced patients from SPIRIT-P2. While a significantly greater proportion of patients who received either of the ixekizumab doses achieved an ACR 20 response at week 24 compared to placebo, a comparison of the integrated data set with the ACR response rates from the ITT populations in the SPIRIT-P1 and SPIRIT-P2 trials would be confounded by prior bDMARD exposure as a treatment effect modifier.

The clinical outcomes of more or less heavily pre-treated patients on the clinical effectiveness of comparator treatments listed in the scope were not widely reported in the trials identified in the systematic review of clinical efficacy. As it would not be possible to facilitate a comparison to other treatments, it is not possible to comment on the impact of these patient groups on the cost-effectiveness of ixekizumab.

c) Please provide 12 and 16 weeks results for all reported outcomes in the subgroup of patients eligible for treatment with biologics (referred to as the "NICE ITT population" in the company submission).

The availability of week 12 and week 16 data for the 'NICE ITT' population for the reported outcomes was limited, given the small patient numbers. As it was not possible to obtain this data for all outcomes, only ACR 20/50/70 outcomes in SPIRIT-P2 and PASI 75/90/100 are presented in Table 5. Where available, results obtained using a non-responder imputation (NRI) are presented.

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Table 5 - ACR 20/50/70 and PASI 75/90/100 outcomes at weeks 12 and 16 in the 'NICE ITT' population

Study *Endpoint*	Placebo	Adalimumab	IXE80Q4W	IXE80Q2W
SPIRIT-P1 (observed)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75, week 12 *n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75, week 16 *n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90, week 12 *n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90, week 16 *n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100, week 12 *n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100, week 16 *n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
SPIRIT-P2 (NRI)	[redacted]	NA	[redacted]	[redacted]
PASI 75, week 12 *n (%)*	[redacted]	NA	[redacted]	[redacted]
PASI 75, week 16 *n (%)*	[redacted]	NA	[redacted]	[redacted]
PASI 90, week 12 *n (%)*	[redacted]	NA	[redacted]	[redacted]
PASI 90, week 16 *n (%)*	[redacted]	NA	[redacted]	[redacted]
PASI 100, week 12 *n (%)*	[redacted]	NA	[redacted]	[redacted]
PASI 100, week 16 *n (%)*	[redacted]	NA	[redacted]	[redacted]
SPIRIT-P2 (NRI)	[redacted]	NA	[redacted]	[redacted]
ACR 20, week 12 *n (%)* *95% CI*	[redacted]	NA	[redacted]	[redacted]
ACR 20, week 16 *n (%)* *95% CI*	[redacted]	NA	[redacted]	[redacted]
ACR 50, week 12 *n (%)* *95% CI*	[redacted]	NA	[redacted]	[redacted]
ACR 50, week 16 *n (%)*	[redacted]	NA	[redacted]	[redacted]

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Study *Endpoint*	Placebo	Adalimumab	IXE80Q4W	IXE80Q2W
95% CI				
ACR 70, week 12 *n (%)* *95% CI*	[redacted]	NA	[redacted]	[redacted]
ACR 70, week 16 *n (%)* *95% CI*	[redacted]	NA	[redacted]	[redacted]

d) Please provide 12 and 16 week results for the NMA outcomes listed in Tables 15 and 16 of the company submission (CS) appendices.(1) Please only include results of trials conducted in patients eligible for biologic treatment for psoriatic arthritis (PsA) in the UK, according to the final scope issued by NICE.(6)

The clinical outcomes of interest for the economic model were not reported for the 'NICE ITT population' in the publications identified in the systematic literature review of clinical efficacy. An NMA based on the NICE ITT population data from the SPIRIT-P1 and SPIRIT-P2 trials would not compare similar populations and given the small numbers of patients meeting this criteria in the treatment arms of the SPIRIT trials, a large amount of heterogeneity would be expected in the results, therefore NMA were not conducted for this population.

e) Please provide the footnote for the asterisk used in Table 15 of the CS appendices.(1)

The footnote associated with the asterisk is: * Outcomes were not reported for bDMARD-naive subgroup at the response assessment timepoint specified in NICE guidance, therefore overall population data are used.

A6. The number of patients and percentages by region reported for SPIRIT-P2 does not add up. Please provide a corrected breakdown of regions and countries of participants in the SPIRIT-P1 and SPIRIT-P2 trials (cf. Table 9 of the CS(7)).

The corrected breakdown of regions and countries of participants are presented in Table 6.

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Table 6 - Breakdown of regions and countries of participants in the SPIRIT-P1 and SPIRIT-P2 trials

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)
Number of patients by region, n (%)									
Europe	76 (71.7)	73 (72.3)	80 (74.8)	77 (74.8)	306 (73.4)	50 (42.4)	49 (40.2)	50 (40.7)	149 (41.0)
Rest of the world	30 (28.3)	28 (27.7)	27 (25.2)	26 (25.2)	111 (26.6)	68 (57.6)	73 (59.8)	73 (59.3)	214 (59.0)
Numbers of patients by countries, n (%)									
Australia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Belgium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bulgaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Czech Republic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)
Germany	[redacted]								
Japan	[redacted]								
Italy	[redacted]								
Mexico	[redacted]								
Netherlands	[redacted]								
Ireland	[redacted]								
Poland	[redacted]								
Russia	[redacted]								
Spain	[redacted]								
Taiwan, Province of China	[redacted]								
Ukraine	[redacted]								
United Kingdom	[redacted]								

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Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	PBO (N=106)	ADA40Q2W (N=101)	IXE80Q4W (N=107)	IXE80Q2W (N=103)	Total (N=417)	PBO (N=118)	IXE80Q4W (N=122)	IXE80Q2W (N=123)	Total (N=363)
United States	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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A7. Please discuss the differences in outcomes (e.g. Tender Joint Count (TJC), Swollen Joint Count (SJC), DAS-28, HAQ-DI) when comparing the British Society for Rheumatology Biologics Registry (BSRBR), SPIRIT-P1, and SPIRIT-P2 trials. Please discuss the potential impact on the study generalisability (cf. Table 32 of the CS(7)).

To be eligible for a biologic in England and Wales, and therefore to be included in the BSRBR cohort, patients must have had an inadequate response to at least two prior cDMARDs whereas the inclusion criteria for SPIRIT-P1 permitted patients with inadequate response to one or more prior cDMARD. The more stringent criteria of entry into the BSRBR may explain the more severe baseline disease scores relative to the SPIRIT trial populations. However, the BSRBR study was published in 2010 and is based on data collected between 2002 and 2006, therefore it may not be reflective of current experience of patients with PsA in the UK.

Baseline DAS28 in the BSRBR cohort is greater than the threshold defined as active disease whereas in the SPIRIT-P1 and SPIRIT-P2 trial populations, DAS-28 at baseline lies in the range of moderate disease activity. (2, 8, 9) Similarly, baseline HAQ-DI is lower in the SPIRIT trial populations.

TJC and SJC were measured using the abbreviated measure of 28 joints in BSRBR and using 68 and 66 joints respectively in the SPIRIT trials, therefore it is difficult to comment on the comparability of these outcomes. The absolute change from baseline DAS-28 scores were of a similar magnitude across the BSRBR and SPIRIT-P1 and SPIRIT-P2 trials. As the baseline score in BSRBR was over the threshold of 5.1, the level of response would be considered moderate whereas given that the baseline scores in SPIRIT-P1 and SPIRIT-P2 fall at or below the threshold, these patients would be considered to have a good response.

The median HAQ-DI scores in the overall SPIRIT-P1 and SPIRIT-P2 trial populations at baseline and 24 weeks as compared to baseline and six months in the BSRBR is also suggestive of less severe disease in the SPIRIT-P1 and SPIRIT-P2 trial populations (Table 7).

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Table 7 - HAQ-DI at baseline, week 24 and 6 months in SPIRIT-P1, SPIRIT-P2 and the BSRBR cohort

	SPIRIT-P1	SPIRIT-P2	BSRBR
Baseline	1.13 (0.75-1.63)	1.25 (0.75-1.63)	1.88 (1.38-2.25)
Week 24	0.75 (0.25-1.13)	0.88 (0.25-1.38)	NA
Month 6	NA	NA	1.25 (0.63-1.88)

Network meta-analysis

A8. **Priority question:** Some of the outcomes defined in company's decision problem (Table 1 of the CS) were not included in either the NMA or the economic model, namely ACR 20/ 50/ 70, minimal disease activity (MDA), Leeds Enthesitis Index (LEI), nail psoriasis severity index (NAPSI), Leeds Dactylitis Index (LDI), modified total Sharp score (mTSS), adverse events, and mortality. Please provide all relevant results, including NMA results, for at least ACR 20 and adverse events (e.g. any adverse events (AE), any serious adverse events (SAE), ≥ 1 treatment emergent adverse events (TEAE), treatment discontinuation, malignancies).

ACR20/50/70, NAPSI, LDI, MTA and mTSS outcomes from the SPIRIT trials are described in Appendices N, O and P of the company submission. As the economic model is based on the York model, these outcomes were not used to inform the cost-effectiveness analysis. As such, network meta-analyses were not conducted for these endpoints, with the exception of ACR20/50/70, although a feasibility assessment of NAPSI in the bDMARD-naïve and bDMARD-experienced populations was conducted following the initial clinical efficacy systematic review.

The networks for NAPSI at all time points are presented in Figure 1 and Figure 2. Given the small number of studies in the network and the inconsistency of time points with response assessment timepoints specified by NICE, the analysis of NAPSI was not considered feasible. Due to the limited data availability in the initial SLR of clinical efficacy, the NMA feasibility assessments following the updated clinical efficacy SLR focussed only on key clinical measures and those used to informed the economic analysis.

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Figure 1 - feasibility assessment network of NAPSI in bDMARD-naive population (all timepoints)

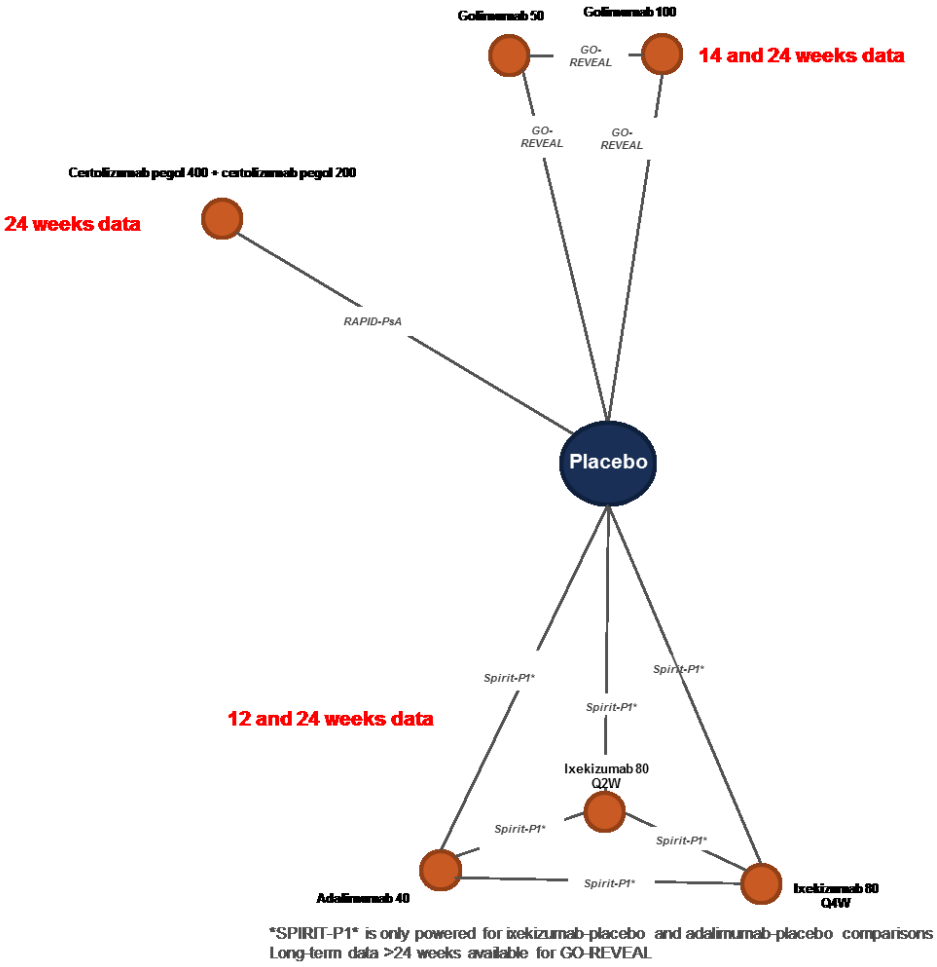

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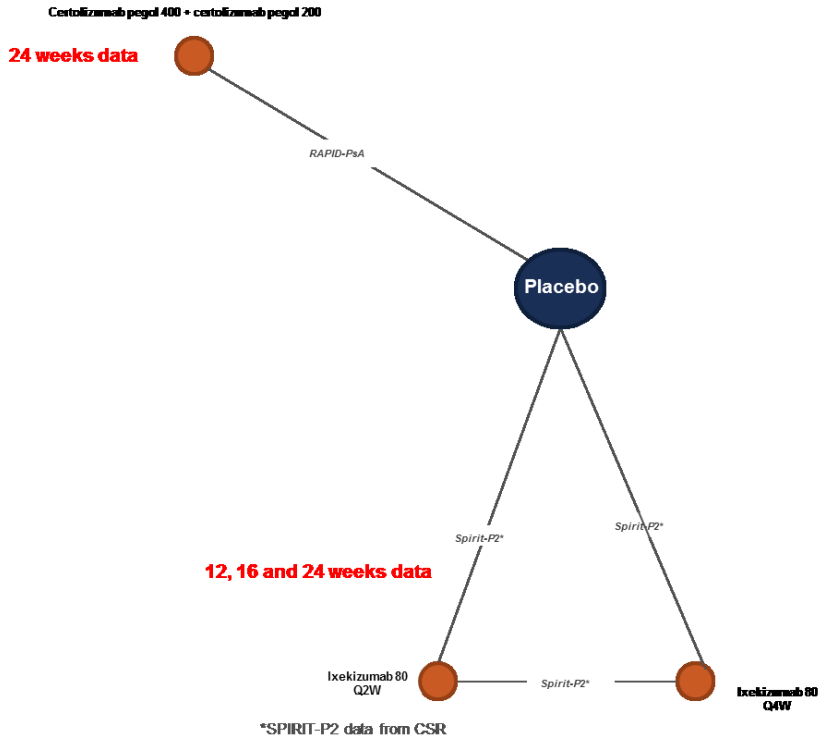
Figure 2 - feasibility assessment network of NAPSI in bDMARD-experienced population (all timepoints)



The results of the ACR 20/50/70 NMAs are presented for the bDMARD-naïve population in Table 8 and for the bDMARD-experienced population in Table 9.

Table 8 – Conditional probabilities of achieving ACR20, ACR50 and ACR70 response - bDMARD-naive population

Treatment	ACR20	ACR50	ACR70
Placebo	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg Q2W	[redacted]	[redacted]	[redacted]
Apremilast 30 mg BID	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	[redacted]
Golimumab 50 mg Q4W	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]

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Secukinumab 150 mg Q4W	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg Q4W	[redacted]	[redacted]	[redacted]

Table 9 - ACR20, ACR50 and ACR70 response rates - bDMARD-experienced population

Treatment	ACR20	ACR50	ACR70
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg Q12W	[redacted]	[redacted]	[redacted]

Network meta-analyses were conducted for the overall population on the following endpoints: the proportion of patients experiencing treatment-emergent adverse events (TEAEs) in Table 10, serious adverse events (SAEs) in Table 11; and treatment discontinuation due to AEs in Table 12.

Table 10 – Conditional probabilities of experiencing a TEAE for each treatment

Treatment	TEAEs
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Certolizumab pegol pooled doses	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]
Placebo	[redacted]

Table 11 – Conditional probabilities of experiencing a SAE for each treatment

Treatment	SAEs
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]
Certolizumab pegol pooled doses	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]
Golimumab 50 mg Q4W	[redacted]

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Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]
Secukinumab 150 mg Q4W	[redacted]
Secukinumab 300 mg Q4W	[redacted]
Ustekinumab 45 mg Q12W	[redacted]
Ustekinumab 90 mg Q12W	[redacted]

Table 12 – Conditional probabilities of experiencing a DAE for each treatment

Treatment	DAEs
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]
Certolizumab pegol pooled doses	[redacted]
Golimumab 50 mg Q4W	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]
Ustekinumab 45 mg Q12W	[redacted]
Ustekinumab 90 mg Q12W	[redacted]
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]

A9. **Priority question:** Please provide a discussion of the clinical similarity of the trials included in each NMA, e.g. disease severity, previous treatments and length of follow-up. This should expand on the information presented in Tables 13, 17, and 18 of the appendices.(1)

Tables 17 and 18 describe the population characteristics of the included trials. Table 17 includes details about patient age, proportions of male patients, proportions of patients of different races and/or ethnicity, BMI and weight; while Table 18 reports baseline disease characteristics such as tender and swollen joint counts, CRP concentration and ESR, PASI, HAQ-DI and mTSS scores.

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Across the 12 studies included in the bDMARD-naive PASI analysis, the mean age of patients was broadly similar, ranging between 45.2 and 51.4 years. One study, Mease 2000, reported estimates of age as medians, which ranged from 43.5 to 46.0 years. The proportion of males in each treatment arm varied somewhat, with a majority of studies including between 40.0% and 61.0% of male patients. A notable exception to this, was the infliximab arm of the IMPACT 2 trial, where 71.0% of patients were male. All the studies included predominantly white/Caucasian participants (between 83.0% and 99.0% of patients in each treatment arm). In the six trials where it was reported, BMI was similar, with values ranging from 28.6 to 32.1. Compared to BMI, there was a wider variability in mean weight (range from 81.6 to 91.6 kg) across the majority of trials. In Mease 2000, where weight was reported as median, values were 81.4 and 90.7 kg.

With regards to baseline disease characteristics, joint counts were available for the majority of studies included in the bDMARD-naive network and varied widely: mean tender joint count ranges were 17.1–25.8 and 18–29.3 in trials informing the PASI and PsARC analyses, respectively; mean swollen joint count ranged from 9.2 to 14.7 and 9.2 to 18.4 across the trials informing the PASI and PsARC analyses, respectively.

Of the included 14 studies, 11 reported baseline CRP and two reported baseline ESR. There was a large variance in the reported baseline CRP: for trials informing PASI as well as trials informing PsARC, the mean CRP concentration ranged from 8.4–23.0 (median values reported for Mease 2000, RAPID-PsA and OPAL BROADEN ranged from 4.3 to 14.0). Baseline ESR was only reported in two trials (Mease 200 and Rapid-PsA), as median estimate, with values ranging from 16.0 to 35.0.

In trials informing the PASI analysis, mean baseline PASI scores varied widely, with reported values ranging between 4.2–16.2; although the majority of trials reported relatively consistent values around the 7–10 range, large variances were reported in the FUTURE 2 (11.9, 16.2 and 11.6 in the SEC 300mg Q4W, SEC 150mg Q4W and placebo arms, respectively) and IMPACT trials (5.1 and 4.2 in the IFX 5mg Q8W and placebo arms, respectively). In trial reporting median PASI scores, values ranged from 6.0 to 10.1. Similar mean values were reported in the trials informing the PsARC trials.

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Baseline HAQ-DI data were consistent between trials, with reported values ranging between 0.9–1.3.

Only half of the included trials reported baseline mTSS data (ADEPT, SPIRIT-P1, GO-REVEAL, RAPID-PsA, Mease 2004 and OPAL BROADEN; only median values were available for OPAL BROADEN). A large discrepancy in mTSS scores was observed across the studies informing the PASI analysis as well as studies informing the PsARC analysis: 15.2–24.4 and 15.2–25.89, respectively.

The mean age reported in the SPIRIT-P2 and PSUMMIT 2 trials were not comparable between studies as PSUMMIT 2 reported median values and SPIRIT-P2 reported mean values. Within the SPIRIT-P2 trial however, the mean ages between treatment arms were consistent, ranging from 51.5 to 52.6 years.

Across the two studies in the base case bDMARD-experienced network, there was moderate variance in the proportions of male patients (range 40.7–51.6%). Only the SPIRIT-P2 trial reported proportions of patients of different races/ethnicity, with most participants included in the study being of white/Caucasian ethnicity.

Similarly to mean age, baseline BMI values were not comparable between studies due to differences in reported estimates (medians for the PSUMMIT 2 trial and means for the SPIRIT-P2 trial). Weight was only reported in the SPIRIT-P2 trial (85.2–91.0 kg).

With respect to baseline disease characteristics, PSUMMIT 2 and SPIRIT-P2 primarily reported median and mean values, respectively. In general, the median values reported in the PSUMMIT 2 trial are numerically lower, but not dissimilar, to the mean values reported in the SPIRIT-P2 trial for joint counts and CRP concentration. A reverse trend was observed for PASI and HAQ-DI scores.

Table 19 summarises the patient baseline data in trials informing the PsARC and PASI analyses for the bDMARD-naïve and -experienced networks pertaining to the following: duration of PsA, proportion of patients with history of prior biologic use, proportion of patients with history of prior cDMARD use and patients with cDMARD at baseline.

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For trials informing the bDMARD-naïve PASI analysis, duration of PsA were relatively similar across the various treatment arms, mostly falling within the 6–9 year range (complete range was 5.3 to 11.7). The lowest duration of 5.3 years was reported in the ADA 40mg Q2W arm of the OPAL BROADEN trial; whereas the highest duration of 11.7 years was reported in the INF 5mg/kg Q8W arm of the IMPACT trial.

For trials informing the bDMARD-naïve PsARC analysis, the durations of PsA across trials were also similar across the various treatment arms, with most values within the 7–9 year range (complete range was 6.2 to 11.7). The lowest duration of 6.2 years was reported in the IXE 80mg Q4W arm of the SPIRIT-P1 trial; whereas the highest duration of 11.7 years was reported in the INF 5mg/kg Q8W arm of the IMPACT trial, the same value reported in the PASI analysis.

Please note, Mease 2000 reported duration of PsA data; however, these were only available as median values.

Of the 14 included trials, the majority (n=8; 66.7%) included patients with no prior history of biologic use. Five trials (FUTURE 2, PALACE 1, PALACE 2, RAPID-PsA and PALACE 3) included patients with prior history of biologic use. One trial, Mease 2000, did not report this data/information. In studies including participants with prior biologic use, the proportions of biologic-experienced patients ranged from 14.2% (APR 30mg BID) to 37.0% (SEC 150mg Q4W).

Of the 14 included trials, only half (n=7) reported data on prior history of cDMARD use. In the remaining trials which do report the data, the proportion of patients with prior history of cDMARDs varied widely, with values ranging from 19.8% in the ADA 40mg Q2W arm of the SPIRIT-P1 trial to 100% in the ADA 40mg Q2W arm of the Genovese 2007 and OPAL BROADEN studies. Additionally, a wide range was also reported for the proportion of patients with cDMARD use at baseline, with values falling between 41.0% and 100% across studies and treatment arms.

In the trials informing the bDMARD-experienced networks, PsA duration data were also reported as median in the PSUMMIT 2 trial and mean in the SPIRIT-P2 trial, with values numerically lower in the PSUMMIT 2 trial (4.5–5.5 years versus 11.1–13.8).

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The overall PSUMMIT 2 trial included a mixed population (however, biologic-experienced data was available) whereas the entire SPIRIT-P2 trial population had prior history of biologic use. Prior cDMARD data were not reported for PSUMMIT 2.

cDMARD use at baseline was similar between the treatment arms of PSUMMIT 2 and SPIRIT-P2, with all arms reporting >40%; the lowest percentage was 44.1% in the placebo arm, while the highest proportion (59.3%) was reported in the IXE 80mg Q2W arm, both from the SPIRIT-P2 trial.

A10. The NMA results have been reported as percentages or means for each treatment without statistical comparisons between treatments in the NMA, especially between ixekizumab and other treatments. Please provide odds ratios with 95% credible intervals (CrI) for the treatment comparisons of interest for binary outcomes or mean differences with CrI for continuous outcomes.

Odds ratios with 95% CrIs are presented for PsARC and PASI in the base case bDMARD-naïve population in Table 13 and in the base case bDMARD-experienced population in Table 14.

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Table 13 - UK 1A (biologic naive) network, PsARC - Odds Ratio (OR) cross tabulation (row treatment versus column treatment)

Placebo	Adalimumab 40 mg Q2W	Apremilast 30 mg BID	Certolizumab pegol pooled doses	Etanercept 25 mg BIW/50 mg QIW	Golimumab 50 mg Q4W	Infliximab 5 mg/kg Q8W	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Secukinumab 150 mg Q4W	Secukinumab 300 mg Q4W
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**Adalimumab 40 mg Q2W**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Apremilast 30 mg BID**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Certolizumab pegol pooled doses**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Etanercept 25 mg BIW/50 mg QIW**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Golimumab 50 mg Q4W**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Infliximab 5 mg/kg Q8W**	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Ixekizumab 80 mg Q2W**	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Ixekizumab 80 mg Q4W**	[redacted]	[redacted]

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Placebo	Adalimumab 40 mg Q2W	Apremilast 30 mg BID	Certolizumab pegol pooled doses	Etanercept 25 mg BIW/50 mg QIW	Golimumab 50 mg Q4W	Infliximab 5 mg/kg Q8W	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Secukinumab 150 mg Q4W	Secukinumab 300 mg Q4W
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Secukinumab 150 mg Q4W**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Secukinumab 300 mg Q4W**
Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*										

Table 14 - UK 1B (biologic experienced) network, PsARC - Odds Ratio (OR) cross tabulation (row treatment versus column treatment)

	Placebo	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Ustekinumab 45 mg Q12W
Placebo		[redacted]	[redacted]	[redacted]
[redacted]		**Ixekizumab 80 mg Q2W**	[redacted]	[redacted]
[redacted]		[redacted]	**Ixekizumab 80 mg Q4W**	[redacted]
[redacted]		[redacted]	[redacted]	**Ustekinumab 45 mg Q12W**
Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*				

Table 15 - Mean difference in HAQ-DI changes from baseline versus placebo

	Mean ± SD	95% LCrL	95% CrI UCrL
Ixekizumab Q4w	[redacted]	[redacted]	[redacted]

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Ixekizumab Q2w	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]

Table 16 - Mean difference in HAQ-DI changes from baseline versus placebo

	Mean ± SD	**95% LCrL**	**95% CrI UCrL**
Ixekizumab Q4w	[redacted]	[redacted]	[redacted]
Ixekizumab Q2w	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]

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A11. **Priority question:** Please provide the data used in each NMA model in a format suitable for entering directly into R and/or WinBUGs.

The datasets used in each NMA model are saved in the following files in the folder 'A11. NMA datasets'.

- ***PsARC:***
    - ***12 week data for ixekizumab, bDMARD-naïve: psarc_UK1A.xlsx***
    - ***16 week data for ixekizumab, bDMARD-experienced: psarc_UK1B.xlsx***
    - ***16 week data for ixekizumab, bDMARD-naïve: psarc_UK2A.xlsx***
    - ***16 week data for ixekizumab, bDMARD-experienced: psarc_UK2B.xlsx***
    - ***12 week data for ixekizumab, placebo response adjustment, bDMARD-naïve: psarc_UK1A_baserisk.xlsx***
    - ***12 week data for ixekizumab, inclusion of secukinumab and certolizumab pegol, bDMARD-experienced: psarc_UK3B.xlsx***
- ***PASI:***
    - ***12 week data for ixekizumab, bDMARD-naïve: pasi_UK1A.xlsx***
    - ***16 week data for ixekizumab, bDMARD-experienced: pasi_UK1B.xlsx***
    - ***16 week data for ixekizumab, bDMARD-naïve: pasi_UK2A.xlsx***
    - ***16 week data for ixekizumab, bDMARD-experienced: pasi_UK2B.xlsx***
    - ***12 week data for ixekizumab, placebo response adjustment, bDMARD-naïve: pasi_UK1A_baserisk.xlsx***
    - ***12 week data for ixekizumab, inclusion of secukinumab and certolizumab pegol, bDMARD-experienced: pasi_UK3B***
- ***HAQ-DI conditional on PsARC response:***

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- ***HAQ conditional on PsARC response.csv***
- ***HAQ conditional on PsARC non-response.csv***

A12. **Priority question:** Please provide the results of all random effects NMA models.

Random effects model results are presented here for the PASI and PsARC endpoints for the UK bDMARD-naïve population. PASI and PsARC results are presented for the base case network using week 12 data for ixekizumab in Table 17 and Table 18; the network using week 16 data for ixekizumab in Table 19 and

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Table 20, and the meta-regression adjusting for baseline risk in Table 21 and Table 22.

As expected, the pattern of modelled treatment effects and magnitudes of benefit are similar from the fixed and random effects NMAs, but the credible intervals were wider with random effects. The UK bDMARD-experienced networks (UK1B, UK2B, UK3B) only have a single study on each edge and therefore there are no data to estimate the between study heterogeneity needed to fit random effects models in these networks.

Table 17 - Conditional probabilities from a random effects model of achieving each PASI response category for each treatment in the bDMARD-naïve population; ixekizumab data at week 12

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30 mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]

Table 18 - Probability from a random effects model of achieving PsARC response for each treatment in the bDMARD-naive population; ixekizumab data at week 12

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]
Certolizumab pegol pooled doses	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]
Golimumab 50 mg Q4W	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]

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Secukinumab 150 mg Q4W	[redacted]
Secukinumab 300 mg Q4W	[redacted]

Table 19 - Conditional probabilities of achieving each PASI response category for each treatment in the bDMARD-naïve population; ixekizumab data at week 16

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30 mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]

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Table 20 – Probability from a random effects model of achieving PsARC response for each treatment in the bDMARD-naive population; ixekizumab data at week 16

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]
Certolizumab pegol pooled doses	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]
Golimumab 50 mg Q4W	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]
Secukinumab 150 mg Q4W	[redacted]
Secukinumab 300 mg Q4W	[redacted]

Table 21 - Conditional probabilities from a random effects model of achieving each PASI response category with placebo-response adjustment for each treatment in the bDMARD-naïve population; ixekizumab data at week 12

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30 mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]

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Table 22 – Probability from a random effects model of achieving PsARC response for each treatment with placebo-response adjustment in the bDMARD-naive population; ixekizumab data at week 12

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]
Certolizumab pegol pooled doses	[redacted]
Etanercept 25 mg BIW/50 mg QIW	[redacted]
Golimumab 50 mg Q4W	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]
Secukinumab 150 mg Q4W	[redacted]
Secukinumab 300 mg Q4W	[redacted]

Random effects NMA results are presented in Table 23 for HAQ-DI conditional on PsARC response and Table 24 for PsARC non-response.

Table 23 - Random effects model for change from baseline HAQ-DI conditional on PsARC response

	Mean	95% LCrL	95% CrI UCrL
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab Q4w	[redacted]	[redacted]	[redacted]
Ixekizumab Q2w	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]

Table 24 - Random effects model for change from baseline HAQ-DI conditional on PsARC non-response

	Mean	95% LCrL	95% CrI UCrL
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab Q4w	[redacted]	[redacted]	[redacted]

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Ixekizumab Q2w	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]

A13. **Priority question:** Please present and discuss the main conclusion from the NMA regarding the clinical effectiveness of ixekizumab compared to other treatments.

The number of studies in each NMA network was generally small, often with only one study per pairwise comparison of treatments. For PASI in the bDMARD-naïve population, the best performing treatment was [redacted], but it was [redacted] [redacted]. [redacted] from all therapies. For PsARC response, the best performing treatments were [redacted], [redacted] and [redacted], which were [redacted]. [redacted] from all other therapies.

In the bDMARD-experienced population, the networks were particularly small, usually consisting of at most five studies. The PsARC response rates for both ixekizumab schedules were [redacted] ustekinumab. A key assumption of the probit model used to estimate PASI response rates was the assumption that the treatment effect on the probit scale is the same for all PASI response categories. This allows the model to use all studies in the network even if they do not report data for all PASI outcomes. However, as only the ixekizumab studies reported data in the PASI 100 category, the predicted PASI 100 results for the other treatments are all dependent on the ixekizumab trials. In the bDMARD-experienced population, the small sample of patients informing the two studies in the network results in a higher estimated PASI responses than would be expected based on a naïve comparison of the PASI 75 outcomes from the SPIRIT-P2 and PSUMMIT2 trials.

From the Bayesian NMA of HAQ-DI score change from baseline, it appears that all biologic treatments except [redacted] separated from placebo in the

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population of biologic-naive PsARC responders. In this population, [redacted] ***were associated with the largest absolute change from baseline. Among the PsARC non-responders, the magnitude of change was much smaller than the one observed in the PsARC responder population, showing the responsiveness of HAQ-DI over changes in joint improvement over time.*** [redacted] ***were the treatments associated with the largest observed change from baseline.***

A14. Please discuss which of the reported NMAs you consider to be the most clinically relevant.

PsARC is the basis of the NICE treatment continuation rule for all recommended b/tsDMARDs and as such, is a major determinant of transition probabilities in the model. Lilly would consider this NMA to be the most clinically relevant across model subgroups; however, the NMAs for HAQ-DI and PASI are also important. HAQ-DI measures the functional capacity of a patient with PsA and so the NMA for HAQ-DI conditional on PsARC response is relevant to all model subgroups. PASI is clinically relevant only in the subgroups with concomitant mild-to-moderate or moderate-to-severe psoriasis.

Section B: Clarification on cost effectiveness data

Literature searching

B1. Please explain why the cost-effectiveness model input searches were limited to English, French, German, Italian or Spanish language publications only.

The cost-effectiveness model input searches were conducted as part of a wider review covering a European scope, therefore publications in other languages were not expected to have a country setting that would be relevant to the scope of the search. Language restrictions were applied as exclusion criteria for the screening process; no language restriction was applied in the search strategies.

B2. For all cost-effectiveness and model input searches documented in pages 154-174 of the appendices,(1) please provide the following information for each individual search strategy:
   a) Date parameters of search
   b) Database host/interface (e.g. Ovid, ProQuest etc.)

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c) Number of results retrieved by each search line and the overall number retrieved from each database.

An initial review was undertaken in 2015 and the updated review in 2017. As the updated search included additional sources and search terms, the time period of the updated review encompassed that of the initial review and the results were deduplicated against the records identified in the initial review in order to capture any additional studies identified by the expansion of the search terms.

The requested information is presented along with the search strategies for published CEM studies in Table 25 to Table 28 and Table 34 to Table 37; for model inputs studies in Table 29 to Table 32 and Table 38 to Table 41; and for HTA agency websites in Table 33 and Table 42.

Table 25 Search for CEM studies in PubMed

Search	Query - models	Items found
1	"Arthritis, psoriatic"[Mesh] OR psoria*[tiab]	33816
2	"Economics, Pharmaceutical"[Mesh] OR pharmacoeconomic*[tiab]	4412
3	"health economic"[tiab] OR "health economics"[tiab]	3832
4	"economic evaluation"[tiab]	5430
5	"economic models"[tiab] OR "economic model"[tiab]	1559
6	"economic analysis"[tiab]	3113
7	"decision analytic model"[tiab] OR "decision analytic models"[tiab]	1165
8	"cost-effectiveness"[tiab] OR "cost effectiveness"[tiab]	36540
9	"cost-minimisation"[tiab] OR "cost minimisation[tiab]" OR "cost-minimization"[tiab] OR "cost minimization"[tiab]	881
10	"Cost-Benefit Analysis"[Mesh] OR "cost-benefit"[tiab] OR "cost benefit"[tiab]	64285
11	"cost-utility"[tiab] OR "cost utility"[tiab]	2606
12	"budget impact"[tiab]	459
13	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	90119
14	#1 AND #13	232
15	animals[mesh] NOT (animals[mesh] AND human[mesh])	3946733
16	#14 NOT #15	232
17	"Letter" [Publication Type] OR "Editorial" [Publication Type] OR "Historical Article" [Publication Type]	1526917
18	#16 NOT #17	219

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Search	Query - models	Items found
19	#16 AND #17 Filters: Publication date from 2000/01/01	202

*PubMed.gov. Available at: www.ncbi.nlm.nih.gov/pubmed. Search date: 2014-11-13

Table 26 Search for CEM studies in EMBASE

Search	Query - models	Items found
1	Arthritis, Psoriatic/ or psoria$3.ti,ab.	33516
2	*pharmacoeconomics/ or pharmacoeconomic*.ti,ab.	9520
3	*health economics/ or health economic$1.ti,ab.	10096
4	*economic evaluation/ or economic evaluation$1.ti,ab.	9384
5	economic model$1.ti,ab.	1915
6	economic analysis.ti,ab.	3504
7	decision analytic model$1.ti,ab.	1591
8	*cost effectiveness analysis/ or cost-effectiveness.ti,ab.	45371
9	*cost minimization analysis/ or cost minimi?ation.ti,ab.	1375
10	*cost benefit analysis/ or cost benefit.ti,ab.	10197
11	*cost utility analysis/ or cost utility.ti,ab.	3733
12	budget impact.ti,ab.	1220
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	77669
14	1 and 13	425
15	(letter or editorial or historical article).pt	933493
16	14 not 15	414
17	animal/ not (animal/ and human/)	438969
18	16 not 17	414
19	limit 18 to yr="2000 -Current"	403

*Embase. Available at: http://www.ovid.com/. Search date: 2014-11-13

Table 27 Search for CEM studies in CRD-HTA

Search	Query - models	Items found
1	(psoriatic arthritis) IN HTA	26
2	(pharmacoeconomic) OR (pharmacoeconomics) IN HTA	20
3	(health economic) OR (health economics) IN HTA	239
4	(economic evaluation) IN HTA	520
5	(economic model) OR (economic models) IN HTA	93
6	(economic analysis) IN HTA	160
7	(decision analytic model) IN HTA	27
8	(cost effectiveness) IN HTA	1677

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Search	Query - models	Items found
9	(cost minimization) OR (cost minimisation) IN HTA	23
10	(cost benefit) IN HTA	471
11	(cost utility) IN HTA	92
12	(budget impact) IN HTA	78
13	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	2339
14	#1 AND #13	2

*Centre for Reviews and Dissemination. Available at: www.york.ac.uk/inst/crd/. Search date: 2014-11-13

Table 28 Search for CEM studies in HEED

Search	Query	Items found
1	*psoriatic arthritis* ***in All data*** *AND ((pharmacoeconomic) OR (pharmacoeconomics) OR (health economic) OR (health economics) OR (economic evaluation) OR (economic model) OR (economic models) OR (economic analysis) OR (decision analytic model) OR (cost effectiveness) OR (cost minimization) OR (cost minimisation) OR (cost benefit) OR (cost utility) OR (budget impact))* ***in All data***	17

*Health Economic Evaluations Database (HEED). Available at: http://onlinelibrary.wiley.com/book/10.1002/9780470510933. Search date: 2014-11-13

Table 29 Search for model inputs studies in PubMed

Search	Query	Items found
1	"Arthritis, psoriatic"[Mesh] OR psoria*[tiab]	33860
2	"instrument"[text] OR "instruments"[text] OR "Questionnaires"[Mesh] OR "questionnaire"[text] OR "questionnaires"[text]	606457
3	"Quality of Life"[Mesh] OR "life quality"[text] OR "life qualities"[text] OR "utilities"[text] OR "utility"[text] OR "health assessment questionnaire"[text] OR "HAQ"[text] OR "quality of well being"[text] OR "quality of wellbeing"[text] OR "quality adjusted life year"[tiab] OR "quality adjusted life years"[tiab] OR "QALY"[tiab] OR "patient reported outcome"[tiab] OR "patient reported outcomes"[tiab] OR "PRO"[tiab]	367225
4	#2 AND #3	60513
5	"Euroqol"[text] OR "euro qol"[text] OR "EQ5D" [text] OR "EQ 5D"[text] OR "EQ-5D"[text]	4589
6	"Short form 6 dimension"[text] OR "Short form 6 dimensions"[text] OR "short form six dimension"[text] OR "short form six dimensions"[text] OR (("short form"[text] OR "shortform"[text]) AND ("6 dimension"[text] OR "6 dimensions"[text] OR "six dimension"[text] OR "six dimensions"[text])) OR "SF6D"[text] OR "SF-6D"[text] OR "SF 6D"[text]	485
7	"Health Utilities Index"[text] OR "HUI"[text]	1114
8	"standard gamble"[text] OR "time trade-off"[text] OR "time trade off"[text]	1259
9	(#4 OR #5 OR #6 OR #7 OR #8)	63897
10	"Economics"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Health Expenditures"[Mesh] OR "Health Care Costs"[Mesh] OR "burden of illness"[tiab] OR cost[text] OR costs[text] OR "resource use"[text]	724406

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Search	Query	Items found
	OR "resource utilization"[text] OR "resource utilisation"[text] OR "work productivity"[text]	
11	"Great Britain"[Mesh] OR (("Great"[text] AND "Britain"[text]) OR "Great Britain"[text] OR ("United"[text] AND "Kingdom"[text]) OR "United Kingdom"[text] OR "UK"[text]) OR ("Japan"[Mesh] OR "Japan"[text]) OR "Japanese"[text] OR ("Germany"[Mesh] OR "Germany, West"[Mesh] OR "Germany, East"[Mesh] OR Germany[text] OR German[text]) OR ("France"[Mesh] OR “France”[text] OR “French”[text]) OR ("Italy"[Mesh] OR “Italy”[text] OR “Italian”[text]) OR ("Netherlands"[Mesh] OR “Netherlands”[text] OR “Dutch”[text] OR “Holland”[text]) OR (“Sweden”[Mesh] OR “Swedish”[text] OR “Sweden”[text]) OR (Spain[Mesh] OR “Spanish”[text] OR “Spain”[text])	1141467
12	#10 AND #11	82550
13	#9 OR #12	144766
14	#13 AND #1	751
15	animals[mesh] NOT (animals[mesh] AND human[mesh])	3948006
16	#14 NOT #15	751
17	"Letter" [Publication Type] OR "Editorial" [Publication Type] OR "Historical Article" [Publication Type]	1527646
18	#16 NOT #17	732
19	(#16 NOT #17) Filters: Publication date from 2000/01/01	683

*PubMed.gov. Available at: www.ncbi.nlm.nih.gov/pubmed. Search date 2014-11-17

Table 30 Search for model inputs studies in EMBASE

Search	Query	Items found
1	Arthritis, Psoriatic/ or psoria$3.ti,ab.	33546
2	(instrument or instruments).tw. or exp *questionnaire/ or questionnaire*.tw.	482512
3	exp *"quality of life"/ or life quality.tw. or life qualities.tw. or utilities.tw. or utility.tw. or health assessment questionnaire.tw. or HAQ.tw. or quality of well being.tw. or quality of wellbeing.tw. or quality adjusted life year$1.ti,ab. or QALY.ti,ab. or patient reported outcome$1.ti,ab. or PRO.ti,ab.	347100
4	2 and 3	43937
5	("Euroqol" or "euro qol" or "EQ5D" or "EQ 5D" or "EQ-5D").tw.	7637
6	exp *Short Form 36/ or "Short form 6 dimension".tw. or "Short form 6 dimensions".tw. or "short form six dimension".tw. or "short form six dimensions".tw. or (("short form" or "shortform") and ("6 dimension" or "6 dimensions" or "six dimension" or "six dimensions")).tw. or "SF6D".tw. or "SF-6D".tw. or "SF 6D".tw.	1203
7	("Health Utilities Index" or "HUI").tw.	1369
8	("standard gamble" or "time trade-off" or "time trade off").tw.	1485
9	4 or 5 or 6 or 7 or 8	50690
10	1 and 9	907
11	exp *"cost of illness"/ or exp *"cost"/ or exp *"health care cost"/ or exp *"hospitalization cost"/ or exp *health economics/ or ("burden of illness" or cost or costs or "resource use" or "resource utili?ation").tw.	430201

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Search	Query	Items found
12	(exp *United Kingdom/ or ("great" and "britain").tw. or "great britain".tw. or ("united" and "kingdom").tw. or "united kingdom".tw. or "UK".tw.) or (exp *Japan/ or Japan.tw. or Japanese.tw.) or (exp *Germany/ or Germany.tw. or German.tw.) or (exp *France/ or France.tw. or French.tw.) or (exp *Italy/ or Italy.tw. or Italian.tw.) or (exp *Netherlands/ or Netherlands.tw. or Dutch.tw. or Holland.tw.) or (exp *Sweden/ or Sweden.tw. or Swedish.tw.) or (exp *Spain/ or Spanish.tw. or Spain.tw.)	851316
13	11 and 12	39375
14	1 and 13	245
15	10 or 14	1118
16	animal/ not (animal/ and human/)	439221
17	15 not 16	1118
18	(letter or editorial or historical article).pt	930908
19	17 not 18	1114
20	limit 19 to yr="2000 -Current"	1089

*Embase. Available at: http://www.ovid.com/. Search date 2014-11-17

Table 31 Search for model inputs studies in CRD-HTA

Search	Query	Items found
1	(psoriatic arthritis) IN HTA	26
2	(instrument or instruments or questionnaire or questionnaires) IN HTA	255
3	("quality of life" or "life quality" or "life qualities" or utilities or utility or "health assessment questionnaire" or "HAQ" or "quality of well being" or "quality of wellbeing" or "quality adjusted life year" or "quality adjusted life years" or "QALY" or "patient reported outcome" or "patient reported outcomes" or "PRO") IN HTA	1207
4	#2 AND #3	72
5	("Euroqol" or "euro qol" or "EQ5D" or "EQ 5D" or "EQ-5D") IN HTA	19
6	("Short form 6 dimension" or "short form six dimensions" or (("short form" or "shortform") and ("6 dimension" or "six dimensions")) or "SF6D" or "SF-6D" or "SF 6D") IN HTA	2
7	("Health Utilities Index" or "HUI") IN HTA	2
8	("standard gamble" or "time trade-off" or "time trade off") IN HTA	5
9	#4 OR #5 OR #6 OR #7 OR #8	88
10	#1 AND #9	1
11	("cost" or "costs" or "health economics" or "burden of illness" or "resource use" or "resource utilization" or "resource utilisation" or "Health Expenditures") IN HTA	3331
12	("United Kingdom" or ("great" and "Britain") or "great Britain" or ("united" and "kingdom") or "UK") or (Japan or Japanese) or (Germany or German) or (France or French) or (Italy or Italian) or (Netherlands or Dutch or Holland) or (Sweden or Swedish) or (Spain or Spanish) IN HTA	7698
13	#11 AND #12	2090

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14	#1 AND #13	2
15	#10 OR #14	2

*Centre for Reviews and Dissemination. Available at: www.york.ac.uk/inst/crd/. Search date 2014-11-14

Table 32 Search for model inputs studies in HEED

Search	Query	Items found
1	*psoriatic arthritis in All data*	42

*Health Economic Evaluations Database (HEED). Available at: http://onlinelibrary.wiley.com/book/10.1002/9780470510933. Search date 2014-11-13

Table 33 Search strings for HTA agencies

HTA agency	Query	Link	Items found*
Germany - IQWiG	psoriatic arthritis	https://www.iqwig.de/en/search.1029.html	6
	Psoriasis Arthritis	https://www.iqwig.de/de/suche.1029.html?sp%5Bid%5D=5465cbab-e928-40bb-82da-4865c0a83502&sp%5Bquery%5D=psoriatische+arthritis&sp%5Blanguage%5D=de&sp%5Bpage%5D=1&sp%5Bgroup%5D=grouped&sp%5Blimit%5D=10&sp%5Bfiltertyp%5D=2&sp%5Bvon%5D=&sp%5Bbis%5D=&sp%5Bsort%5D=1&sp%5Bsort_order%5D=1	7
UK- NICE	psoriatic arthritis	http://www.nice.org.uk/search?q=psoriatic+arthritis	47
Canada- CADTH	psoriatic arthritis	http://www.cadth.ca/en/search?q=psoriatic+arthritis	10
France- HAS	psoriatic arthritis	http://www.has-sante.fr/portail/jcms/c_39085/en/recherche?portlet=c_39085&text=psoriatic+arthritis&opSearch=&lang=en	0
	rhumatisme psoriasique	http://www.has-sante.fr/portail/jcms/c_39085/en/recherche?portlet=c_39085&text=rhumatisme+psoriasique&opSearch=&lang=en	0
Australia- PBAC	psoriatic arthritis	http://agencysearch.australia.gov.au/s/search.html?query=psoriatic+arthritis&collection=agencies&scope_disable=off&scope=%2Finfo%2F&num_ranks=20&profile=pbs	127
Sweden- TLV	psoriatic arthritis	http://www.tlv.se/-/sok/?q=psoriatic+arthritis	0
	psoriasisartit	http://www.tlv.se/-/sok/?q=psoriasisatrit&tlvso=1&resid=1106811944&uaid=6AE7235E83946F0A034E6D5B12BCC3D2%3A3139322E37312E38352E313639%3A5247201666105236734&tlvst=true&tlvff=0&tlva=0&tlvl=-2	0
Netherlands- CVZ	psoriatic arthritis	http://www.zorginstituutnederland.nl/zoeken?query=psoriatic+arthritis	3

*Search date 2014-11-14

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Table 34 Search string for CEM studies in PubMed

Search	Query - models	Items found*
1	"Arthritis, psoriatic"[Mesh] OR psoria*[tiab]	40717
2	"Economics, Pharmaceutical"[Mesh] OR pharmacoeconomic*[tiab]	5074
3	"health economic"[tiab] OR "health economics"[tiab]	6080
4	"economic evaluation"[tiab]	7511
5	"economic models"[tiab] OR "economic model"[tiab]	2360
6	"economic analysis"[tiab]	4067
7	"decision analytic model"[tiab] OR "decision analytic models"[tiab]	1446
8	"cost-effectiveness"[tiab] OR "cost effectiveness"[tiab] OR "cost-effectiveness"[Mesh] OR "cost effectiveness"[Mesh]	47645
9	"cost control"[Mesh] OR "economic evaluation"[Mesh] OR "economic models"[Mesh] OR "economic model"[Mesh] OR "decision tree"[Mesh]	31504
10	"cost-minimisation"[tiab] OR "cost minimisation[tiab]" OR "cost-minimization"[tiab] OR "cost minimization"[tiab]	1128
11	"Cost-Benefit Analysis"[Mesh] OR "cost-benefit"[tiab] OR "cost benefit"[tiab]	76472
12	"cost-utility"[tiab] OR "cost utility"[tiab] OR "cost utility analysis"[Mesh]	3632
13	"markov chains"[tiab] OR "markov chaines"[Mesh] OR "monte carlo method"[tiab] OR "monte carlo method"[Mesh]	26738
14	"budget impact"[tiab]	975
15	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	138829
16	#1 AND #15	348
17	animals[mesh] NOT (animals[mesh] AND human[mesh])	4415233
18	#16 NOT #17	348
19	"Letter" [Publication Type] OR "Editorial" [Publication Type] OR "Historical Article" [Publication Type]	1753546
20	#18 NOT #19	326
21	#18 AND #19 Filters: Publication date from 2000/01/01	312

*PubMed.gov. Available at: www.ncbi.nlm.nih.gov/pubmed; Search date: 2017-06-12

Table 35 Search string for CEM studies in EMBASE via Ovid

Search	Query - models	Items found*
1	Arthritis, Psoriatic/ or psoria$3.ti,ab.	58,663
2	*pharmacoeconomics/ or pharmacoeconomic*.ti,ab.	10,968
3	*health economics/ or health economic$1.ti,ab.	23,388
4	*economic evaluation/ or economic evaluation$1.ti,ab.	13,731
5	economic model$1.ti,ab.	3,002
6	economic analysis.ti,ab.	5,349

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Search	Query - models	Items found*
7	decision analytic model$1.ti,ab.	2,320
8	*cost effectiveness analysis/ or cost-effectiveness.ti,ab.	69,764
9	exp "cost effectiveness analysis"/	124,488
10	exp "cost control"/	59,110
11	exp economic evaluation/	258,526
12	exp "cost utility analysis"/	7,547
13	exp "decision tree"/	8,572
14	exp economic model/	690
15	exp Markov chain/	1,379
16	exp Monte Carlo method/	29,899
17	markov chains.ti,ab.	518
18	monte carlo method.ti,ab.	2,249
19	*cost minimization analysis/ or cost minimi?ation.ti,ab.	1,856
20	*cost benefit analysis/ or cost benefit.ti,ab.	19,107
21	*cost utility analysis/ or cost utility.ti,ab.	5,552
22	budget impact.ti,ab.	2,317
23	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	338,486
24	1 and 23	1,004
25	(letter or editorial or historical article).pt	1,507,721
26	24 not 25	959
27	animal/ not (animal/ and human/)	1,355,915
28	26 not 27	959
29	limit 28 to yr="2000 -Current"	918

*Embase via Ovid. Available at: http://ovidsp.ovid.com/; search date: 2017-05-29; NOTE: Due to technical issues, the hits of the final search run on 2017-06-12 with the end result of 922 hits cannot be displayed; therefore, the hits of the search protocol are displayed here as approximation

Table 36 Search string for CEM studies in Medline via Ovid

Search	Query - models	Items found*
1	Arthritis, Psoriatic/ or psoria$3.ti,ab.	40,465
2	exp Economics, Pharmaceutical/ or pharmacoeconomic*.ti,ab.	5,081
3	*health economics/ or health economic$1.ti,ab.	5,650
4	*economic evaluation/ or economic evaluation$1.ti,ab.	14,832
5	economic model$1.ti,ab. or economic analysis.ti,ab. or economic evaluation.ti,ab.	12,599
6	decision analytic model$1.ti,ab.	1,519
7	*cost effectiveness analysis/ or cost-effectiveness.ti,ab. or exp "cost effectiveness analysis"/	94,495

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Search	Query - models	Items found*
8	exp "cost control"/ or cost control.ti,ab	32,327
9	exp Models, Economic/ or economic model.ti,ab.	13,733
10	exp Decision Trees/ or decision tree.ti,ab.	13,368
11	exp Markov Chains/ or markov chains.ti,ab.	12,486
12	exp Monte Carlo Method/ or monte carlo method.ti,ab.	27,549
13	*cost minimization analysis/ or cost minimi?ation.ti,ab. or exp "Costs and Cost Analysis"/	212,537
14	*cost benefit analysis/ or cost benefit.ti,ab. or exp cost-benefit analysis/	76,702
15	*cost utility analysis/ or cost utility.ti,ab. or exp "cost utility analysis"/	73,066
16	budget impact.ti,ab.	954
17	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	295,534
18	1 and 17	629
19	(letter or editorial or historical-article).pt	1,746,915
20	18 not 19	597
21	animal/ not (animal/ and human/)	4,383,369
22	20 not 21	596
23	limit 22 to yr="2000 -Current"	560

*Medline via Ovid. Available at: http://ovidsp.ovid.com/; Search date: 2017-06-12

Table 37 Search string for CEM studies in CRD-HTA

Search	Query - models	Items found*
1	(psoriatic arthritis) IN HTA	33
2	(pharmacoeconomic) OR (pharmacoeconomics) IN HTA	22
3	(health economic) OR (health economics) IN HTA	209
4	(economic evaluation) IN HTA	614
5	(economic model) OR (economic models) IN HTA	107
6	(economic analysis) IN HTA	191
7	(decision analytic model) IN HTA	26
8	(cost effectiveness) IN HTA	2036
9	(cost minimization) OR (cost minimisation) IN HTA	26
10	(cost benefit) IN HTA	572
11	(cost utility) IN HTA	99
12	(budget impact) IN HTA	94
13	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	2739
14	#1 AND #13	2

*Centre for Reviews and Dissemination. Available at: https://www.crd.york.ac.uk/CRDWeb/; Search date: 2017-06-12

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Table 38 Search string for model input studies in PubMed

Search	Query	Items found*
1	"Arthritis, psoriatic"[Mesh] OR psoria*[tiab]	40717
2	"instrument"[text] OR "instruments"[text] OR "Questionnaires"[Mesh] OR "questionnaire"[text] OR "questionnaires"[text]	694812
3	"Quality of Life"[Mesh] OR "life quality"[text] OR "life qualities"[text] OR "utilities"[text] OR "utility"[text] OR "health assessment questionnaire"[text] OR "HAQ"[text] OR "quality of well being"[text] OR "quality of wellbeing"[text] OR "quality of well-being" OR "quality adjusted life year"[tiab] OR "quality adjusted life years"[tiab] OR "QALY"[tiab] OR "patient reported outcome"[tiab] OR "patient reported outcomes"[tiab] OR "PRO"[tiab]	440018
4	"Health utilit$"[text] OR disutilit$[text] OR DALY[text] OR QALD[text] OR QALE[text] OR "value of life"[text] OR health year equivalent[text] OR QoL[text] OR HRQL[text] OR HRQoL[text] OR QWB[text] OR "visual analog$"[text] OR "disability adjusted"[text] OR "quality adjusted"[text] OR "utility weight$"[text] OR "utility preference$"[text] OR "index of well being"[text] OR "index of well-being"[text]	76924
5	#2 AND (#3 OR #4)	81047
6	"Euroqol"[text] OR "euro qol"[text] OR "EQ5D" [text] OR "EQ 5D"[text] OR "EQ-5D"[text]	6106
7	"Short form 6 dimension"[text] OR "Short form 6 dimensions"[text] OR "short form six dimension"[text] OR "short form six dimensions"[text] OR (("short form"[text] OR "shortform"[text]) AND ("6 dimension"[text] OR "6 dimensions"[text] OR "six dimension"[text] OR "six dimensions"[text])) OR "SF6D"[text] OR "SF-6D"[text] OR "SF 6D"[text]	588
8	"Short form 36"[text] OR "Short form 36"[text] OR "short form thirty six"[text] OR "short form thirty six"[text] OR (("short form"[text] OR "shortform"[text]) AND ("36"[text] OR "36"[text] OR "thirty six"[text] OR "thirty six"[text])) OR "SF36"[text] OR "SF-36"[text] OR "SF 36"[text]	21388
9	"Short form 12"[text] OR "Short form 12"[text] OR "short form twelve"[text] OR "short form twelve"[text] OR (("short form"[text] OR "shortform"[text]) AND ("12"[text] OR "12"[text] OR "twelve"[text] OR "twelve"[text])) OR "SF12"[text] OR "SF-12"[text] OR "SF 12"[text]	8485
10	"Short form 16"[text] OR "Short form 16"[text] OR "short form sixteen"[text] OR "short form sixteen"[text] OR (("short form"[text] OR "shortform"[text]) AND ("16"[text] OR "16"[text] OR "sixteen"[text] OR "sixteen"[text])) OR "SF16"[text] OR "SF-16"[text] OR "SF 16"[text]	2247
11	"Short form 20"[text] OR "Short form 20"[text] OR "short form twenty"[text] OR "short form twenty"[text] OR (("short form"[text] OR "shortform"[text]) AND ("20"[text] OR "20"[text] OR "twenty"[text] OR "twenty"[text])) OR 1344"SF20"[text] OR "SF-20"[text] OR "SF 20"[text]	278
12	"Health Utilities Index"[text] OR "HUI"[text]	1261
13	"standard gamble"[text] OR "time trade-off"[text] OR "time trade off"[text]	1403
14	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	99010
15	"Economics"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Health Expenditures"[Mesh] OR "Health Care Costs"[Mesh] OR "burden of illness"[tiab] OR cost[text] OR costs[text] OR "resource use"[text] OR "resource utilization"[text] OR "resource utilisation"[text] OR "work productivity"[text]	812885

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Search	Query	Items found*
16	“cost estimate$”[text] OR “cost variable$”[text] OR “cost of illness”[text] OR “cost of disease*”[text] OR “cost of sickness*”[text] OR “health?care cost*”[text] OR “drug costs/” OR (economic* OR cost*)[text] OR (price* OR budget* OR expenditure* OR fee*)[text] OR “value of money”[text] OR “monetary value”[text] OR (economic* OR pharmacoeconomic* OR “pharmaco economic*”)[text] OR “unit cost*”[text] OR “economic burden of disease/” OR “burden of illness/” OR “burden of illness”[text] OR “burden of disease*”[text] or “burden of sickness*”[text]	54226
17	“resource* use*”[text] OR “resource* used”[text] OR “resource* user”[text] OR (hospital OR doctor OR GP OR general practitioner OR nurse OR clinic OR surgery and (use* OR visit* OR attendance OR admission OR readmission))[text]	2630
18	medical leave/ OR “sick leave”[text] OR “disability leave$”[text] OR “work productivity”[text] OR “loss of productivity”[text] OR absenteeism[text] OR “absen* from work”[text]	22212
19	"Great Britain"[Mesh] OR (("Great"[text] AND "Britain"[text]) OR "Great Britain"[text] OR ("United"[text] AND "Kingdom"[text]) OR "United Kingdom"[text] OR "UK"[text]) OR ("Japan"[Mesh] OR "Japan"[text]) OR "Japanese"[text] OR ("Germany"[Mesh] OR "Germany, West"[Mesh] OR "Germany, East"[Mesh] OR Germany[text] OR German[text]) OR ("France"[Mesh] OR “France”[text] OR “French”[text]) OR ("Italy"[Mesh] OR “Italy”[text] OR “Italian”[text]) OR ("Netherlands"[Mesh] OR “Netherlands”[text] OR “Dutch”[text] OR “Holland”[text]) OR (“Sweden”[Mesh] OR “Swedish”[text] OR “Sweden”[text]) OR (Spain[Mesh] OR “Spanish”[text] OR “Spain”[text])	1153944
20	#15 OR #16 OR #17 OR #18	845962
21	#20 AND #19	89581
22	#14 OR #21	186082
23	#22 AND #1	1007
24	animals[mesh] NOT (animals[mesh] AND human[mesh])	4329741
25	#23 NOT #24	1007
26	"Letter" [Publication Type] OR "Editorial" [Publication Type] OR "Historical Article" [Publication Type]	1692376
27	#25 NOT #26	1007
28	(#25 NOT #26) Filters: Publication date from 2000/01/01	1006

*PubMed.gov. Available at: www.ncbi.nlm.nih.gov/pubmed; Search date: 2017-06-12

Table 39 Search string for model input studies in EMBASE via Ovid

Search	Query	Items found*
1	Arthritis, Psoriatic/ or psoria$3.ti,ab.	58,663
2	(instrument or instruments).tw. or exp *questionnaire/ or questionnaire*.tw.	730,561
3	exp *"quality of life"/ or life quality.tw. or life qualities.tw. or utilities.tw. or utility.tw. or health assessment questionnaire.tw. or HAQ.tw. or quality of well being.tw. or quality of wellbeing.tw. or quality of well-being.tw. or quality adjusted life year$1.ti,ab. or QALY.ti,ab. or patient reported outcome$1.ti,ab. or PRO.ti,ab.	537,765

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Search	Query	Items found*
4	"Health utilit$".tw. or disutilit$.mp. or DALY.tw. or QALD.tw. or QALE.tw. or value of life.tw. or health year equivalent.tw. or ((disability or quality) adj adjusted).tw. or QoL.tw. or HRQL.tw. or HRQoL.tw. or visual analog$.tw. or exp visual analog scale/ or (utility adj (weigh$ or preference$)).tw. or qwb.tw. or ((index of) and (wellbeing or well being or well-being)).tw. or (quality adj4 life).tw.	407,791
5	3 or 4	838,271
6	2 and 5	126,240
7	("Euroqol" or "euro qol" or "EQ5D" or "EQ 5D" or "EQ-5D").tw.	12,660
8	exp *Short Form 36/ or "Short form 6 dimension".tw. or "Short form 6 dimensions".tw. or "short form six dimension".tw. or "short form six dimensions".tw. or (("short form" or "shortform") and ("6 dimension" or "6 dimensions" or "six dimension" or "six dimensions")).tw. or "SF6D".tw. or "SF-6D".tw. or "SF 6D".tw.	2,312
9	exp *Short Form 36/ or "Short form 36".tw. or "Short form 36".tw. or "short form thirty six".tw. or "short form thirty six".tw. or (("short form" or "shortform") and ("36" or "36" or "thirty six" or "thirty six")).tw. or "SF36".tw. or "SF36".tw. or "SF36".tw.	20,386
10	exp *Short Form 12/ or "Short form 12".tw. or "Short form 12".tw. or "short form twelve".tw. or "short form twelve".tw. or (("short form" or "shortform") and ("12" or "12" or "twelve" or "twelve")).tw. or "SF12".tw. or "SF12".tw. or "SF12".tw.	9,873
11	exp *Short Form 20/ or "Short form 20".tw. or "Short form 20".tw. or "short form twenty".tw. or "short form twenty".tw. or (("short form" or "shortform") and ("20" or "20" or "twenty" or "twenty")).tw. or "SF12".tw. or "SF12".tw. or "SF12".tw.	5,637
12	("Health Utilities Index" or "HUI").tw.	1,847
13	("standard gamble" or "time trade-off" or "time trade off").tw.	1,965
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	148,985
15	1 and 14	1,848
16	exp *"cost of illness"/ or exp *"cost"/ or exp *"health care cost"/ or exp *"hospitalization cost"/ or exp *health economics/ or ("burden of illness" or cost or costs or "resource use" or "resource utili?ation").tw.	709,358
17	(Cost adj (estimate$ or variable$)).tw. or (Cost adj3 (illness or disease* or sickness*)).tw. or (Health?care adj cost).tw. or Drug costs/ or (Economic* or cost*).tw. or (Price* or budget* or expenditure* or fee*).tw. or (Value adj1 (money or monetary)).tw. or (Economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).tw. or (Unit adj1 cost).tw. or Economic burden of disease/ or Burden of illness/ or (Burden adj3 (illness or disease* or sickness*)).tw.	1,466,362
18	(Resource* adj4 utili*).tw. or (Resource* adj4 (use* or used or user)).tw. or ((hospital or doctor or GP or general practitioner or nurse or clinic or surgery) adj2 (use* or visit* or attendance or admission or readmission)).tw.	146,706
19	Medical leave/ or sick leave.tw. or Disability leave$.tw. or Work productivity.tw. or Loss of productivity.tw. or Absenteeism.tw. or ((absent or absence) adj from work).tw.	16,130
20	(exp *United Kingdom/ or ("great" and "britain").tw. or "great britain".tw. or ("united" and "kingdom").tw. or "united kingdom".tw. or "UK".tw.) or (exp *Japan/ or Japan.tw. or Japanese.tw.) or (exp *Germany/ or Germany.tw. or German.tw.) or (exp *France/ or France.tw. or French.tw.) or (exp *Italy/ or Italy.tw. or Italian.tw.) or (exp *Netherlands/ or Netherlands.tw. or Dutch.tw. or Holland.tw.)	1,282,117

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Search	Query	Items found*
	or (exp *Sweden/ or Sweden.tw. or Swedish.tw.) or (exp *Spain/ or Spanish.tw. or Spain.tw.)	
21	20 and (16 or 17 or 18 or 19)	127,273
22	1 and 21	663
23	15 or 22	2,400
24	animal/ not (animal/ and human/)	1,355,915
25	23 not 24	2,400
26	(letter or editorial or historical article).pt	1,507,721
27	25 not 26	2,388
28	limit 27 to yr="2000 -Current"	2,325

*Embase via Ovid. Available at: http://ovidsp.ovid.com/; search date: 2017-05-29; NOTE: Due to technical issues, the hits of the final search run on 2017-06-12 with the end result of 2,347 hits cannot be displayed; therefore, the hits of the search protocol are displayed here as approximation

Table 40 Search string for model input studies in Medline via Ovid

Search	Query	Items found*
1	exp Arthritis, Psoriatic/ or psoria$3.ti,ab.	40,465
2	(instrument or instruments).tw. or exp *questionnaire/ or questionnaire*.tw. or exp "Surveys and Questionnaires"/	1,175,505
3	exp "quality of life"/ or life quality.tw. or life qualities.tw. or utilities.tw. or utility.tw. or health assessment questionnaire.tw. or HAQ.tw. or quality of well being.tw. or quality of wellbeing.tw. or quality of well-being.tw. or quality adjusted life year$1.ti,ab. or QALY.ti,ab. or patient reported outcome$1.ti,ab. or PRO.ti,ab.	484,080
4	"Health utilit$".tw. or disutilit$.mp. or DALY.tw. or QALD.tw. or QALE.tw. or value of life.tw. or health year equivalent.tw. or ((disability or quality) adj adjusted).tw. or QoL.tw. or HRQL.tw. or HRQoL.tw. or visual analog$.tw. or exp visual analog scale/ or (utility adj (weigh$ or preference$)).tw. or qwb.tw. or ((index of) and (wellbeing or well being or well-being)).tw. or (quality adj4 life).tw.	273,701
5	3 or 4	634,470
6	2 and 5	132,856
7	("Euroqol" or "euro qol" or "EQ5D" or "EQ 5D" or "EQ-5D").tw.	735
8	exp *Short Form 36/ or "Short form 6 dimension".tw. or "Short form 6 dimensions".tw. or "short form six dimension".tw. or "short form six dimensions".tw. or (("short form" or "shortform") and ("6 dimension" or "6 dimensions" or "six dimension" or "six dimensions")).tw. or "SF6D".tw. or "SF-6D".tw. or "SF 6D".tw.	691
9	exp *Short Form 36/ or "Short form 36".tw. or "Short form 36".tw. or "short form thirty six".tw. or "short form thirty six".tw. or (("short form" or "shortform") and ("36" or "36" or "thirty six" or "thirty six")).tw. or "SF36".tw. or "SF36".tw. or "SF36".tw.	15,126
10	exp *Short Form 12/ or "Short form 12".tw. or "Short form 12".tw. or "short form twelve".tw. or "short form twelve".tw. or (("short form" or "shortform") and	7,322

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Search	Query	Items found*
	("12" or "12" or "twelve" or "twelve")).tw. or "SF12".tw. or "SF12".tw. or "SF12".tw.	
11	exp *Short Form 20/ or "Short form 20".tw. or "Short form 20".tw. or "short form twenty".tw. or "short form twenty".tw. or (("short form" or "shortform") and ("20" or "20" or "twenty" or "twenty")).tw. or "SF12".tw. or "SF12".tw. or "SF12".tw.	3,973
12	("Health Utilities Index" or "HUI").tw.	1,366
13	("standard gamble" or "time trade-off" or "time trade off").tw.	1,562
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	145,241
15	1 and 14	1,493
16	exp "cost of illness"/ or exp *"cost"/ or exp *"health care cost"/ or exp *"hospitalization cost"/ or exp *health economics/ or ("burden of illness" or cost or costs or "resource use" or "resource utili?ation").tw. or exp Economics/ or exp "Costs and Cost Analysis"/ or exp Health Expenditures/ or exp Health Care Costs/	865,181
17	(Cost adj (estimate$ or variable$)).tw. or (Cost adj3 (illness or disease* or sickness*)).tw. or (Health?care adj cost).tw. or Drug costs/ or (Economic* or cost*).tw. or (Price* or budget* or expenditure* or fee*).tw. or (Value adj1 (money or monetary)).tw. or (Economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).tw. or (Unit adj1 cost).tw. or Economic burden of disease/ or Burden of illness/ or (Burden adj3 (illness or disease* or sickness*)).tw.	1,184,178
18	(Resource* adj4 utili*).tw. or (Resource* adj4 (use* or used or user)).tw. or ((hospital or doctor or GP or general practitioner or nurse or clinic or surgery) adj2 (use* or visit* or attendance or admission or readmission)).tw.	101,763
19	Medical leave/ or sick leave.tw. or Disability leave$.tw. or Work productivity.tw. or Loss of productivity.tw. or Absenteeism.tw. or ((absent or absence) adj from work).tw.	10,490
20	(exp United Kingdom/ or ("great" and "britain").tw. or "great britain".tw. or ("united" and "kingdom").tw. or "united kingdom".tw. or "UK".tw.) or (exp Japan/ or Japan.tw. or Japanese.tw.) or (exp Germany, East/ or exp Germany/ or exp Germany, West/ or Germany.tw. or German.tw.) or (exp France/ or France.tw. or French.tw.) or (exp Italy/ or Italy.tw. or Italian.tw.) or (exp Netherlands/ or Netherlands.tw. or Dutch.tw. or Holland.tw.) or (exp Sweden/ or Sweden.tw. or Swedish.tw.) or (exp Spain/ or Spanish.tw. or Spain.tw.)	1,345,673
21	20 and (16 or 17 or 18 or 19)	156,272
22	1 and 21	348
23	15 or 22	1,746
24	animal/ not (animal/ and human/)	4,383,369
25	23 not 24	1,746
26	(letter or editorial or historical-article).pt	1,746,915
27	25 not 26	1,704
28	limit 27 to yr="2000 -Current"	1,632

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*Medline via Ovid. Available at: http://ovidsp.ovid.com/; search date: 2017-06-12

Table 41 Search string for model input studies in CRD-HTA

Search	Query	Items found*
1	(psoriatic arthritis) IN HTA	33
2	(instrument or instruments or questionnaire or questionnaires) IN HTA	341
3	("quality of life" or "life quality" or "life qualities" or utilities or utility or "health assessment questionnaire" or "HAQ" or "quality of well being" or "quality of well-being" or "quality of wellbeing" or "quality adjusted life year" or "quality adjusted life years" or "QALY" or "patient reported outcome" or "patient reported outcomes" or "PRO") IN HTA	1513
4	#2 AND #3	97
5	("Euroqol" or "euro qol" or "EQ5D" or "EQ 5D" or "EQ-5D") IN HTA	25
6	("Short form 6 dimension" or "short form six dimensions" or (("short form" or "shortform") and ("6 dimension" or "six dimensions")) or "SF6D" or "SF-6D" or "SF 6D") IN HTA	2
7	("Health Utilities Index" or "HUI") IN HTA	2
8	("standard gamble" or "time trade-off" or "time trade off") IN HTA	5
9	#4 OR #5 OR #6 OR #7 OR #8	115
10	#1 AND #9	1
11	("cost" or "costs" or "health economics" or "burden of illness" or "resource use" or "resource utilization" or "resource utilisation" or "Health Expenditures") IN HTA	3925
12	("United Kingdom" or ("great" and "Britain") or "great Britain" or ("united" and "kingdom") or "UK") or (Japan or Japanese) or (Germany or German) or (France or French) or (Italy or Italian) or (Netherlands or Dutch or Holland) or (Sweden or Swedish) or (Spain or Spanish) IN HTA	9122
13	#11 AND #12	2459
14	#1 AND #13	2
15	#10 OR #14	2

*Centre for Reviews and Dissemination. Available at: https://www.crd.york.ac.uk/CRDWeb/; Search date: 2017-06-12

Table 42 Search terms used for HTA agencies during updated review

HTA agency	Query	Link	Items found*
UK - NICE	Psoriatic arthritis	https://www.nice.org.uk/	2
UK - SMC	Psoriatic arthritis	https://www.scottishmedicines.org.uk/	9
UK - AWMSG	Psoriatic arthritis	http://www.awmsg.org/	3
France - HAS	rhumatisme psoriasique	http://www.has-sante.fr/portail/	2
Canada - CADTH	Psoriatic arthritis	https://www.cadth.ca/	4
Australia - PBAC	Psoriatic arthritis	http://www.pbs.gov.au/pbs/home	12

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HTA agency	Query	Link	Items found*
Sweden - TLV	Psoriasisartrit	http://tlv.se/	6
Germany - IQWiG	Psoriatic arthritis Psoriasisarthritis Psoriasis-Arthritis Schuppenflechtenarthritis	https://www.iqwig.de/	2
Germany – G-BA	Psoriatic arthritis Psoriasisarthritis Psoriasis-Arthritis Schuppenflechtenarthritis	https://www.g-ba.de/	2
Netherlands - ZIN	Psoriatic arthritis	https://www.zorginstituutnederland.nl/	0
Norway - NOKC	Psoriasisartrit	http://www.kunnskapssenteret.no/en/frontpage	0

*Search date: 2017-06-19

B3. HEED and the HTA database were searched for this submission. Please explain why NHS EED (NHS Economic Evaluation Database) was not searched.

The Centre for Reviews and Dissemination was searched for relevant cost-effectiveness data. The CRD search included the NHS EED, DARE and HTA databases.

Model structure

B4. **Priority question:** Response to treatment is a crucial element of the model structure, and informs the transition to the treatment continuation state. Response to treatment, assessed using the Psoriatic Arthritis Response Criteria (PsARC), is a function of change in disease state and not absolute disease severity. As a result, patients in the treatment continuation health state with response may be heterogeneous with regard to quality of life and costs.

a) Please provide the PsARC response rates for each comparator in each subgroup.

PsARC response rates are not publicly available for each comparator in each model subgroup. PsARC response rates are provided for the treatment arms in the ixekizumab trials in Table 43.

Table 43 PsARC response rates in model subgroups

	Placebo	ADA	IXE 80 Q4W	IXE 80 Q2W
SPIRIT-P1 (bDMARD-naïve)				
No psoriasis (N)	[redacted]	[redacted]	[redacted]	[redacted]
PsARC, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

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Mild-to-moderate psoriasis (N)	[redacted]	[redacted]	[redacted]	[redacted]
PsARC, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Moderate-to-severe psoriasis (N)	[redacted]	[redacted]	[redacted]	[redacted]
PsARC, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SPIRIT-P2 (bDMARD-experienced)				
No psoriasis (N)	[redacted]	[redacted]	[redacted]	[redacted]
PsARC	[redacted]	[redacted]	[redacted]	[redacted]
Mild-to-moderate psoriasis (N)	[redacted]	[redacted]	[redacted]	[redacted]
PsARC, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Moderate-to-severe psoriasis (N)	[redacted]	[redacted]	[redacted]	[redacted]
PsARC, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

b) Please justify the use of PsARC response to determine response. The ERG acknowledges that this measure is commonly used to assess treatment response in PsA patients. However, because it is based on relative reductions, patients in the continuous treatment health states may be heterogeneous in terms of absolute disease severity. .This presents challenges for the accurate estimation of health-related quality of life and costs and resource use associated with these health states.

PsARC response is specified in NICE's treatment continuation rule for all b/tsDMARDs recommended in PsA and has been used as the basis of response assessment in all prior manufacturer submissions and published economic evaluations. The current model therefore aligns with the PsA health economic literature by using PsARC response as the basis of response assessment and treatment continuation rule.

c) Please show that patients achieving response are homogeneous with regards to disease severity (in terms of Psoriasis Area and Severity Index (PASI) and HAQ-DI scores), utility gain from response, and with regards to costs and resource use.

Median PASI score, HAQ-DI score and EQ-5D utility score at baseline and the corresponding IQRs are presented in Table 44 for patients from SPIRIT-P1 and SPIRIT-P2 stratified by PsARC response or non-response at Week 12. Median values

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are not presented for costs and resource use as these were not considered to be informative.

The IQRs for PASI demonstrate that at least 75% of patients achieving PsARC response or non-response have a PASI score that would be considered mild-to-moderate according to the York model definition. The median and 75th percentile HAQ-DI scores across PsARC responders and non-responder in both trials represent moderate-to-severe disability, although the 25th percentile would be considered mild-to-moderate difficulty, indicating some dispersion in functional capacity at baseline. The IQRs for baseline utility are of a similar width between PsARC responders and non-responders in the SPIRIT-P1 trial around the median although in the SPIRIT-P2 trial, there is greater dispersion around the 25th percentile and median compared to the median and 75th percentile.

Table 44 PASI, HAQ-DI and EQ-5D utility score at baseline, stratified by PsARC response at Week 12

	Median	IQR
SPIRIT P1		
PsARC responders at Week 12 (n=217)		
PASI score *	[redacted]	[redacted]
HAQ-DI score	[redacted]	[redacted]
EQ-5D index	[redacted]	[redacted]
PsARC non-responders at Week 12 (n=200)		
PASI score *	[redacted]	[redacted]
HAQ-DI score	[redacted]	[redacted]
EQ-5D index	[redacted]	[redacted]
SPIRIT-P2		
PsARC responders (n=153)		
PASI score *	[redacted]	[redacted]
HAQ-DI score	[redacted]	[redacted]
EQ-5D index	[redacted]	[redacted]
PsARC non-responders (n=210)		
PASI score *	[redacted]	[redacted]
HAQ-DI score	[redacted]	[redacted]
EQ-5D index	[redacted]	[redacted]

*Computed for patients with baseline BSA≥3%

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B5. It is assumed that patients in the 'no psoriasis' subgroup at the beginning of the cost effectiveness model will not develop psoriasis later on. Additionally, it is assumed that PASI scores of patients with psoriasis return to their baseline score in case of non-response to treatment or treatment discontinuation, i.e. the severity of psoriasis does not change over time.

a) Please provide a definition of 'no psoriasis' given that these patients have active psoriatic arthritis.

Patients with no psoriasis have a PASI score of 0. The joint symptoms of these patients may be recognised as psoriatic arthritis due to family history or personal history of psoriasis or psoriatic nail symptoms.

b) Please also provide definitions for 'mild to moderate psoriasis' and 'moderate to severe psoriasis'.

Secukinumab and ixekizumab are the only treatments currently licensed with different dosing regimens that depend on the severity of psoriasis in a patient with PsA. In the UNCOVER trials for ixekizumab in psoriasis, inclusion criteria for moderate-to-severe psoriasis was defined as PASI≥12 and sPGA≥3 and BSA≥10. (10) This definition has been used in the SPIRIT trials for ixekizumab in PsA and, in addition, mild-to-moderate-psoriasis in SPIRIT-P1 and SPIRIT-P2 participants was defined as a diagnosis of psoriasis that did not meet the PASI, BSA or static Physician Global Assessment (sPGA) score criteria for moderate-to-severe psoriasis. The definition of moderate-to-severe psoriasis is also reflected in the inclusion criteria of the psoriasis trials of secukinumab, which defines moderate-to-severe psoriasis as a PASI score of minimally 12 and investigator's global assessment score (IGA mod 2011) of at least 3 and a total BSA of minimally 10. (11)

Prior to the marketing authorisation of these IL-17 agents with psoriasis-specific dosing regimens, the dosing regimens of the bDMARDs appraised in both moderate-to-severe psoriasis and PsA did not differ between these indications (with the exception of the loading dose of adalimumab in moderate-to-severe psoriasis). The 2016 York model defined mild-to-moderate psoriasis as a BSA≥3% and PASI score ≤10, and moderate-to-severe psoriasis as a BSA≥3% and PASI>10. (12)

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Baseline PASI scores from the SPIRIT-P1 and SPIRIT-P2 trials based on the SPIRIT trial and York model definitions are presented in Table 45. The stricter definition of the SPIRIT trials is associated with higher mean values in the moderate-to-severe psoriasis subgroups in both bDMARD-naïve and bDMARD-experienced populations and lower baseline PASI scores in the mild-to-moderate subgroups relative to the York model definition.

Table 45 – Comparison of mean PASI scores (SD) at baseline in model subgroups

Source	bDMARD-naive		bDMARD-experienced	
	Mild-to-moderate psoriasis	Moderate-to-severe psoriasis	Mild-to-moderate psoriasis	Moderate-to-severe psoriasis
SPIRIT trial definition	[redacted]	[redacted]	[redacted]	[redacted]
York model definition	[redacted]	[redacted]	[redacted]	[redacted]

c) Please justify the assumptions of no change in baseline psoriasis over time and elaborate on the potential impact of this assumption on the estimated cost effectiveness.

Psoriasis is a disease with an unpredictable natural history and is characterised by flare-ups and periods of remission. In the absence of data to suggest an underlying rate of skin symptom progression, it is assumed that PASI reverts to baseline when treatment is discontinued. This assumption aligns with previous appraisals in both psoriasis and psoriatic arthritis. (12-18) In contrast, a progression in baseline HAQ-DI is modelled over time in order to reflect the progressive, destructive nature of PsA on joints. Were a progression to be modelled in PASI scores over time, this would occur in the BSC treatment state, therefore cost-effectiveness is likely to improve for treatment sequences associated with better PsARC response rates (and hence more time on active treatment) than treatment sequences that are associated with more time in the BSC treatment state.

B6. Assumptions around changes in PASI and HAQ-DI scores in the model are unclear.

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a) Patients in the 'trial period' health states experience instantaneous PASI and HAQ-DI improvements. Please justify why this improvement takes place at treatment initiation.

The b/tsDMARDs recommended by NICE for the treatment of PsA have trial period lengths varying from 12 to 24 weeks. As it was not clear how PASI and HAQ-DI improvements were implemented in the York model, instantaneous improvements were implemented at the start of the trial period in order not to bias treatments with longer induction periods.

b) Please provide a scenario analysis in which the improvement in PASI and HAQ-DI scores for responders and non-responders is modelled as a gradual improvement until response assessment.

The results of a scenario analysis in which PASI and HAQ-DI improvements are accrued gradually over the trial period are presented in Table 46 for each model subgroup. Modelling a linear accrual of PASI and HAQ-DI improvements over the trial period has a small impact relative to the base case ICER vs BSC of less than 4% across all subgroups.

Table 46 Scenario analysis: gradual improvement in PASI and HAQ-DI over trial period

Sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER vs BSC	Change from baseline ICER vs BSC
No psoriasis							
BSC	£54,046	8.09	Referent	Referent	Referent	Referent	Referent
APR-UST-BSC	£93,399	9.47	£39,353	1.37	Extendedly dominated	£28,686	1.61%
CZP-UST-BSC	£99,913	9.65	£45,867	1.55	Extendedly dominated	£29,516	1.37%
SEC 150-UST-BSC	£100,305	9.75	£46,259	1.66	Extendedly dominated	£27,941	1.71%
ADA-UST-BSC	£101,374	9.68	£47,328	1.59	Dominated	£29,753	1.45%
ETN-UST-BSC	£103,755	9.99	£49,709	1.90	£26,194	£26,194	1.49%
GOL-UST-BSC	£108,246	9.88	£54,200	1.78	Dominated	£30,421	1.26%

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Sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER vs BSC	Change from baseline ICER vs BSC
IXE Q4W-UST-BSC	£116,061	9.67	£62,015	1.58	Dominated	£39,307	1.44%
INF-UST-BSC	£127,366	10.09	£73,320	1.99	£250,195	£36,805	1.68%
Mild-to-moderate psoriasis							
BSC	£70,006	7.74	Referent	Referent	Referent	Referent	Referent
APR-UST-BSC	£105,498	9.14	£35,492	1.39	Extendedly dominated	£25,528	1.72%
CZP-UST-BSC	£111,422	9.32	£41,417	1.58	Extendedly dominated	£26,264	1.45%
SEC 150-UST-BSC	£111,807	9.44	£41,801	1.69	Extendedly dominated	£24,686	1.84%
ADA-UST-BSC	£112,901	9.36	£42,895	1.62	Dominated	£26,479	1.54%
ETN-UST-BSC	£114,719	9.66	£44,714	1.92	£23,301	£23,301	1.55%
GOL-UST-BSC	£119,037	9.57	£49,031	1.82	Dominated	£26,885	1.35%
IXE Q4W-UST-BSC	£127,829	9.36	£57,823	1.61	Dominated	£35,861	1.55%
INF-UST-BSC	£138,148	9.79	£68,142	2.04	£186,013	£33,322	1.78%
Moderate-to-severe psoriasis							
BSC	£99,884	6.21	Referent	Referent	Referent	Referent	Referent
APR-UST-BSC	£127,628	7.67	£27,744	1.46	Extendedly dominated	£18,965	2.12%
CZP-UST-BSC	£132,421	7.87	£32,537	1.67	Extendedly dominated	£19,506	1.76%
ADA-UST-BSC	£133,934	7.94	£34,050	1.74	Extendedly dominated	£19,593	1.87%
ETN-UST-BSC	£134,629	8.21	£34,745	2.00	£17,351	£17,351	1.80%
GOL-UST-BSC	£138,601	8.20	£38,716	2.00	Dominated	£19,403	1.67%
IXE Q2W-UST-BSC	£155,517	8.08	£55,633	1.87	Dominated	£29,742	2.01%
SEC 300-UST-BSC	£155,593	7.94	£55,709	1.73	Dominated	£32,209	2.35%
INF-UST-BSC	£157,679	8.47	£57,795	2.26	£88,859	£25,551	2.17%

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Sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER vs BSC	Change from baseline ICER vs BSC
No psoriasis							
BSC	£55,942	7.38	Referent	Referent	Referent	Referent	Referent
UST	£82,179	8.23	£26,237	0.85	£30,918	£30,918	2.00%
IXE Q4W	£93,387	8.20	£37,445	0.82	Dominated	£45,497	1.04%
Mild-to-moderate psoriasis							
BSC	£70,271	7.06	Referent	Referent	Referent	Referent	Referent
UST	£94,169	7.94	£23,898	0.89	£26,969	£26,969	2.17%
IXE Q4W	£105,581	7.92	£35,309	0.86	Dominated	£41,047	1.07%
Moderate-to-severe psoriasis							
BSC	£99,618	2.26	Referent	Referent	Referent	Referent	Referent
UST	£118,951	3.14	£19,333	0.89	£21,834	£21,834	3.47%
IXE Q2W	£135,088	3.18	£35,471	0.93	£389,919	£38,271	1.71%

c) Please explain why patients who transition to best supportive care (BSC) experience an instant rebound to the baseline PASI, and implement a more gradual rebound if necessary.

An instant rebound to baseline PASI was modelled in accordance with the 2016 York model and with previous appraisals in psoriasis. A gradual rebound to baseline PASI over the first model cycle has been implemented and the results of this scenario analysis are presented in Table 47 for the model subgroups with concomitant psoriasis. The impact of this gradual rebound is a change relative to the base case ICER of less than 0.5%, demonstrating that this scenario has a negligible impact on the results.

Table 47 - Scenario analysis: gradual loss of response in BSC

Sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER vs BSC	Change from baseline ICER vs BSC
Mild-to-moderate psoriasis							
BSC	£70,006	7.74	Referent	Referent	Referent	Referent	Referent

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APR-UST-BSC	£105,446	9.16	£35,440	1.41	Extendedly dominated	£25,095	-0.01%
CZP-UST-BSC	£111,375	9.34	£41,369	1.60	Extendedly dominated	£25,886	-0.01%
SEC 150-UST-BSC	£111,743	9.47	£41,738	1.72	Extendedly dominated	£24,237	-0.01%
ADA-UST-BSC	£112,849	9.39	£42,843	1.64	Dominated	£26,076	-0.01%
ETN-UST-BSC	£114,657	9.69	£44,651	1.95	£22,944	£22,944	0.00%
GOL-UST-BSC	£118,987	9.59	£48,981	1.85	Dominated	£26,526	0.00%
IXE Q4W-UST-BSC	£127,777	9.38	£57,771	1.64	Dominated	£35,311	-0.01%
INF-UST-BSC	£138,072	9.82	£68,066	2.08	£175,924	£32,736	-0.01%
Moderate-to-severe psoriasis							
BSC	£99,884	6.21	Referent	Referent	Referent	Referent	Referent
APR-UST-BSC	£127,576	7.70	£27,692	1.49	Extendedly dominated	£18,564	-0.04%
CZP-UST-BSC	£132,373	7.90	£32,489	1.70	Extendedly dominated	£19,161	-0.04%
ADA-UST-BSC	£133,882	7.97	£33,998	1.77	Extendedly dominated	£19,227	-0.04%
ETN-UST-BSC	£134,567	8.24	£34,683	2.04	£17,039	£17,039	-0.03%
GOL-UST-BSC	£138,550	8.23	£38,666	2.03	Dominated	£19,080	-0.03%
IXE Q2W-UST-BSC	£155,459	8.11	£55,575	1.91	Dominated	£29,146	-0.03%
SEC 300-UST-BSC	£155,532	7.98	£55,648	1.77	Dominated	£31,458	-0.03%
INF-UST-BSC	£157,603	8.52	£57,719	2.31	£84,350	£25,002	-0.03%
Mild-to-moderate psoriasis							
BSC	£70,271	7.06	Referent	Referent	Referent	Referent	Referent
UST	£94,133	7.96	£23,862	0.9	£26,385	£26,385	-0.04%
IXE Q4W	£105,562	7.93	£35,291	0.87	Dom	£40,603	-0.02%
Moderate-to-severe psoriasis							
BSC	£99,618	2.26	Referent	Referent	Referent	Referent	Referent
UST	£118,915	3.17	£19,297	0.92	£21,051	£21,051	-0.24%
IXE Q2W	£135,063	3.2	£35,446	0.94	£604,832	£37,573	-0.15%

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d) Please provide explanation for the HAQ-DI calculations over time for patients receiving BSC.

For the HAQ-DI calculations over time for patients receiving BSC, three patient flows with potentially distinctly different disease scores had to be combined into one value using a weighting equation. This equation was constructed in three parts.

1. ***Surviving Patients who were in BSC during the previous cycle experience the specified progression in HAQ-DI in the subsequent cycle.***

2. ***Patients who have just discontinued from the last specified treatment line rebound according to the selected option, which is either by initial gain (i.e. responder response) or to natural history.***

3. ***Non-responders from the last specified treatment line, who rebound either by their initial gain (i.e. non-responder response) or back to natural history.***

Below is the equation for BSC shown for the base case setting: rebound to initial gain. The three parts of the equation are presented with separation for clarity.

currentHAQ = [(HAQ(previous cycle, in BSC) + yearlyHAQProgression/12) * (stateTrace(previous cycle, in BSC) – stateTrace(previous cycle, in BSC) * transitionProbablility(from BSC to death))] / stateTrace(current cycle, BSC)

+ [(HAQ(previous cycle, in maintenance) + HAQResponderResponse) * stateTrace(previous cycle, in maintenance) * transitionProbability(from maintenance to BSC)] / stateTrace(current cycle, BSC)

+ [baselineHAQ * stateTrace(previous cycle, in last cycle of trial) * transitionProbability(from last cycle in trial to BSC)] / stateTrace(current cycle, BSC)

It is possible to make minor simplifications resulting in a shorter, but equivalent equation:

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currentHAQ = [(HAQ(previous cycle, in BSC) + yearlyHAQProgression/12) * (stateTrace(previous cycle, in BSC) * transitionProbablility(from BSC to BSC))

+ baselineHAQ * stateTrace(previous cycle, in maintenance) * transitionProbability(from maintenance to BSC)

+ baselineHAQ * stateTrace(previous cycle, in last cycle of trial) * transitionProbability(from last cycle in trial to BSC)] / stateTrace(current cycle, BSC)

Patient population

B7. **Priority question:** The baseline PASI scores used for the different subgroups in this submission differ from previous appraisals (i.e. the adaptation of the York model for TA 445(19)) and it is not clear how these scores were obtained.
   a) Please describe how baseline PASI scores have been determined for the 'no psoriasis', 'mild-to-moderate psoriasis', and 'moderate-to-severe psoriasis' subgroups.

The definitions used to derive the three subpopulations based on skin involvement are coming from the SPIRIT clinical studies. A composite criterion was used to evaluate the severity of the skin component. For their psoriasis to be considered as "moderate-to-severe", a patient had to fulfill:

- ***Psoriasis Area and Severity Index (PASI) score > 12***
- ***Body Surface Area (BSA) ≥ 10***
- ***static Physician Global Assessment (sPGA) score ≥ 3***

Patients were categorised among "no psoriasis", "mild-to-moderate psoriasis", or "moderate-to-severe psoriasis" as follows:

- ***"No psoriasis": patients with no diagnosis of plaque psoriasis according to investigator's judgement.***
- ***"Moderate-to-severe psoriasis": patients with a diagnosis of plaque psoriasis AND not fulfilling the psoriasis severity criterion***

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- ***"Mild to moderate psoriasis": patients with a diagnosis of plaque psoriasis AND fulfilling the psoriasis severity criterion.***

As noted in the response to question B5b), this definition of moderate-to-severe psoriasis aligns with the inclusion criteria of the trial programmes for ixekizumab and secukinumab in the treatment of moderate-to-severe chronic plaque psoriasis. (10, 11)

b) Please discuss the differences in these PASI scores compared with TA 445, and the potential impact on cost effectiveness of these differences.

Baseline PASI scores used in TA445 were independent of prior bDMARD exposure. The baseline PASI values from TA445 are higher in the mild-to-moderate psoriasis subgroups (7.5) and lower in the moderate-to-severe psoriasis subgroups (12.5) compared to the SPIRIT trials. The treatment-specific PASI response rates relate to a percentage reduction from baseline PASI score. A higher baseline value would therefore be associated with a greater absolute reduction than a lower baseline score for a given PASI response threshold.

The modelling approach for healthcare resource utilization costs associated with psoriasis assumes that a patient has not achieved PASI 75 response, their healthcare costs associated with psoriasis are greater. The baseline PASI score itself does not affect the costs under this assumption.

In contrast, absolute PASI after response assessment is an explanatory variable in the utility regression model. Using the baseline PASI value from TA445 may result in a slightly higher absolute PASI in the mild-to-moderate psoriasis subgroups and a slightly lower absolute PASI in the moderate-to-severe psoriasis subgroups relative to the baseline PASI scores from the SPIRIT trials for a given response rate. The impact of the choice of baseline PASI score is more likely to affect treatments with higher PASI response rates. However, as the coefficient on PASI in the utility algorithm is small, the overall impact of the choice of baseline PASI score on expected utility and incremental cost-effectiveness results is expected to be minimal.

c) Please explain what is meant by "TA 445 naive baseline" in relation to baseline HAQ and PASI scores (cells J20:K20, 'Main'-tab, cost effectiveness model).

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The "TA 445 naïve baseline" option refers to the use of baseline HAQ-DI and PASI scores as used in the 2016 York model (NICE TA 445) and is applied only to the first line of therapy in a bDMARD-naïve population. Baseline HAQ-DI and PASI were assumed independent of bDMARD treatment history in the 2016 York model.

Intervention and comparators

B8. **Priority question:** CS Tables 39 and 40 provide an overview of treatment sequences used in the cost effectiveness model.(7)

a) Please provide further justification for the selection of treatment sequences (besides the selection in the York model).

The treatment sequences in the base case followed the approach of the 2016 York model, which in turn is based on the licensed positioning of treatments and NICE recommendations.

In the bDMARD-naïve patient population, TNF-alpha inhibitors, apremilast and secukinumab are selected as a first-line treatments in accordance with their NICE recommendation. Ustekinumab is recommended by NICE only in patients who have had inadequate response or intolerance to a prior TNF-alpha inhibitor. Secukinumab and certolizumab pegol are also recommended in patients who have had an inadequate response and/or intolerance to prior TNF-alpha inhibitors. However, ustekinumab was selected as the second-line treatment in the model sequences in order to have consistency and ease of comparability across all treatment sequences.

b) Please justify why treatment sequences are composed of two biologics followed by BSC in the bDMARD-naïve subgroup and of one biologic followed by BSC in the bDMARD-experienced subgroup (i.e. assuming patients would receive a maximum of two biologics).

The treatment sequences follow the approach of the 2016 York model in modelling two bDMARDs followed by BSC in the bDMARD-naïve population and one bDMARD followed by BSC in the bDMARD-experienced population. To support the justification for this approach, Lilly referred to the Adelphi DSP real world dataset to assess the length of a typical treatment sequence by examining the proportion of patients who receive up to two bDMARDs versus patients who receive more than two bDMARDs. (4)

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Of the [redacted] bDMARD-experienced patients enrolled in Adelphi DSP, biologic prescribing history was available for [redacted] patients. [redacted] % of bDMARD-experienced patients (n= [redacted]) had received 1 or 2 biologic therapies, the majority of which ([redacted] %) had only ever received 1 biologic option. Only [redacted] % of patients received 3 or more biologic lines of therapy.

c) Please clarify whether the overview of treatment sequences in Tables 39 and 40 of the CS is exhaustive for the UK context.(7)

Given the range of treatment options and potential combinations, the overview of treatment sequences in Table 39 and Table 40 is not exhaustive for the UK context. As the model follows the precedent of treatment sequencing in the York model and NICE guidance for each of these treatments, the selected treatment sequences are appropriate to use in demonstrating the cost-effectiveness of b/tsDMARDs as part of a treatment sequencing approach.

B9. Please describe the treatments incorporated in BSC, which, according to the CS(7), is a mix of cDMARDs and palliative care, and discuss whether this reflects UK clinical practice.

The definition of BSC stated in the CS aligns with the 2016 York model. In the absence of guidance in UK guidelines on what to do in the event of bDMARD treatment failure, Lilly's medical team gained the agreement of a UK clinical expert that a combination of physiotherapy, NSAIDs, local glucocorticoid injections and cDMARDs may be used.

B10. The present submission differs from the scope in the selection of comparators and concomitant treatments. In the scope, ustekinumab, certolizumab pegol, secukinumab and BSC are listed as comparators for ixekizumab in bDMARD-experienced patients.(6) However, these comparisons are not provided in the company base-case analyses. The scope furthermore states that bDMARDS may be administered with or without methotrexate (and in SPIRIT-P1 54.2% of patients received methotrexate at baseline).(20)

a) Please include all comparators listed in the scope for all subgroups in the base-case cost effectiveness analyses.

No bDMARD-experienced subgroup data was identified in the SLR of clinical efficacy for certolizumab pegol and secukinumab. Approximately a third of patients in the FUTURE-2 trial and 20% in the RAPID-PsA trial were bDMARD-experienced. Prior

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bDMARD exposure is a treatment effect modifier, therefore, in the absence of prior bDMARD-exposed subgroup data, including the ITT population in the base case would bias the results against the treatments for which bDMARD-experienced subgroup data were available, i.e. ustekinumab and both ixekizumab dosing regimens. The ITT population from the FUTURE-2 and RAPID-PsA trials have therefore only been included in a sensitivity analysis network and scenario analysis in the model. Running the base case analysis for the bDMARD-experienced population with these comparators would replicate the results presented in Table 62 of CS Document B.

b) Please include methotrexate in all base-case cost effectiveness analyses. More specifically, please provide an estimate of the proportion of patients who would receive concomitant methotrexate with each comparator and incorporate resource use and costs associated with methotrexate treatment in the cost effectiveness model.

Ixekizumab provides a high-level of efficacy in psoriatic arthritis symptoms in biological naïve as well as biologic experience patients with or without concomitant methotrexate use. The relevant clinical outcomes for the model were not reported in the studies identified in the SLR according to whether patients had received concomitant methotrexate, therefore it is not possible to estimate in an NMA the comparative effectiveness of therapies with or without concomitant methotrexate. As the acquisition cost of methotrexate is low in relation to the b/tsDMARDs listed in the scope, incorporating the cost of methotrexate would have a negligible impact on the cost-effectiveness results.

Treatment effectiveness

B11. **Priority question:** The file "ID1194 ixekizumab PsA model parameters and state trace (AIC).xlsx" provided in advance of the final submission is helpful to understand the economic model. Please provide an updated version of this file, corresponding to the economic model file submitted with an updated trace and transition matrix.

The updated file is provided in the file named 'B11. PsA model parameters and state trace'.

B12. **Priority question:** Section 3.3 "Clinical parameters and variables" of the CS does not provide an overview of the clinical parameters and variables used in the model.(7)

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a) Please provide an overview of all transition probabilities used in the model with sources.

An overview of transition probabilities is provided in Table 48 to depict a single b/tsDMARD followed by BSC and in Table 49 to depict two b/tsDMARDs followed by BSC.

The trial period consists of a series of tunnel states, in which patients transition to the next month of the trial period unless they die within the temporary state. PsARC response rates are specific to treatment and prior bDMARD exposure, and determine the transition from the end of the trial period to the continued treatment period. The time points of the PsARC responses in the studies informing the NMA align with the trial period length in the model, therefore no further adjustment is needed to apply the PsARC response rates in the model. Patients who do not achieve PsARC response discontinue treatment and move to the BSC treatment state (as per Table 48) or to the next treatment in the sequence (Table 49).

In the continued treatment state, patients can either remain in the continued treatment state, die, or discontinue treatment and receive a subsequent b/tsDMARD or BSC. A constant annual discontinuation rate of 16.5% is sourced from Rodgers et al (2011) and converted to a monthly rate of 1.49%. (21) These patients either move to the BSC treatment state or to the next treatment in the sequence. The risk of mortality is applied in each cycle of the continued treatment period and the remaining patients who do not die or discontinue treatment remain in the continued treatment period (1-mortality risk-1.49%).

The risk of death has been derived using UK general population life tables weighted by gender and the excess risk of mortality due to PsA. As general population life tables have been used, the mortality risk is age-dependent.

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Table 48 - Overview of transition probabilities from row health state to column health state

	Treatment 1 trial period month 1	Treatment 1 trial period month 2	Treatment 1 trial period month 3/4	Treatment 1 continued treatment period	BSC	Death
Treatment 1 trial period month 1	NA	1-(mortality risk)	NA	NA	NA	Mortality risk
Treatment 1 trial period month 2	NA	NA	1-(mortality risk)	NA	NA	Mortality risk
Treatment 1 trial period month 3/4	NA	NA	NA	PsARC response rate	1-PsARC response-(mortality risk)	Mortality risk
Treatment 1 continued treatment period	NA	NA	NA	1-(mortality risk)-1.49%	1.49%	Mortality risk
BSC	NA	NA	NA	NA	1-(mortality risk)	Mortality risk
Death	NA	NA	NA	NA	0	1

Table 49 - Overview of transition probabilities in sequencing approach from row health state to column health state

	Treatment 1 trial period month 1	Treatment 1 trial period month 2	Treatment 1 trial period month 3/4	Treatment 1 continued treatment period	Treatment 2 trial period month 1	Treatment 2 trial period month 2	Treatment 2 trial period month 3/4	Treatment 1 continued treatment period	BSC	Death
Treatment 1 trial period month 1	NA	1-(mortality risk)	NA	NA	NA	NA	NA	NA	NA	Mortality risk
Treatment 1 trial period month 2	NA	NA	1-(mortality risk)	NA	NA	NA	NA	NA	NA	Mortality risk

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	Treatment 1 trial period month 1	Treatment 1 trial period month 2	Treatment 1 trial period month 3/4	Treatment 1 continued treatment period	Treatment 2 trial period month 1	Treatment 2 trial period month 2	Treatment 2 trial period month 3/4	Treatment 1 continued treatment period	BSC	Death
Treatment 1 trial period month 3/4	NA	NA	NA	PsARC response rate	1-PsARC response-(mortality risk)	NA	NA	NA	NA	Mortality risk
Treatment 1 continued treatment period	NA	NA	NA	1-(mortality risk)- 1.49%	1.49%	NA	NA	NA	NA	Mortality risk
Treatment 2 trial period month 1	NA	NA	NA	NA	NA	1-(mortality risk)	NA	NA	NA	Mortality risk
Treatment 2 trial period month 2	NA	NA	NA	NA	NA	NA	1-(mortality rate)	NA	NA	Mortality risk
Treatment 2 trial period month 3/4	NA	NA	NA	NA	NA	NA	NA	PsARC response rate	1-PsARC response-(mortality risk)	Mortality risk
Treatment 2 continued treatment period	NA	NA	NA	NA	NA	NA	NA	1-(mortality risk)-1.49%	1.49%	Mortality risk
BSC	NA	NA	NA	NA	NA	NA	NA	NA	1-(mortality risk)	Mortality risk
Death	NA	NA	NA	NA	NA	NA	NA	NA	NA	1

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b) Please justify the sources and calculations used to inform the transition probabilities in the model (including why the calculations in Tables 41 and 42 of the CS are appropriate).(7)
c) According to the calculations in Table 41 and the text below this Table, responders are subdivided into PASI 75 and PASI 50-74.(7) Please justify why the other PASI categories (e.g. < PASI 50) are not used.

A description of the sources and calculations used to inform the transition probabilities in the model is provided in part a).

In the base case analysis, the calculations in Table 41 and Table 42 of Document B are not used to calculate transition probabilities between health states in the model but instead are used to inform the calculation of health state utilities and costs associated with psoriasis.

In the absence of information on the distribution of PASI 75 response across PsARC responders and non-responders, the calculations in Table 41 approximates the proportion of PsARC responders and non-responders who have a PASI 75 or less than PASI 75 response, using the PsARC and PASI 75 rates estimated in the NMA and the approach described in Appendix 10 of Rodgers et al (2011). (21) In the York model, the correlation coefficient ρ was assumed to be 0.4. However, given the outputs of the NMA commissioned by Lilly, the maximum feasible value for the formulae in Table 41 to return positive values was 0.26.

For simplicity, it is assumed that PASI 50-74 responders (as derived from the NMA) all achieved PsARC response (i.e. are captured in cell B of Table 41) unless the proportion of PASI50-74 responders exceeded the value in cell B. In this case, the remaining proportion of PASI 50-74 responders were allocated as PsARC non-responders in cell D. It follows logically that after the PASI 50-74 responders have been allocated as PsARC responders or non-responders, the remaining proportions of patients in cells B and/or D of Table 41 are assumed to have a less than PASI 50 response. PASI 90 and PASI 100 were not incorporated in the base case due to the absence of information on how these responders are distributed across PsARC responders and non-responders.

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In scenario analyses, the formula in cell A in Table 41 is used to derive a combined PsARC and PASI response rate, which is applied as the transition probability from the end of a trial period to the continued treatment period.

The formulae in Table 42 are used to calculate the absolute PASI score for PASI responders and non-responders when the response criteria are either based on PsARC alone or PsARC and PASI 75/90/100. Improvements in PASI score have been calculated as the percentage reduction from baseline score associated with each PASI response threshold weighted by the proportion of patients achieving each response threshold. PASI 90 and PASI 100 are captured in the calculation only when they are part of the combined response criteria. As a less than PASI 50 response runs from a 0-49% reduction from baseline score, it is assumed that patients who do not achieve PASI 50 do not experience a change in their PASI score.

B13. **Priority question:** CS Table 38 specifies the model trial period for each treatment after which treatment response is assessed.(7) However, for some treatments the model trial period is inconsistent with the time points used in the NMA as specified in CS appendix section 1.8 (e.g. for secukinumab data from the 12 week time point from the FUTURE 2 trial is used in the NMA while the model trial period is 16 weeks).(1)

a) Please justify this inconsistency regarding the model trial period and time point used in the NMA.

The discrepancy between the time point informing the NMA and the model trial period aligns with the use in the 2016 York model of week 12 data from the FUTURE-2 trial and a model trial period of 16 weeks in accordance with the marketing authorisation for secukinumab. As noted in the Assessment Group report for TA445, a common time point for the assessment of response between 12 and 16 weeks was justified based on the Assessment Group's conclusion that there appeared to be a lack of clinically meaningful difference in bDMARD responses rates for joint disease or psoriasis between 12 to 24 weeks. (12)

b) Please incorporate necessary adjustments to correct this inconsistency in the economic model.

This inconsistency has not been adjusted for based on the justification provided in part a).

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c) The CS states that "the trial period length is dependent on the biologic and can last from 10 to 16 weeks in alignment with the response assessment time points in NICE guidance for each treatment of interest." (pages 106-107).(7) The 10-16 weeks period is inconsistent with CS Table 38 where the model trial period length is reported to be 12-24 weeks.(7) Please clarify this discrepancy.

The statement on pages 106-107 is a typo and should refer to 12-24 weeks, as stated in CS Table 38.

B14. In absence of alternative data, treatment discontinuation is assumed to be constant and equal for all biological treatments (independent of treatment line).
a) Please clarify whether this assumption is consistent with expert opinion.

Expert opinion was not sought on this assumption. The assumption is supported by findings from Stober et al (2018), which evaluated TNF-alpha inhibitor persistence in a real world cohort. (3) An analysis of baseline predictors of TNF-alpha inhibitor persistence indicated an unadjusted HR for adalimumab versus etanercept of 0.97 (0.59, 1.60) (p-0.920) in patients initiating TNF-alpha inhibitor therapy and an unadjusted HR of 0.73 (0.28,1.89) (p=0.51) in patients who had switched to a second TNF-alpha inhibitor. No difference in persistence was demonstrated between adalimumab and etanercept, which supports the assumption of applying the same long term discontinuation rate to all treatments. However, a Cox proportional hazards ratio of 2.02 (95% CI: 1.20, 3.42; p=0.01) for persistence in second-line versus first-line users of TNF-inhibitors suggests that in practice, treatment discontinuation rates may not be independent of treatment line.

b) Please justify why treatment discontinuation was not based on the SPIRIT trials and/or elicited expert opinion.

In the absence of comparative data on long-term discontinuation rates, the model follows the assumption in previous economic evaluations and the York model of applying an annual rate of 16.5% to all treatments independent of treatment line.

c) Please provide the NMA results for treatment discontinuation, where and if possible.

An NMA was conducted for treatment discontinuation, the results of which are provided in Table 50.

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Table 50 – Conditional probabilities of all-cause discontinuation for each treatment

Treatment	Discontinuations
Placebo	[redacted]
Adalimumab 40 mg Q2W	[redacted]
Apremilast 30 mg BID	[redacted]
Certolizumab pegol pooled doses	[redacted]
Golimumab 50 mg Q4W	[redacted]
Infliximab 5 mg/kg Q8W	[redacted]
Ixekizumab 80 mg Q2W	[redacted]
Ixekizumab 80 mg Q4W	[redacted]
Secukinumab 150 mg Q4W	[redacted]
Secukinumab 300 mg Q4W	[redacted]
Ustekinumab 45 mg Q12W	[redacted]
Ustekinumab 90 mg Q12W	[redacted]

Adverse events

B15. **Priority question:** The CS states that adverse events "were thought to be captured only to the extent that they affect the initial response and the long-term withdrawal rates" (page 121).(7) However, long-term withdrawal rates were treatment-independent in the model, and the extent to which these rates capture treatment-associated adverse events is questionable. Furthermore, the scope identified adverse events as relevant outcomes for this appraisal.(6) Please include the impact of health-related quality of life and resource use and costs associated with adverse events in the cost effectiveness model.

Adverse events were not incorporated in the 2016 York model or in other previous NICE appraisals in PsA and the only manufacturer submission to include AE costs based the costs on an appraisal in ankylosing spondylitis. (12, 22-24) Given the lack of data on the health-related quality of life impact of AEs in PsA, AEs have not been incorporated into the model.

Health-related quality of life

B16. Please provide further information and justification for the estimation of health-related quality of life.

a) Section 3.4 of the CS stated that "no imputation method was applied in case of missing information on EQ-5D as only a small proportion of patients in each trial had a missing EQ-5D score (20/417 in SPIRIT-P1 and 32/331 in SPIRIT-P2)" (page 120).(7) This implicitly assumes that these data were missing at random.

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Please provide justification for this assumption and provide additional analysis imputing missing data, if necessary.

The data were explored, first, to identify if there was a specific pattern of missing information at a scale level (i.e. how many items were missing, what items were missing) and, second, to investigate any potential association between missing information and study- as well as patient-related characteristics. From these investigations, no clear missing data pattern was identified.

In addition to the data exploration described above, an alternative approach wherein all EQ-5D missing items were imputed using the "Last-Observation-Carried-Forward" (LOCF) methodology was undertaken. After imputing the missing data points, the same mapping methodology was performed by applying ordinary least-square regression model to predict LOCF EQ-5D values with HAQ-DI score and PASI score in each study. The results of this approach are shown in Table 51 using the SPIRIT-P1 and SPIRIT-P2 trials in the bDMARD-naïve and bDMARD-experienced populations, respectively.

Table 51 - OLS model from SPIRIT-P1 main analysis ("active treatment ITT" population) and SPIRIT-P2 main analysis ("active treatment ITT" population)

	Estimate	Standard error	t	P>t
SPIRIT-P1				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]	[redacted]	[redacted]
PASI	[redacted]	[redacted]	[redacted]	[redacted]
SPIRIT-P2				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]	[redacted]	[redacted]
PASI	[redacted]	[redacted]	[redacted]	[redacted]

The resulting equations are presented in Equation 2 and Equation 4, for the bDMARD-naïve and bDMARD-experienced populations respectively, for comparison with Equation 1 and Equation 3 using the no imputation approach. The differences between the respective equations remain marginal and small in magnitude.

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Equation 1 – utility regression model in bDMARD-naïve population (no imputation)

Expected EQ-5D = [redacted] ***–*** [redacted] ***x HAQ-DI –*** [redacted] ***x PASI***

Equation 2 – utility regression model in bDMARD-naïve population (LOCF)

Expected EQ-5D$_{LOCF}$ = [redacted] ***–*** [redacted] ***x HAQ-DI –*** [redacted] ***x PASI***

Equation 3 – utility regression model in bDMARD-experienced population (no imputation)

Expected EQ-5D = [redacted] ***–*** [redacted] ***x HAQ-DI –*** [redacted] ***x PASI***

Equation 4 – utility regression model in bDMARD-experienced population (LOCF)

Expected EQ-5D$_{LOCF}$ = [redacted] ***–*** [redacted] ***x HAQ-DI –*** [redacted] ***x PASI***

b) Please provide more explanation and justification for how utility values were estimated using both data points (baseline and at 12 weeks). In particular, please explain whether a mixed effects model was used, and if not, please comment on why this was not used and provide a scenario where utility estimates are based on a mixed effects model (using all available data).

Utility values at week 12 were estimated through a direct application of the van Hout et al (2012) crosswalk methodology. (25) Subsequently, the ordinary least-square regression model was run, predicting observed EQ-5D with HAQ-DI score and PASI score. No adjustment on baseline EQ-5D values was made on this approach.

A potential alternative could have been to estimate EQ-5D week 12 values using Mixed Model for Repeated Measures (MMRM), accounting for potential influence of baseline EQ-5D values as well as external factors. Estimates from this model could have been used to be mapped using HAQ-DI and PASI.

The structure of the cost-effectiveness model mostly relies on the evolution over time of HAQ-DI score conditional on PsARC response, with PsARC response rate being the main treatment-specific clinical parameter. In order to replicate as closely as possible the approach used in the previous economic evaluations of biologic therapies in active psoriatic arthritis, an assumption was made that baseline PASI and HAQ-DI values would be sufficient information to further inform the patients' baseline characteristics, including utility via the mapping equation.

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With this in mind, estimating patient-level EQ-5D through a MMRM model would have substantially reduced the variability of this parameter. This would not be a realistic depiction of the natural course of such a heterogeneous disease as PsA, and its impact on patients' daily life and health-related quality of life.

B17. Please provide a scenario analysis in which utility values are adjusted for the general population utility values.

A scenario analysis has been implemented in which utility values predicted by the algorithm are capped by the general population utility values taken from Sullivan et al 2011. (26) The results presented in Table 52 demonstrate that this adjustment does not have a major impact on the ICERs vs BSC.

Table 52 - Scenario analysis - utility values adjusted for population utility norms

Sequence	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER	ICER vs BSC	Change from baseline ICER
No psoriasis							
BSC	£70,006	7.74	Referent	Referent	Referent	Referent	Referent
APR-UST-BSC	£105,446	9.15	£35,440	1.41	Extendedly dominated	£25,195	0.39%
CZP-UST-BSC	£111,375	9.34	£41,369	1.59	Extendedly dominated	£25,969	0.31%
SEC 150-UST-BSC	£111,743	9.45	£41,738	1.70	Extendedly dominated	£24,533	1.21%
ADA-UST-BSC	£112,849	9.38	£42,843	1.64	Dominated	£26,159	0.31%
ETN-UST-BSC	£114,657	9.64	£44,651	1.90	£23,548	£23,548	2.63%
GOL-UST-BSC	£118,987	9.59	£48,981	1.84	Dominated	£26,571	0.17%
IXE Q4W-UST-BSC	£127,777	9.34	£57,771	1.59	Dominated	£36,278	2.73%
INF-UST-BSC	£138,072	9.72	£68,066	1.97	£299,355	£34,475	5.31%
Mild-to-moderate psoriasis							
BSC	£70,006	7.74	Referent	Referent	Referent	Referent	Referent
APR-UST-BSC	£105,446	9.15	£35,440	1.41	Extendedly dominated	£25,195	0.39%

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CZP-UST-BSC	£111,375	9.34	£41,369	1.59	Extendedly dominated	£25,969	0.31%
SEC 150-UST-BSC	£111,743	9.45	£41,738	1.70	Extendedly dominated	£24,533	1.21%
ADA-UST-BSC	£112,849	9.38	£42,843	1.64	Dominated	£26,159	0.31%
ETN-UST-BSC	£114,657	9.64	£44,651	1.90	£23,548	£23,548	2.63%
GOL-UST-BSC	£118,987	9.59	£48,981	1.84	Dominated	£26,571	0.17%
IXE Q4W-UST-BSC	£127,777	9.34	£57,771	1.59	Dominated	£36,278	2.73%
INF-UST-BSC	£138,072	9.72	£68,066	1.97	£299,355	£34,475	5.31%
Moderate-to-severe psoriasis							
BSC	£99,884	6.21	Referent	Referent	Referent	Referent	Referent
APR-UST-BSC	£127,576	7.70	£27,692	1.49	Extendedly dominated	£18,572	0.00%
CZP-UST-BSC	£132,373	7.90	£32,489	1.69	Extendedly dominated	£19,168	0.00%
ADA-UST-BSC	£133,882	7.97	£33,998	1.77	Extendedly dominated	£19,234	0.00%
ETN-UST-BSC	£134,567	8.24	£34,683	2.03	£17,045	£17,045	0.01%
GOL-UST-BSC	£138,550	8.23	£38,666	2.03	Dominated	£19,085	0.00%
IXE Q2W-UST-BSC	£155,459	8.11	£55,575	1.91	Dominated	£29,157	0.01%
SEC 300-UST-BSC	£155,532	7.97	£55,648	1.77	Dominated	£31,471	0.01%
INF-UST-BSC	£157,603	8.51	£57,719	2.31	£84,394	£25,011	0.01%
No psoriasis							
BSC	£55,942	7.38	Referent	Referent	Referent	Referent	Referent
UST	£82,143	8.24	£26,201	0.86	£30,313	£30,313	0.01%
IXE Q4W	£93,369	8.21	£37,427	0.83	Dominated	£45,034	0.01%
Mild-to-moderate psoriasis							
BSC	£70,271	7.06	Referent	Referent	Referent	Referent	Referent
UST	£94,133	7.96	£23,862	0.9	£26,397	£26,397	0.01%
IXE Q4W	£105,562	7.93	£35,291	0.87	Dominated	£40,617	0.01%
Moderate-to-severe psoriasis							
BSC	£99,618	2.26	Referent	Referent	Referent	Referent	Referent

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UST	£118,915	3.17	£19,297	0.91	£21,102	£21,102	0.00%
IXE Q2W	£135,063	3.2	£35,446	0.94	£586,393	£37,628	0.00%

Resource use and cost

B18. Please justify why costs of BSC are assumed to be zero, given that BSC is a mix of cDMARDs and palliative care according to the CS.(7) Please provide a scenario in which the appropriate costs for BSC are included.

The cost of BSC is assumed to be captured by the algorithms used to estimate healthcare resource use associated with joint disease and skin symptom management, therefore in alignment with the 2016 York model, a separate acquisition cost was not applied to BSC. (12)

B19. Please provide justification for why the mean weight from SPIRIT-P1 and -P2 was deemed appropriate (i.e. representative of UK clinical practice) to calculate the drug acquisition costs for infliximab.

Mean BMI ranged across treatments arms from 28.6 to 32.1 in the SPIRIT-P1 trial and 30.1 to 31.6 in the SPIRIT-P2 trial. (8, 9)This is comparable to the mean BMI range of 31.9 to 33.2 reported in Stober et al (2018), a real world Cambridge hospital cohort and the mean BMI of [redacted] reported in the Adelphi DSP. (3, 4) It is therefore likely that the mean weights from the SPIRIT-P1 and SPIRIT-P2 trials are representative of UK patients with PsA and are appropriate to calculate the drug acquisition cost of infliximab.

B20. Please provide justification for estimating resource use associated with the HAQ-DI score.

a) Neither the Kobelt et al (2002) nor the Poole et al (2010) studies were considered ideal for estimating resource use and costs associated with the HAQ-DI score given that a) Kobelt et al is a study in rheumatoid arthritis patients, b) resource use associated with rheumatoid arthritis may have changed since the publication of this study, and c) Poole et al (2010) was associated with limitations in the calculation of the estimates.(27, 28) Please explain whether alternative data sources, such as the SPIRIT trials or studies included in the recent review by D'Angiolella et al (2018),, were considered for this submission, and explain why they were not used.(29)

The rationale for using the Kobelt et al (2002) and Poole et al (2010) studies to estimate healthcare resource utilization associated with the HAQ-DI score is the use

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of these studies in previous published economic evaluations, including the recent 2016 York model. Despite the limitations associated with these studies, neither the SPIRIT trials or the studies included in D'Angiolella et al (2018) would have been appropriate to inform UK healthcare resource use estimates in the cost-effectiveness model. As less than 5% of participants in the SPIRIT trials were based in the UK, costs and resource use from the trials would not be reflective of UK clinical practice, and a subsample of 36 patients may not have been sufficient to inform this parameter in the model. Moreover, resource use in an RCT setting may overestimate healthcare resource utilization associated with PsA compared to real world data due to the Hawthorne effect. (30) The cost studies identified in the D'Angiolella review were related to non-UK settings and as such would not reflect UK treatment practice.

b) Please explain how the estimate of 15% for the reduction in resource use estimates to avoid double-counting of drug acquisition costs was obtained.

The reduction in resource use estimates of 15% was based on an estimate of drug costs in a rheumatoid arthritis audit described in McIntosh (1996). (31) The audit estimated that drug costs comprised 15% of the total direct costs associated with RA in an audit undertaken in 1991/92. This assumption was applied in the 2007 York model and the subsequent iterations. (12, 21, 32)

Validation

B21. **Priority question:** Please provide a cross-validation of all cost effectiveness analyses identified in the SR, including a Table that considers for each study:
a) Model structure and major assumptions
b) Intervention and comparators
c) Response rates and other (influential) transition probabilities
d) HRQoL data used
e) Results
f) If applicable, possible explanation(s) for discrepant results compared with the present assessment.

The tabulation of these model characteristics is presented in the Excel file 'B21. Cross-validation of CEA studies.xlsx'.

B22. The CS states that "the second revision of the York model (2016) served as the foundation of the current de novo analysis" (page 103).(19) However, the economic

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model submitted by the company deviated from the York model in several aspects (e.g. incorporating additional PASI response thresholds: PASI 50, PASI 90 and PASI 100).

a) Please specify all deviations from the York model with regards to model structure as well as model assumptions.
b) Please justify the abovementioned deviations from the York model.

A summary of the deviations from the York model and rationale is presented in Table 53.

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Table 53 - Deviations from York model

Model feature	York model	Current assessment	Rationale
Treatment history	- bDMARD-naïve; one prior cDMARD - bDMARD-naïve; at least two prior cDMARDs - bDMARD-experienced	- bDMARD-naïve - bDMARD-experienced	The positioning of biologic therapy in patients with only one prior standard DMARD is not in line with current NICE pathways or BSR guidance (except in the case of adverse prognostic factors). As noted in the Final Appraisal Determination document for the multiple technology appraisal of secukinumab and certolizumab pegol, the committee questioned whether biologic therapy is established clinical practice in the NHS after failure on only one prior DMARD and which specific group of patients would use a biologic at this stage in the pathway. Moreover, subgroup-specific data by prior number of cDMARDs were not identified in the SLR to inform this comparison.
Baseline HAQ-DI	- 1.22 irrespective of psoriasis severity and prior bDMARD exposure	- No concomitant psoriasis: 1.17 in bDMARD-naïve patients; 1.39 in bDMARD-experienced patients - Mild to moderate psoriasis: 1.17 in bDMARD-naïve patients; 1.2 in bDMARD-experienced patients - Moderate to severe psoriasis: 1.19 in bDMARD-naïve patients; 1.16 in bDMARD-experienced patients	As prior bDMARD treatment was expected to be a treatment effect modifier, HAQ-scores at baseline were estimated for the prior bDMARD-exposed subgroups. HAQ scores for each psoriasis subgroup were also used.
Baseline PASI	- No concomitant psoriasis: 0 - Mild to moderate psoriasis: 7.3 - Moderate to severe psoriasis: 12.5	- No concomitant psoriasis: 0 - Mild to moderate psoriasis: 3.9 in bDMARD-naïve patients; 3.7 in bDMARD-experienced patients - Moderate to severe psoriasis: 20.4 in bDMARD-naïve patients; 23.4 in bDMARD-experienced patients	As prior bDMARD treatment was expected to be a treatment effect modifier, PASI-scores at baseline were estimated for the prior bDMARD-exposed subgroups.

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Model feature	York model	Current assessment	Rationale
Response criteria	PsARC	- PsARC (base case) - PsARC+PASI75 (sensitivity analysis) - PsARC+PASI90 (sensitivity analysis) - PsARC+PASI100 (sensitivity analysis)"	Given the greater efficacy in skin outcomes of the newer generation biologics, such as the IL-17 agents, PASI response in conjunction with PsARC response was incorporated as the treatment continuation rule in the model in sensitivity analyses.
Efficacy	- Treatment efficacy similar between psoriasis subgroups - PASI and PsARC assumed to be correlated (rho=0.4) - Comparative efficacy estimates derived from NMA based on SLR of clinical efficacy and data from manufacturers on comparator efficacy	- PASI and PsARC assumed to be correlated with rho-value dependent on treatment and response criterion - Comparative efficacy estimates obtained from NMA based on SLR of clinical efficacy undertaken in 2017	A correlation coefficient of 0.4 was not feasible given the PsARC and PASI response rates estimated for etanercept in the bDMARD-naïve population. The maximum feasible value for the correlation coefficient was therefore used. The 2016 York model used confidential data provided by the manufacturers to inform the the evidence synthesis, therefore networks with bDMARD-naïve and -experienced subgroup data for certolizumab pegol and secukinumab were feasible. As these data were not publicly available, they were therefore not identified in the SLR of clinical efficacy conducted for the current assessment.
Cycle length	3 months	Monthly	Monthly cycles are implemented to allow for sufficiently short cycles to capture trial periods when patients switch treatments, and for flexibility to adapt the trial period to the different trial period durations of the treatments included in the model
Cost year	- Cost year 2015/2016 - Health state costs based on HAQ and PASI according to Bansback et al based on Kobelt et al (2002)	- Cost year 2016/2017 - Health state costs based on HAQ and PASI according to Bansback et al based on Kobelt et al (2002) (inflated to 2017)	Costs updated to most recent cost year available
Utilities	Expected utility=0.897-0.298*HAQ-0.004*PASI	Expected utility in bDMARD-naïve patients = [redacted] -[redacted] *HAQ-[redacted] *PASI Expected utility in bDMARD-experienced patients = [redacted] -[redacted] *HAQ-[redacted] *PASI	The SPIRIT trials were used to estimate coefficients in York utility function. Prior bDMARD subgroups were analysed separately to reflect inherent differences in terms of functional capacity between the two populations.

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Section C: Textual clarifications and additional points

C1. **Priority question:** Please provide all references used in the CS appendices.(1)

The references are provided in the compressed folder titled 'C1. Appendices references'.

References

1. Eli Lilly and Company Limited. Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194]: Appendices. Feb 2018 [accessed 8.2.18].
2. Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. Arthritis care & research. 2010;62(3):345-53.
3. Stober C, Ye W, Guruparan T, Htut E, Clunie G, Jadon D. Prevalence and predictors of tumour necrosis factor inhibitor persistence in psoriatic arthritis. Rheumatology (Oxford, England). 2018;57(1):158-63.
4. DSP AP. Patient Demographics & Treatment History Analysis : UK. 2015.
5. Ogdie A, Langan S, Love T, Haynes K, Shin D, Seminara N, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. Rheumatology (Oxford, England). 2013;52(3):568-75.
6. National Institute for Health and Care Excellence. Single Technology Appraisal Appendix B. Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs: Final scope London: NICE; Nov 2017 [accessed 8.2.18].
7. Eli Lilly and Company Limited. Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194]. Document B: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA). 2018 [accessed 8.2.18].
8. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017;76(1):79-87.
9. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet (London, England). 2017;389(10086):2317-27.
10. European Medicines Agency. Assessment Report: Ixekizumab 2016 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf.

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11. European Medicines Agency. Assessment Report: Secukinumab 2014 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf.
12. Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M, et al. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation 2017 [updated OctPMC5641819]. 1-326]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28976302.
13. National Institute for Health and Care Excellence. Adalimumab for the treatment of adults with psoriasis [TA146]. 2008.
14. National Institute for Health and Care Excellence. Infliximab for the treatment of adults with psoriasis [TA134]. 2008.
15. National Institute for Health and Care Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis [TA180]. 2009.
16. National Institute for Health and Care Excellence. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis [TA199] 2010 [Available from: https://www.nice.org.uk/guidance/ta199.
17. National Institute for Health and Care Excellence. Apremilast for treating moderate to severe plaque psoriasis [TA368]. 2015.
18. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis [TA350]. 2015.
19. National Institute for Health and Care Excellence. Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (Technology Appraisal TA445) [Internet]. London: NICE; 2017 [accessed 20.2.18].
20. Eli Lilly and Company. 1. RHAP Clinical Study Report: a multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis. LY2439821 (Ixekizumab) - Psoriatic Arthritis. Protocol I1F-MC-RHAP [PDF provided with the company's submission]. Eli Lilly and Company; 3 Aug 2016 [accessed 8.2.18].
21. Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2011;15(10):i-xxi, 1-329.
22. National Institute for Health and Care Excellence. Apremilast for treating active psoriatic arthritis [TA433] 2017 [Available from: https://www.nice.org.uk/guidance/ta433.
23. National Institute for Health and Care Excellence. Ustekinumab for treating active psoriatic arthritis [TA340] 2015 [Available from: https://www.nice.org.uk/guidance/ta340.
24. National Institute for Health and Care Excellence. Golimumab for the treatment of psoriatic arthritis [TA220] 2011 [Available from: https://www.nice.org.uk/guidance/ta220.
25. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
26. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011;31(6):800-4.
27. Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. Arthritis Rheum. 2002;46(9):2310-9.

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28. Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. Rheumatology (Oxford). 2010;49(10):1949-56.
29. D'Angiolella LS, Cortesi PA, Lafranconi A, Micale M, Mangano S, Cesana G, et al. Cost and Cost Effectiveness of Treatments for Psoriatic Arthritis: A Systematic Literature Review. Pharmacoeconomics. 2018.
30. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ. 2015;351:h4672.
31. McIntosh E. The cost of rheumatoid arthritis. Br J Rheumatol. 1996;35(8):781-90.
32. Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006;10(31):iii-iv, xiii-xvi, 1-239.

A10. Odds ratios with 95% CrIs are presented for PASI 50/75/90/100 outcomes in the base case bDMARD-naïve network in Table 1, Table 2, Table 3 and Table 4; and for PASI 75/90/100 outcomes in the base case bDMARD-experienced network in Table 5, Table 6 and Table 7.

Table 1 UK 1A (biologic naive) network, PASI 50 - Relative Risk (RR) cross tabulation (row treatment versus column treatment)

	Placebo	Adalimumab 40 mg Q2W	Apremilast 30 mg BID	Certolizumab pegol pooled doses	Etanercept 25 mg BIW/50 mg QIW	Golimumab 50 mg Q4W	Infliximab 5 mg/kg Q8W	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Secukinumab 150 mg Q4W	Secukinumab 300 mg Q4W
Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**Adalimumab 40 mg Q2W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Apremilast 30 mg BID**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Certolizumab pegol pooled doses**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Etanercept 25 mg BIW/50 mg QIW**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Golimumab 50 mg Q4W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Infliximab 5 mg/kg Q8W**		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Ixekizumab 80 mg Q2W**		[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]	**Secukinumab 150 mg Q4W**		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Secukinumab 300 mg Q4W**	

Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*

Table 2 UK 1A (biologic naive) network, PASI 75 - Relative Risk (RR) cross tabulation (row treatment versus column treatment)

	Placebo	Adalimumab 40 mg Q2W	Apremilast 30 mg BID	Certolizumab pegol pooled doses	Etanercept 25 mg BIW/50 mg QIW	Golimumab 50 mg Q4W	Infliximab 5 mg/kg Q8W	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Secukinumab 150 mg Q4W	Secukinumab 300 mg Q4W
Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**Adalimumab 40 mg Q2W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Apremilast 30 mg BID**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Certolizumab pegol pooled doses**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Etanercept 25 mg BIW/50 mg QIW**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Golimumab 50 mg Q4W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Infliximab 5 mg/kg Q8W**		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Ixekizumab 80 mg Q2W**		[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]	**Secukinumab 150 mg Q4W**		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Secukinumab 300 mg Q4W**	

Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*

Table 3 UK 1A (biologic naive) network, PASI 90 - Relative Risk (RR) cross tabulation (row treatment versus column treatment)

	Placebo	Adalimumab 40 mg Q2W	Apremilast 30 mg BID	Certolizumab pegol pooled doses	Etanercept 25 mg BIW/50 mg QIW	Golimumab 50 mg Q4W	Infliximab 5 mg/kg Q8W	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Secukinumab 150 mg Q4W	Secukinumab 300 mg Q4W
Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**Adalimumab 40 mg Q2W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Apremilast 30 mg BID**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Certolizumab pegol pooled doses**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Etanercept 25 mg BIW/50 mg QIW**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Golimumab 50 mg Q4W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Infliximab 5 mg/kg Q8W**		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Ixekizumab 80 mg Q2W**		[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]	**Secukinumab 150 mg Q4W**		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Secukinumab 300 mg Q4W**	

Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*

BID=Twice daily dosing regimen, BIW=Twice weekly dosing regimen, QIW=Once weekly dosing regimen, Q2/4/8/12W=Every 2nd/4th/8th/12th week dosing regimen. Certolizumab pegol pooled doses are 200 mg Q2W and 400 mg Q4W.

Mixed biologic naive and experienced population for the following treatments: Apremilast 30 mg BID, Placebo, Secukinumab 150 mg Q4W, Secukinumab 300 mg Q4W

Table 4 UK 1A (biologic naive) network, PASI 100 - Relative Risk (RR) cross tabulation (row treatment versus column treatment)

	Placebo	Adalimumab 40 mg Q2W	Apremilast 30 mg BID	Certolizumab pegol pooled doses	Etanercept 25 mg BIW/50 mg QIW	Golimumab 50 mg Q4W	Infliximab 5 mg/kg Q8W	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Secukinumab 150 mg Q4W	Secukinumab 300 mg Q4W
Placebo		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**Adalimumab 40 mg Q2W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Apremilast 30 mg BID**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Certolizumab pegol pooled doses**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Etanercept 25 mg BIW/50 mg QIW**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Golimumab 50 mg Q4W**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Infliximab 5 mg/kg Q8W**		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Ixekizumab 80 mg Q2W**		[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]	**Secukinumab 150 mg Q4W**		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Secukinumab 300 mg Q4W**	

Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*

Table 5 UK 1B (biologic experienced) network, PASI 75 - Relative Risk (RR) cross tabulation (row treatment versus column treatment)

	Placebo	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Ustekinumab 45 mg Q12W
Placebo		[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]		[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]		[redacted]
Ustekinumab 45 mg Q12W	[redacted]	[redacted]	[redacted]	

Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*

Table 6 UK 1B (biologic experienced) network, PASI 90 - Relative Risk (RR) cross tabulation (row treatment versus column treatment)

	Placebo	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Ustekinumab 45 mg Q12W
Placebo		[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]		[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]		[redacted]
Ustekinumab 45 mg Q12W	[redacted]	[redacted]	[redacted]	

Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*

Table 7 UK 1B (biologic experienced) network, PASI 100 - Relative Risk (RR) cross tabulation (row treatment versus column treatment)

	Placebo	Ixekizumab 80 mg Q2W	Ixekizumab 80 mg Q4W	Ustekinumab 45 mg Q12W
Placebo		[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg Q2W	[redacted]		[redacted]	[redacted]
Ixekizumab 80 mg Q4W	[redacted]	[redacted]		[redacted]
Ustekinumab 45 mg Q12W	[redacted]	[redacted]	[redacted]	

Posterior median (95% credible interval). Statistically significant results are shown in **bold** *text*

NICE National Institute for Health and Care Excellence

Professional organisation submission

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]

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

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

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

Information on completing this submission

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

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society for Rheumatology**
3. Job title or position	**Consultant Rheumatologists**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**I represent the British Society for Rheumatology – the UK's leading specialist society for Rheumatology and musculoskeletal professionals**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To control disease activity (across all the domains of psoriatic arthritis (joints, entheses (where tendons attach to bone), spine, skin psoriasis) and thus control pain, prevent progression to irreversible damage and ensuing disability. PsA is also associated with a variety of comorbidities which increase morbidity and mortality. Treating the condition appropriately can reduce these associated comorbidities. Overall the aim of treatment is to improve quality of life.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Accepted treatment response for previously approved TAs have largely been based around achievement of PsARC (PsA response Criteria) which is an adequate outcome measure and the most widely used outcome across the UK for PsA. This requires a 30% improvement in either the tender or swollen joint count (based on a 66/68 joint count) and an improvement of at least 1 point out of a 5 point Likert score in either the patient or physician global score, with no worsening of any criteria. Newer outcome measures such as MDA (minimal Disease activity) require multiple measures to be taken in the clinic which is too complicated and timeconsuming for the majority of centres assessing patients for response but does represent outcomes in different modalities such as skin and enthuses rather than just joints. The skin response should be measured as recommended in previous TAs such that a dramatic skin response and an acceptable joint response could allow continuation of treatment. Many clinical trials use ACR20 / 50 / 70 but this is less acceptable in the UK clinics as an outcome than PsARC
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes There is a relative paucity of agents available to treat PsA. Non-biologic treatments eg methotrexate, sulphasalazine and leflunomide have a very poor evidence base. Although there are now 5 NICE approved TNFi, there is only one approved IL17 inhibitor (sekukinumab), one IL12/23 inhibitor (ustekinumab) and apremilast. We know from published studies and registries that many patients who do not respond to one agent or have side effects from it will respond to another agent – even within the same class eg TNFi). For this reason alone it is most useful to patients and physicians to have access to more than one agent within the same class as well as different agents targeting different classes. There are now an increasing number of patients who have quite simply run out of options and are left with unremitting symptoms, a very poor quality of life and disease progression. IL17 is proven to be an important cytokine in PsA and has potential to address various comorbities eg spinal disease, skin disease to improve multiple aspects of the patients disease.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	DMARDs (methotrexate, sulfasalazine en, leflunomide and occasionally ciclosporin) Corticosteroids (predominantly intramuscular / intraarticular) Anti TNF therapy (etanercept, adalumimab, etc) Apremilast Secukinumab
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSR Gudelines EULAR Guidelines GRAPPA Guidelines NICE TAs NICE Clinical guideline for Spondyloarthritis
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes although many non-specialist clinicians continue to treat PsA like RA eg only measuring DAS scores (Disease activity scores) based on a 28 joint count rather than 66/68 joint count. Many centres will not have expertise or knowledge to adequately assess skin psoriasis.
• What impact would the technology have on the current pathway of care?	It will give patients more chance of achieving successful treatment of their condition. Many patients will either not respond to or develop a side effect to other agents and therefore having more agents available is vital. There is only one agent targeting IL17 available currently under NICE guidance and a further agent would be extremely useful for patients who have tried and failed this or prefer to try this instead of sekukinumab.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used identically to secukinumab
• How does healthcare resource use differ between the technology and current care?	Additional choice but no other differences
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care Rheumatology centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – for patients unresponsive to DMARDs, anti-TNF and possibly secukinumab

• Do you expect the technology to increase length of life more than current care?	Yes – additional ability to control the disease will lead to fewer complications related to comorbidities, cardiovascular disease, less use of steroids / NSAIDs and associated morbidity.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – further agent to choose from will offer more patients a chance of disease control
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Likely to be especially helpful in patients with concurrent significant skin psoriasis and axial disease
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	The same as other biologics

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Same as other biologics / TAs
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Skin psoriasis and its impact (social, psychological, comorbidities eg depression / anxiety,) not particularly well reflected in QALY Other aspects of PsA such as fatigue, anxiety / depression not adequately reflected

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Another agent in the class already established but we know from experience with TNFi that many patients respond to one agent in the class but not another for reasons we do not fully understand and equally can have side effects to one agent within the class but not another.
• Is the technology a 'step-change' in the management of the condition?	Not as significant a step change as a whole new class but still much needed
• Does the use of the technology address any particular unmet need of the patient population?	As above some patients fail to respond to all currently approved agents so they definitely represent an unmet need.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects unlikely to be any more apparent than current biologics. Patients are fully consented on the potential risks and data on adverse effects should be reported by the yellow card system and hopefully soon be collected on a registry.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes – PsARC, 66/68 joint score, HAQ, PASI, enthesitis and dactylitis scores
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Many of the trials were of sufficient duration to provide some data on long term outcome (1-2 years)
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA340 (ustekinumab), TA433 (apremilast), TA445 (certolizumab pegol and secukinumab), TA199 (etanercept, infliximab and adalimumab) or TA220 (golimumab)?	Some ongoing trials with JAK inhibitors and targeted IL23 inhibitor.
21. How do data on real-world experience compare with the trial data?	Little real world experience with Ixekizumab in the UK (other than within trials). The other anti IL-17 (Secukinumab) is growing in popularity amongst clinicians as particularly effective in skin psoriasis, enthesitis and axial inflammation occurring in patients with peripheral PsA

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None apparent (other than the female preponderance of non-radiographic axial inflammation – which currently precludes the use of secukinumab in more women than men with AxSpA – but this probably falls outside the remit of this TA)
22b. Consider whether these issues are different from issues with current care and why.	Similar to the other anti IL-17

Key messages

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

- Ixekizumab offers a second choice IL17 inhibitor for patients with PsA
- !L 17 inhibitors offer excellent treatment efficacy across the spectrum of disease (joints, skin, spine)
- Many patients with PsA are now running out of all the available biologic agents (failed due to inefficacy, loss of response or adverse events) and represent a definite unmet need.
- Ixekizumab would require no new assessments or resources and could be easily integrated into the pathway alongside sekukinumab
- PsA is a progressive, significant disease which has a major impact on a patients quality of life across all modalities including pain, disability, depression, anxiety, fatigue, inability to work and any agent which has the potential to improve this represents a major breakthrough in the treatment of this chronic disease.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]

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

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

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Rheumatology Pharmacists UK (RPUK) on behalf of the United Kingdom Clinical Pharmacy Association (UKCPA)**
3. Job title or position	**Rheumatology Specialist Pharmacist**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	Rheumatology Pharmacists UK Rheumatology Pharmacists UK is a group of clinical pharmacy practitioners working in the field of rheumatology, affiliated to the UKCPA (communication portal NHS networks)
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Relieve symptoms: (joint inflammation, periarticular inflammation, skin psoriasis) Slow disease progression (e.g. radiographic progression) Maintain health-related quality of life (e.g. improved functional capacity, mental well-being)

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Psoriatic Arthritis Response Criteria (PsARC) (using a 78/76 joint count) An adequate response is defined as an improvement in at least 2 out of the 4 response criteria (one must be joint tenderness or swelling score). No worsening of any of the criteria must occur. Improvement is defined as >30% improvement in the joint scores or improvement by at least 1 point on the Likert scale.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Few biologic treatment options with alternative mechanism of action to TNF inhibition. Currently only ustekinumab (IL-12/23 inhibitor) or secukinumab (IL-17A inhibitor).
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Conventional synthetic DMARDs (e.g. methotrexate, sulfasalazine) Targeted synthetic DMARD (e.g. apremilast) Biologic therapy (TNF inhibitors or alternative mechanism of action) Flare ups / bridging therapy with corticosteroids (PO, IM, IA or IV) and NSAIDs Non pharmacological management (e.g. Physiotherapy, OT)

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Spondyloarthritis in over 16s: diagnosis and management NICE guideline [NG65] https://www.nice.org.uk/guidance/ng65 Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis http://ard.bmj.com/content/75/3/490 Related NICE TAs 199, 220, 340, 433, 445
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	NICE recommend pathway of non biological DMARDs before trying biological DMARDs. NICE TAs govern which therapies can be used as first line biologic or after previous biologic failure. NICE TAs suggest ustekinumab, certolizumab pegol or secukinumab following failure to TNF inhibitors or ustekinumab or secukinumab if TNF inhibitors are contraindicated. However there is likely to be some local variation between treatment following previous biologic failure / intolerance (i.e. TNFi cycling vs switching to an alternative mechanism of action therapy)
• What impact would the technology have on the current pathway of care?	Provide another option for IL17A inhibition Will patients cycle between IL17A inhibitors like they do for TNF inhibitors?
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – TA 199, 220, 340, 445
• How does healthcare resource use differ	Same cohort of patients. Would be used as an alternative to existing biologic DMARDs. Initial set up costs / resources for setting up a new therapy but once running, should fit into existing resources (e.g. homecare

between the technology and current care?	teams, pharmacy screening, specialist nurses) as this therapy will be prescribed in place of another biologic, not a new cohort of patients.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care – in rheumatology specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Would be used instead of other therapies so should require minimal cost beyond initial implementation.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes in line with other treatments (similar response rates to secukinumab and adalimumab when compared with placebo in biologic naïve patients).
• Do you expect the technology to increase length of life more than current care?	No (as there is already one IL17A inhibitor in current practice)
• Do you expect the technology to increase health-related quality of	In line with current treatments. May provide another treatment option for patients who have exhausted all other therapies but currently no evidence for use after previous IL17A inhibitor treatment failure or intolerance?

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Caution in patients with a history of IBD (risk of exacerbation of CD and UC have been reported) as for secukinumab. Will provide a latex free IL17A inhibitor (as Cosentyx needle cap contains derivative of natural rubber) May be preferable to secukinumab depending on cost information and only requiring one injection following loading (rather than two per dose for secukinumab in PsA in TNFi non responders)
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Same – usually states same criteria as for TA199 PsA would benefit from a new multi technology appraisal (MTA)

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Assess response at 16-20 weeks (SPC) or 24 weeks (trial data) Only continue if significant response using PsARC assessment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not known
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Same mechanism of action as secukinumab so not innovative Secukinumab is a human IgG1 mAb that neutralizes IL-17A Ixekizumab is a humanized IgG4 mAb that neutralizes IL-17A

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Latex free IL17A inhibitor product (compared to Cosentyx)
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	FDA - During Taltz treatment, monitor patients for onset or exacerbations of inflammatory bowel disease. Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the Taltz group (Crohn's disease 0.1%, ulcerative colitis 0.2%) than in the placebo group (0%) during clinical trials in patients with plaque psoriasis. EMA EPAR - The most common side effects with Taltz (which may affect more than 1 in 10 people) are pain and redness at the injection site, and nose, throat or chest infections. Taltz must not be given to patients who have potentially serious infections such as tuberculosis. All other adverse effects discussed in SPC
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Do not have full access to SPIRIT-P1 and SPIRIT-P2 trials for appraisal. SPIRIT-P1 - ACR 20 response in comparison with placebo arm, adalimumab control arm and two dosing schedules for ixekizumab SPIRIT-P2 – patients who had previously failed / not tolerated TNFi. FDA: The efficacy and safety of Taltz was determined from findings from two randomized, double-blind, placebo-controlled Phase 3 studies - SPIRIT-P1 and SPIRIT-P2 - which included more than 670 adult patients with active PsA.1 SPIRIT-P1 evaluated the safety and efficacy of Taltz compared to placebo in patients with active PsA who had never been treated with a biologic disease-modifying antirheumatic drug.1 SPIRIT-P2 evaluated the safety and efficacy of Taltz compared to placebo in tumor necrosis factor inhibitor (TNFi)-experienced patients with active PsA who failed one or two TNF inhibitors.1 Across both studies, patients were required to have a diagnosis of active PsA for at least six months and at least three tender and three swollen joints.1 Non-responder imputation (NRI) methods were used. Inadequate responders (defined by blinded tender and swollen joint count criteria) at Week 16 received rescue therapy and were analyzed as non-responders.1 In studies of biologic-naïve and TNFi-experienced patients, the primary efficacy endpoint was the proportion of patients at 24 weeks achieving ACR20 response, which represents a 20 percent reduction in a composite measure of disease activity as defined by the American College of Rheumatology (ACR).1 Results from both studies demonstrated that patients treated with Taltz achieved significant improvement in joint symptoms, as measured by ACR20, compared with placebo.1 At 24 weeks, patients achieved ACR20 at the following response rates: •SPIRIT-P1: 58 percent of patients treated with Taltz vs. 30 percent for placebo1 •SPIRIT-P2: 53 percent of patients treated with Taltz vs. 20 percent for placebo1
• If not, how could the results be extrapolated to the UK setting?	

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- What, in your view, are the most important outcomes, and were they measured in the trials?

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ACR 20 reported in trials but also need to look at PsARC response criteria (secondary outcome) as this is used to assess response in clinical practice (SPIRIT-P1) – comparable to adalimumab.

Measured Values

	Placebo	Adalimumab Q2W	Ixekizumab Q4W	Ixekizumab Q2W
Participants Analyzed [Units: Participants]	106	101	107	103
Percentage of Participants Meeting the Psoriatic Arthritis Response Criteria (PsARC Modified) [Units: Percentage of participants]	32.1	58.4	57.9	66.0

No statistical analysis provided for Percentage of Participants Meeting the Psoriatic Arthritis Response Criteria (PsARC Modified)

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- If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?

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Duration of extension study in SPIRIT-P1 24 weeks? – not clear without full access to trial

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- Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?

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See SPC

Will need to look at most up to date MHRA DAPs / registry data

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19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?

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No

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20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA340 (ustekinumab), TA433 (apremilast), TA445 (certolizumab pegol and secukinumab), TA199 (etanercept, infliximab and adalimumab) or TA220 (golimumab)?	Would like to see head to head comparison data with secukinumab or ustekinumab and sequential use after secukinumab intolerance / failure. Some indirect comparison meta-analyses have been published that compare ixekizumab with secukinumab for psoriasis but not psoriatic arthritis (but these have been funded by Eli Lilly)
21. How do data on real-world experience compare with the trial data?	Not available
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

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

- Another IL17A blocker (same mechanism of action as secukinumab) for the management of active psoriatic arthritis.
- Demonstrated efficacy comparable to other biologics (e.g. adalimumab) and comparable safety (from EPAR assessment) – need to check studies when full access available.
- In comparison to secukinumab, perhaps more favourable dosing schedule (only one loading dose, one injection per maintenance dose), latex free device.
- Would benefit from further head to head comparison with other available biologics / guidance on appropriate sequential use.
- Costing information required to assess likely uptake in clinical practice compared to existing IL17A inhibitor.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PAPAA is a national charity, which provides information and support to people affected by psoriasis and psoriatic arthritis. The current incarnation followed the merger of two separate organisations, with the oldest dating back to 1992. Although the charity has no formal membership, it has a supporter register of >13,000 people which includes both patients and healthcare professionals. In a changing 21st century, activity and support has evolved with more taking place online, with most interaction via that medium. The main charity website had >850,000 page views during the past year. Regular use of feedback forms and online surveys help to direct the charity's work and how it represents its constituent group. Funding is via donations, subscriptions and from the sale of promotional items. Financial support is not accepted from the pharmaceutical industry, either as direct payment or in-kind, this includes third-party work via PR or research agencies. The organisation values its independence and feels this provides an agenda which is patient-centred and not driven by marketing or promotional activities that may be behind such support, however arms-length or segmented.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	Data for this submission has been gathered via our online surveys and direct feedback. We compile ongoing views and opinions of those who interact with us to provide a broad consensus that we think reflects the general psoriasis population that is likely to be those who would potentially qualify for ixekizumab.

carers to include in your submission?	We receive many calls via our information line and questions are often about treatments and in particular the use of biological therapies, therefore we get a lot of feedback about how these are being offered and prescribed to patients.
Living with the condition	
6. What is it like to live with the condition?What do carers experience when caring for someone with the condition?	Psoriatic arthritis is often diagnosed by default due to the lack of dedicated tests, with many people being surprised and shocked to learn that there is a form of inflammatory arthritis, which is associated with their psoriasis. This is often more surprising to them because due to the onset often happening between the ages of 20 and 30 years, people do not usually expect arthritis to affect them at this young age. Although psoriatic arthritis can be found in people without psoriasis or a very mild form, for most they would have had psoriasis for a few years, which is often very difficult to cope with both physically and psychologically. Adding a painful, disabling connective tissue and joint disease creates a worse scenario for people and provides a further huge psychological and physical impact, which often can dominate their life. Generally, it affects hands and feet, but many people find they have issues with other joints and in particular their spine. At first diagnosis people feel devastated and thoughts about their future play heavily on their minds, such as the ability to work, care for their children, or conceive a family, holding on to and developing new relationships. Carers often feel helpless and often find it difficult to cope, particularly partners whose life and plans are often intertwined with the individual who has developed the condition. We often hear that people feel a sense of guilt about not being able to support their family with the responsibility often put onto the carer which can lead to relationships becoming fractured. Both those with the condition and their carers report to us how low they feel with anxiety and depression beginning to creep in, this often persists even once treatment is established as people experience flares which can be debilitating or fear a return of the condition long term. Apart from the widespread pain, the condition has other issues that are often difficult to cope with. Many people tell us they feel fatigued and have what is described as ‘brain fog’ where they find it difficult to cope

	and concentrate with simple day-to-day activities. Sleep or rest fails to relieve the symptoms. Another issue which people find difficult to deal with is stiffness after rest, particularly first thing in the morning, this can play havoc with those still able to work as they tend to need more time to get ready and carry out tasks that many people would take for granted. Stiff hands make dressing and personal hygiene tasks more difficult and painful feet and toes often make early morning movement more complicated. People tell us they often drop objects or feel clumsy until this stiffness alleviates, commonly once they have been up and about for a while.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Dependent on the severity, psoriatic arthritis is managed with a number of treatments, singularly or in combination these include non-steroidal anti-inflammatory medicines (NSAIDs), corticosteroids (injection, orally), disease-modifying anti-rheumatic drugs (DMARDs) and targeted biologic agents. The use of physiotherapy for mobility is common as is pain management techniques. The treatments all provide differing results and are dependent upon patient preference, fears and prejudice. The use of NSAIDs often lead to gastric problems, or with targeted NSAIDs increased cardiovascular risk. Corticosteroids are associated with weight gain and risks to bone health. The use of DMARDs such as methotrexate worry patients with side-effect profiles being of concern and for younger men the limiting or abstinence from alcohol can be a reason for not wanting to start methotrexate. Biologic agents are increasingly becoming of interest to patients, as the convenient less frequent dosage helps to alleviate the burden of more regular medication, although there is concern about the long-term effects of these drugs from the younger population. There is also concern about failure of these agents and what happens when a drug doesn't work adequately or stops working after initial benefit. Current guidance limits use, therefore patients become anxious about what options will be available once those therapies have been exhausted.

8. Is there an unmet need for patients with this condition?	For those where therapies fail or lose efficacy, there is a need for more options. Tackling the issue of fatigue and relief from those symptoms would be welcomed as would a therapy that also provides benefit to the aspects of psoriasis such as nail disease which is very common in people with psoriatic arthritis.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As ixekizumab is not currently routinely available within the NHS for psoriatic arthritis, we have no information on the patients and carers views of the advantages of the technology.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As ixekizumab is not currently routinely available within the NHS for psoriatic arthritis, we have no information on the patients and carers views of the disadvantages of the technology.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who also have psoriasis who do not meet the NICE criteria for ixekizumab alone, may benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We don't believe there are issues which are considered under equality legislation that need to be taken into account.
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Reduction in pain, inflammation and fatigue. • Avoid disabling consequences of psoriatic arthritis by maintaining mobility, stopping further deterioration and joint destruction. • Reduced drug adverse events, without loss of efficacy. • Access and choice to a wide range of therapies • Improve psoriasis including nails.

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About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The reach of the Psoriasis Association now extends further than that of the traditional member. There were 566,961 visits to the main Psoriasis Association website in 2017, with 8,490 people registered to participate in our online forums. Traditional Membership numbers stand at 1,670. There are 4,950 people registered to contribute in our Facebook Group and 9,462 people keeping up to date with Psoriasis news via our Twitter account. The Psoriasis Association also operates a telephone and email helpline with over 850 people per year contacting us via these means.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Psoriasis Association analyses the data gathered from all communication channels (numbers in 4a) and monitors for trends in addition to interesting new requests. We are part way through a Priority Setting Partnership on Psoriasis which has provided valuable insight into issues affecting people living with Psoriasis and Psoriatic Arthritis, their relatives and carers, healthcare professionals and researchers.
Living with the condition	
6. What is it like to live with the condition? What do carers	Psoriatic Arthritis is a destructive form of arthritis with a peak onset in people between 30 and 40 years of age. Owing to the age of onset of the condition (and the joints affected often being the fingers and toes right through to larger joints) impact on work, social life and relationships can be marked. Being unable to

experience when caring for someone with the condition?	do top buttons up on a shirt can be frustrating, but being unable to change your babies nappy due to the pain and destruction of your finger joints can be utterly devastating. Many jobs now have an element of computer work associated with them, but if you have PsA in the finger joints it can be extremely difficult to do any dexterous work. For those for whom PsA affects the joints in the toes, walking can be extremely painful and therefore impacts again on the types of job an individual can do, if they can work at all. PsA, unlike other more common forms of arthritis is often worse after a period of rest, and so early morning tasks may not be possible, or would take a longer amount of time compared to someone without PsA. Symptoms of PsA vary from mild to very severe, and can include swollen fingers and toes, tendonitis (particularly in the Achilles) and joints in the back. It is a destructive form of arthritis and so without timely, suitable treatment, joints can be destroyed quickly owing to the quick onset of inflammation. Patients therefore experience pain associated with the inflammation and current destruction of their joints, but also once the flare-up has subsided are left with pain due to the damage caused by the flare. It is key then that patients should have access to the relevant therapies to prevent the destruction (hence avoiding the need for joint replacement operations) and to continue to lead a full and active life. Nail psoriasis is common in people with psoriatic arthritis, and this too can be extremely disabling, painful and limits the tasks that a person can perform. Nail psoriasis affecting the toenails can make it difficult to wear shoes, which in turn can affect employment eligibility not to mention negatively impacting someone's quality of life. Fingernail psoriasis is painful and unsightly, limiting a person's day-to-day activities. Of course many people with psoriatic arthritis have a level of skin involvement also. Combined Dermatology / Rheumatology clinics are rare yet provide much needed expertise in managing two inflammatory diseases. Owing to the rarity of the combined clinics, patients frequently have the added pressure of attending double the amount of appointments as necessary, putting added pressure on work situations. With psoriatic arthritis affecting the fine motor joints as well as the larger mechanical joints, application of topical treatments to manage psoriasis can be difficult and patients become reliant on carers to help, or watch their skin condition deteriorate owing to inability to apply treatments.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Combined dermatology / rheumatology clinics would improve the treatment pathway for people with concomitant psoriasis and psoriatic arthritis greatly. Access to early treatment for this disease population is vital owing to the disabling nature of the condition that affects young adults, consequently impacting on work, life and family prospects. Whilst treatments are available to treat psoriatic arthritis, sadly a large treatment armamentarium is required in order to manage the disease over a lifetime, with early biologics losing efficacy in a number of patients.
8. Is there an unmet need for patients with this condition?	Yes – sadly there remains very few treatments available specifically to treat psoriatic arthritis, mainstream, traditional treatments may be more suitable for those with other forms of arthropathy. As psoriatic arthritis often occurs in young adults, treatments need to be efficacious over a lifetime. It is well documented that treatments can lose efficacy, and so wide availability is vital. Some of the more traditional systemic treatments are limited in their use for younger people wishing to start a family which in turn restricts their treatment options.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Following a successful introduction to Ixekizumab a four-weekly injection offers patients the opportunity to get on with their lives without the constraints of infusions in hospital, or more frequent injections which can hamper travelling / holidays and prove difficult in those whose finger joints are affected. Advantages also include known benefit to concomitant psoriasis – one treatment that can treat both diseases is always preferable.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There is always reluctance amongst some individuals to use new technologies until longer term safety data has been established. The Psoriasis Association advocates the participation of patients on biologics registries such as those overseen by the British Association of Dermatologists and the British Society for Rheumatology. Of course there is reluctance amongst some patients regarding self injection, but through careful coaching this can often be overcome.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who also have skin involvement would benefit more from this treatment (TA442)
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

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

- Psoriatic arthritis can not only destroy the joints affected, but also the lives of those affected
    - Having a treatment that can work on both the skin and joints affected by psoriasis is of importance to patient choice
- There are currently few treatments available for psoriatic arthritis, and so an extension to the treatment armoury is most welcomed.

Thank you for your time.

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

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Academic in confidence (AiC) data are highlighted in yellow throughout the report.

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

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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. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Xavier Pouwels, Willem Witlox and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Piet Portegijs and Elizabeth Matovinovic acted as systematic reviewers, 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. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore critiqued the manufacturer's economic evaluation, contributed to the writing of the report and provided general guidance. 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

ACR	American College of Rheumatology
ACR 20	At least 20% improvement in both tender and swollen joint counts
ACR 50	At least 50% improvement in both tender and swollen joint counts
ACR 70	At least 70% improvement in both tender and swollen joint counts
ADA	Adalimumab
ANA	Antinuclear antibody
APLAR	Asia Pacific Rheumatology Congress
APR	Apremilast
ARHP	Association for Rheumatology Health Professionals
AWMSG	All Wales Medicines Strategy Group
b/tsDMARD	Biologic/targeted synthetic disease-modifying anti-rheumatic drug
BC	Base-case
bDMARD	Biologic disease-modifying anti-rheumatic drug
bid	Twice daily
biw	Twice weekly
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
cDMARD	Conventional disease-modifying anti-rheumatic drug
CEA	Cost effectiveness analysis
CEM	Cost effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CODA	Convergence Diagnostic and Output Analysis
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CrI	Credible interval
CS	Company submission
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CSR	Clinical study report
CZP	Certolizumab pegol
DAE	Discontinuation due to adverse events
DARE	Database of abstracts of reviews of effects
DAS28-CRP	Disease activity score 28 diarthrodial joint count based on c-reactive protein
DCE	Discrete choice experiment
DIC	Deviance information criteria
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
Ds	Double-stranded
DSA	Deterministic sensitivity analyses
DSP	Disease specific programme
DSU	Decision Support Unit
EBM	Evidenced-based medicine
EED	Economic Evaluation Database
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESR	Erythrocyte sedimentation rate
ETA	Etanercept
ETN	Enbrel
EULAR	European League Against Rheumatism

EUR	Erasmus University Rotterdam
FBC	Full blood count
FE	Fixing errors
FV	Fixing violations
GOL	Golimumab
GP	General practitioner
HAQ-DI	Health Assessment Questionnaire-Disability Index
HCRU	Health Care Resource Utilisation
HEED	Health Economic Evaluations Database
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Intra-articular
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IL	Interleukin
INF	Infliximab
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IXE	Ixekizumab
kg	Kilogram
KSR	Kleijnen Systematic Reviews
LDI	Leeds Dactylitis Index
LDI-B	Leeds Dactylitis Index-Basic
LEI	Leeds Enthesitis Index
LFT	Liver Function Test
LOCF	Last observation carried forward
LSM	Least squares mean
mAb	monoclonal antibody
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
mBOCF	Modified baseline observation carried forward
MDA	Minimal Disease Activity
MeSH	Medical Subject Heading
mg	Milligram
MIMS	Monthly Index of Medical Specialities
MJ	Matters of judgement
MMRM	Mixed-effects model repeated measures
mTSS	Modified Total Sharp Score
NA	Not applicable
NAPSI	Nail Psoriasis Severity Index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient Access Scheme
PASI	Psoriasis Area and Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PDE	Phosphodiesterase
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analysis
PsARC	Psoriatic Arthritis Response Criteria
PSS	Personal Social Services

PSSRU	Personal Social Services Research Unit
q2w	Once every two weeks
q4w	Once every four weeks
q8w	Once every eight weeks
q12w	Once every 12 weeks
QALY	Quality-adjusted life year
qd	Once daily
qiw	Once weekly
RCT	Randomised controlled trial
RTF	Restriction to focus
SA	Scenario analysis
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF	Short Form
SJC	Swollen joint count
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SPARCC	Spondyloarthritis Research Consortium of Canada Enthesitis Index
sPGA	Static physician's global assessment
SR	Systematic review
TA	Technology appraisal
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
THIN	The Health Improvement Network
TJC	Tender joint count
TLV	Tandvårds- och läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Board)
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
TTO	Time Trade-Off
U&E	Urea and electrolytes test
UK	United Kingdom
UMC	University Medical Center
URL	Uniform Resource Locator
UST	Ustekinumab
UVB	Ultraviolet B
VBA	Visual Basic for Applications
WHO	World Health Organisation

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population in the company submission (CS) is as defined in the National Institute for Health and Care Excellence (NICE) scope, i.e. adults with active psoriatic arthritis (PsA) whose disease has not responded adequately to previous disease-modifying anti-rheumatic drugs (DMARDs) or for whom DMARDs are not tolerated or contraindicated. However, ixekizumab is a biological DMARD (bDMARD) and under NICE guidance bDMARDs are normally given after failure of two or more conventional DMARDs (cDMARDs). Whilst the company aligns ixekizumab with NICE guidance, not all patients meet this criterion in the main trials of the submission (SPIRIT-P1 and P2). Furthermore, across the two trials, [redacted] patients were recruited to [redacted] centres in the UK which represents approximately [redacted] of the patients in the trials. The committee will need to decide, based on the factors highlighted by the Evidence Review Group (ERG) in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to clinical practice in the United Kingdom (UK).

However, the main weakness in the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope. The two main trials in the CS compare ixekizumab to placebo. The evidence in relation to the other DMARDs mentioned in the scope comes from indirect comparisons obtained through network meta-analyses (NMAs). The outcomes listed in the NICE scope are evaluated in the trials in the submission with the exception of mortality. The ERG recognises that short-term trials are unlikely to demonstrate any effect of treatment on mortality in PsA should one exist.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS presented direct evidence from two RCTs, SPIRIT-P1 and SPIRIT-P2 that compared ixekizumab to placebo in adults with PsA. SPIRIT-P1 was conducted in biological DMARD naïve patients whilst SPIRIT-P2 was conducted in those with experience of biological DMARDs. SPIRIT-P1 included 417 patients and SPIRIT-P2 363 patients. Both trials were well conducted, multinational trials. Across the two trials approximately [redacted] of patients were from the UK.

In both SPIRIT trials, significantly more patients achieved an ACR 20 response at week 24 with ixekizumab compared to placebo (SPIRIT-P1: IXE 80 once every four weeks (q4w) 57.9%, IXE 80 once every two weeks (q2w) 62.1%, placebo 30.2%; SPIRIT-P2: IXE 80 q4w 53.3%, IXE 80 q2w 48.0%, placebo 19.5%; $p<0.001$ for all comparisons to placebo). In both SPIRIT trials, the percentages of patients who achieved a Psoriatic Arthritis Response Criteria (PsARC) response at week 12 as well as week 24 were statistically significantly greater for both ixekizumab groups compared to placebo in all cases (Week 12 – SPIRIT-P1: IXE 80 q4w 55.1%, IXE 80 q2w 61.2%, placebo 34.0%; SPIRIT-P2: IXE 80 q4w 50.0%, IXE 80 q2w 52.0%, placebo 23.7%. Week 24 – SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 66.0%, placebo 32.1%; SPIRIT-P2: IXE 80 q4w 55.7%, IXE 80 q2w 47.2%, placebo 20.3%). In terms of quality of life at week 12, patients in the two ixekizumab groups achieved significantly greater mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) total scores in both SPIRIT trials. As not all participants in the SPIRIT trials would have been eligible for biological therapy under current NICE criteria, the company conducted a subgroup analysis using an integrated set of patients from SPIRIT-P1 and P2 who met the NICE criteria. The total number of patients available for analysis was [redacted]. [redacted] patients who received ixekizumab 80 mg q4w or q2w, respectively, achieved an ACR 20 response at week 24 compared to placebo ([redacted] and [redacted] vs. [redacted] respectively). In the 24-week double-blind treatment phase patients experienced more adverse events in the ixekizumab groups than in the placebo group in

both SPIRIT trials. Adverse events (AEs) across the two SPIRIT trials were mainly of mild or moderate severity and the proportion of patients who discontinued medication due to AEs was low across all treatment groups. There were no deaths across the two trials in the double-blind periods. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials.

In the absence of trials directly comparing the active treatments specified in the NICE scope, the company conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, Psoriasis Area and Severity Index (PASI) 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, PASI response and PsARC response, ixekizumab was [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders and [redacted] were the most effective treatments.

There was less evidence for bMARD-experienced patients (fewer than five trials in most analyses) and ixekizumab was [redacted] to ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate but it was [redacted] to ixekizumab.

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab but the differences were [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company conducted a systematic review of the evidence for ixekizumab and its potential comparators in adults with PsA as per the NICE scope. The submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. A range of databases were searched, and additional searches of conference proceedings, trials registers and websites were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. However, the ERG has major concerns regarding the searches, as detailed in section 1.6.2.

The company presented two multicentre, randomised controlled trials of ixekizumab (SPIRIT-P1 and P2). Randomised trials represent the highest level of primary studies in medical research. This evidence base includes patients with experience of bDMARDs and those without and outcomes relevant to the NICE scope. Both trials are well-conducted. Both compare ixekizumab to placebo. The double-blind period of the SPIRIT trials is 24 weeks so long-term effectiveness results cannot be fully determined. The extension periods do, however, provide information on long-term safety. At week 16 in the trials, patients were permitted rescue therapy in case of inadequate response so results up to 16 weeks are

more reliable for the comparison between ixekizumab and placebo. Although the trials were multinational, across the two trials, just [redacted] patients were recruited by [redacted] centres in the UK. This represents approximately [redacted] of patients. Non-white participants are underrepresented across the two trials. Mean BMI in the SPIRIT trials is within the obese category so patients in the trials may be more overweight than those seen in practice in the UK. Patients in SPIRIT-P1 and SPIRIT-P2 may have more severe disease than seen in UK practice. Further information of comparisons made by the company to UK practice and the ERG's interpretation are given in this report.

Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. The company demonstrated efficacy of ixekizumab in relation to placebo for a population reflective of NICE current guidance on use of bDMARDs after failure of two cDMARDs. However, this analysis was based on [redacted] patients across both trials so percentages of responders should be treated with some caution.

No direct evidence is available on ixekizumab in relation to the other comparators in the scope. Comparisons between ixekizumab and other comparators were obtained from Bayesian NMA. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients and although the analysis methods were appropriate and followed recommended guidance on performing NMA the results need to be treated with caution. This is because NMA results use indirect treatment comparisons across trials, in this case via placebo, and are less reliable than comparisons between different treatments within the same trial due to potential clinical and statistical heterogeneity between the trials.

1.4 Summary of cost effectiveness evidence submitted by the company

The company's systematic literature review (SLR) identified several cost effectiveness models in the present indication. The company developed a de novo cohort state transition model in Visual Basic for Applications (VBA) with a Microsoft Excel interface that was heavily based on the so-called "revised York model", a cost effectiveness model used in a previous technology appraisal (TA) 445 on secukinumab and certolizumab pegol for treating active psoriatic arthritis. In the base-case analysis, PsARC was used to determine treatment response while PASI (in the presence of concomitant psoriasis) and HAQ-DI scores were used to determine resource use and costs, and health state utility values. The model structure consisted of the following treatment states: the trial period, the continued treatment period, best supportive care (BSC), and death. The cycle length was one month and no half-cycle correction was applied, because the cycle length was considered to be sufficiently short.

The population in the CS was more narrowly defined than that for which ixekizumab was granted marketing authorisation by the European Medicines Agency (EMA). In the CS, the company considers patients who have responded inadequately to, or who are intolerant to, *at least two* cDMARD therapies. This represents the population which would be eligible for biological or targeted synthetic DMARD (b/tsDMARD) treatment according to NICE guidance while the EMA granted marketing access to patients who have responded inadequately to, or who are intolerant of *one or more* cDMARD therapies. Six subgroups were considered for this appraisal: b/tsDMARD-naive and b/tsDMARD-experienced patient populations, each stratified by psoriasis severity levels: no psoriasis, mild-to-moderate psoriasis and moderate-to-severe psoriasis.

The cost effectiveness of ixekizumab, q2w or q4w, was assessed against all b/tsDMARDs recommended by NICE for patients with PsA whose disease has not responded to two prior cDMARDs. A treatment sequencing approach was adopted by the company. Treatment sequences for b/tsDMARD-naïve patients were composed of two b/tsDMARD treatments, ustekinumab being the second-line treatment in all sequences, and then BSC, while treatment sequences for b/tsDMARD-experienced

patients included one b/tsDMARD treatment before BSC. All treatment sequences of the intervention began with ixekizumab while comparator treatment sequences began with another b/tsDMARD. These included adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, ustekinumab, and secukinumab. Dosing regimens and stopping rules (determining the length of the trial period) of each treatment were based on NICE guidance. The length of the trial period for ixekizumab was set to 12 weeks in the company's base-case analysis, while the summary of product characteristics (SmPC) for ixekizumab advises that treatment should be discontinued in patients who did not show response after 16 to 20 weeks of treatment.

The analysis took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The company adopted a lifetime time horizon.

Treatment effectiveness in the economic model was informed by PsARC, HAQ-DI and PASI, all sourced from the NMA. PsARC and PASI were estimated separately for patients with and without prior b/tsDMARD exposure while HAQ-DI was estimated for patients without prior b/tsDMARD exposure (due to lack of evidence). After the trial period, treatment was continued for patients classified as responders based on PsARC while treatment was discontinued for PsARC non-responders. An annual treatment discontinuation of 16.5% per year was applied (independent of both time and treatment) to the continued treatment state and represented treatment discontinuation due to any cause. It was assumed that 1) the change from baseline HAQ-DI and PASI occurred instantly after initiating treatment (in the trial period) and 2) patients maintained this improvement until treatment discontinuation. After active treatment discontinuation, patients received BSC, and both the HAQ-DI and PASI scores were assumed to immediately rebound to its baseline value. HAQ-DI then progressed at a rate equivalent to the natural history progression and plateaued at its maximum value. In contrast with HAQ-DI scores, the baseline PASI scores were assumed to be constant over time.

No adverse events were considered in the economic model. The company argued that adverse events were implicitly captured to the extent that they affected the initial response and the long-term treatment discontinuation rates.

To inform health-related quality of life (HRQoL), the company used the data from the SPIRIT trials in which the European Quality of Life-5 Dimensions (EQ-5D)-5L questionnaire was administered to patients at baseline and week 12. In line with NICE's position statement on EQ-5D-5L data, the obtained data were mapped to EQ-5D-3L using an indirect mapping approach. The company used the resulting EQ-5D-3L data to establish a relationship between patients' HAQ-DI and PASI scores and HRQoL using an ordinary least squares regression model, in accordance to how HRQoL was estimated in the York model.

Drug acquisition costs for b/tsDMARDs were sourced from the online version of the Monthly Index of Medical Specialities (MIMS). The list price of 80 mg ixekizumab is £1,125. Ixekizumab is provided with a confidential simple discount patient access scheme (PAS), lowering its price to [redacted] per 80 mg. Secukinumab and apremilast are also provided with a PAS but list prices were used for these two comparators in the CS model as these PAS prices were not publicly available. Certolizumab pegol and ustekinumab are recommended by NICE with complex PAS schemes in place, which were modelled in the CS. The cost of administration was obtained from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2016 and the National Health Service (NHS) Reference Costs 2015-16. Costs for monitoring during treatment were obtained from the NHS Reference Costs. Furthermore, the company estimated the costs associated with HAQ-DI and PASI scores separately. HAQ-DI related costs were estimated using a linear regression informed by a study

with sample size of 916 rheumatoid arthritis patients in the UK, dated 2002. PASI-related costs were sourced from the York model and justification was not provided for each cost item.

The company's deterministic base-case incremental cost effectiveness ratios (ICERs) of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per quality-adjusted life year QALY gained in the b/tsDMARD-experienced population when compared with BSC. It was [redacted] when compared with ustekinumab in that population in the no and mild-to-moderate psoriasis groups [redacted] in the moderate-to-severe group. The cost effectiveness results were fairly robust to scenario- and one-way sensitivity analyses conducted by the company. The most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab. Scenario analyses indicated that assumptions with the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, alternative (i.e. the York model) utility model coefficients, an alternative (i.e. the Poole et al. 2010) algorithm for costs associated with HAQ-DI and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab being accounted for).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The cost effectiveness searches in the company submission and clarification response were reported in enough detail for the ERG to appraise them. Separate searches were conducted to identify cost effectiveness models and model input studies.

Reviewing the overall evidence, the ERG considers that the company's approach to use the revised York model as a basis for developing their model was appropriate. However, a limitation with this and the York model was that the allocation of patients to health states in the model was based on a relative measure of response (based on reductions in symptoms). This may lead to health states being composed of heterogeneous patient populations for which it is arguably difficult to assign costs and HRQoL estimates.

The economic model described in the CS is considered by the ERG to meet the NICE reference case, with the notable exceptions of a) the exclusion of comparators identified in the scope and b) a NMA (in the CS base-case) that did not consider all the relevant outcomes as identified in the scope, such as adverse events. Addressing a), the company justified the absence of secukinumab and certolizumab pegol from the b/tsDMARD-experienced patient population analysis by the unavailability of data in that population. However, it should be noted that studies on these two treatments were conducted in mixed populations, i.e. b/tsDMARD-naive and –experienced patients. Regarding b), the omission of adverse events from the NMA and economic model was considered a major limitation by the ERG, given that these differ per treatment and their inclusion would lead to potential differences in HRQoL, costs, and treatment discontinuation rates. Furthermore, the use of a limited network for the b/tsDMARD-experienced patient population, which omitted PASI 50 as an outcome, was considered by the ERG to result in potential bias in favour of treatments with a higher PsARC response (given PASI 50 response was presumably set to 0% in this case). This also resulted in the exclusion of certolizumab pegol and secukinumab as comparators in this population, i.e. deviating from the scope, which again likely favoured ixekizumab in this population. Furthermore, treatment sequences used in

the model for the b/tsDMARD-naive patient population exclude relevant treatments as, in addition to ustekinumab, certolizumab pegol and secukinumab could also be used in second line.

The ERG is concerned about the representativeness of the patient population in the SPIRIT trial programme and its impact on the relevance and validity of the NMA results for the UK context. BSC was not accurately described in the model and the ERG was unable to assess whether BSC was representative of the UK context and whether the effectiveness as well as the costs associated with BSC in the cost effectiveness model were valid.

The assumption of equal treatment discontinuation rates for all b/tsDMARD treatments was viewed as a major and influential limitation. Of further concern were the excess mortality which was considered potentially too high and the fact that the HAQ-DI reduction estimate for ixekizumab q4w responders and non-responders based on the NMA was inconsistent with the trial data. Furthermore, the ERG considers there to be large uncertainty about the resource use and cost estimates associated with HAQ-DI and PASI, with several limitations identified in both estimates.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. The company's clarification response provided sufficient details for the ERG to appraise the searches. Additional searches were carried out for conference abstracts and clinical trials. The clinical evidence is based on two multinational RCTs covering a group of patients naïve to bDMARDs and those with prior experience of bDMARDs.

The cost effectiveness model is well built and transparent. The treatment effectiveness estimates from a network of studies are a strength as is the attempt to consider treatment sequences. The company performed many relevant sensitivity- and scenario analyses to reflect uncertainty about the cost effectiveness results. The model was relatively robust to these changes, with some notable exceptions as detailed in section 1.5 of this report.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned about the overall quality of the searches for studies on clinical effectiveness as it identified numerous inconsistencies, omissions, inaccuracies and errors. This and the application of an English language restriction mean that it is possible that relevant evidence was missed.

The main trials in the submission included a small number of UK patients (approximately [redacted] across the two trials). Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. The committee will need to decide, based on the factors highlighted by the ERG in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice. Another weakness of the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope.

Cost effectiveness searches of Medline and Embase contained extensive focussed MeSH and Emtree indexing which may have adversely impacted on search strategy recall. The ERG noted several typographical errors, incorrect truncation and syntax mistakes in several of the cost effectiveness PubMed searches. Searches of the health technology assessment database (HTA) and the Health Economic Evaluations Database (HEED) contained unnecessary costs or HRQoL/Utilities search filters which were overly restrictive. Searching the NHS Economic Evaluation database would have been

beneficial. Due to these issues, it is possible that potentially relevant studies may have been missed, however the impact of this is difficult to assess without undertaking these reviews independently.

Health states in the cost effectiveness model are based on a relative measure of response (reductions in symptoms), which may lead to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. Further limitations are the exclusion of comparators identified in the scope and the omission of adverse events from the economic model. For the b/tsDMARD-experienced patient population, only a limited network was used, which omitted PASI 50 as an outcome. Moreover, the ERG considers the assumption of equal treatment discontinuation rates for all b/tsDMARD treatments as a weakness. The representativeness of the patient population in the SPIRIT trial programme, excess mortality in this population, resource use and cost estimates associated with HAQ-DI and PASI pose areas of uncertainty.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The company's deterministic base-case ICERs of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. In the b/tsDMARD-experienced population, ixekizumab (with PAS) had ICERs [redacted] per QALY gained when compared with BSC. It was [redacted] when compared with ustekinumab in no and mild-to moderate psoriasis and [redacted] in moderate-to severe psoriasis. The ERG incorporated various adjustments to the company base-case (probabilistic results for the b/tsDMARD-naïve population and deterministic results for the b/tsDMARD-experienced population). In the ERG base-case, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses). Additionally, the ERG explored different scenarios based on the ERG base-case analysis. In those analyses, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population except in the scenario in which both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In that scenario, ixekizumab had an ICER of [redacted] per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab had ICERs below [redacted] per QALY gained versus BSC in all psoriasis severity levels in all scenarios, expect when both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In this scenario, ixekizumab [redacted].

In conclusion, despite the ERG criticism and amendments to the company cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab provided ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. In this population, when compared to ustekinumab, ixekizumab [redacted] in all psoriasis severity levels. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

2. BACKGROUND

In this report the ERG provides a review of the evidence submitted by Eli Lilly in support of ixekizumab, trade name Taltz®, for the treatment of adult patients with active psoriatic arthritis (PsA) following inadequate response to previous disease-modifying anti-rheumatic drugs (DMARDs). In this section, we outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken from Chapter 1 of Document B of the company's submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying problem of this appraisal is psoriatic arthritis which is described in the CS as a '*chronic progressive, inflammatory arthropathy associated with psoriasis'*.[1]

The CS describes the burden to patients of '*pain, stiffness and swelling of joints, which can affect the whole body and, if untreated, cause permanent joint and tissue damage and ultimately disability'*.[1]

The company describes the heterogeneity of PsA and clarifies that joint and skin symptoms can range from mild to severe and do not always correlate with each other. The CS states that in around 70% of people, psoriasis precedes PsA with the onset of arthritis tending to occur from seven to 10 years after the onset of symptoms.[2] Importantly, the CS also notes that some patients present with no skin disease but have a family history of skin disease.[3]

The CS covers the main presenting symptoms and highlights the high frequency of dactylitis, enthesitis and nail psoriasis in PsA.[1] The CS states that more than half of patients have at least one comorbidity and provides a table of the incidence of PsA comorbidities reproduced from Husni 2015.[4]

The CS highlights the impact of the disease on a patient's health-related quality of life (HRQoL) including activities of daily living and notes that HRQoL is lower than the general population and compared to patients with other forms of inflammatory arthritis (based on a literature review by Lee et al.).[5] The CS cites a Canadian study based at the University of Toronto PsA Clinic between 1978 and 2004 which estimates a reduced life expectancy of approximately three years in patients with PsA compared to the general population.[6] A submission by the Psoriasis Association, a British patient organisation, provides examples of the challenges of living and working with PsA.[7]

The CS highlights that PsA affects men and women equally and that the age of onset tends to be between 30 and 50 years of age. Prevalence is cited to be 0.19% of the adult population in the UK based on a large cross-sectional study.[8] In a psoriasis population, the CS notes that prevalence of PsA will be higher (between one and two of every five people with psoriasis) particularly among those with severe psoriasis.[8]

ERG comment: The ERG checked the references cited by the company to support the statements made above and considered the company to have given overall an appropriate description of the underlying health problem relevant to this appraisal. However, the ERG would like to add the following:

- The prevalence of PsA is based on a UK study which is most relevant to the submission (variability between countries has been observed).[8] However even here, the prevalence of PsA should be treated with some caution as PsA may be underdiagnosed.[2, 9] The diagnosis of PsA in the UK study cited was based on a medical records diagnosis code recorded by general practitioners.
- Currently, there are no definitive guidelines for diagnosing psoriatic arthritis. Traditionally, the Moll and Wright (1973) criteria have been used.[10] The criteria are:
  - an inflammatory arthritis,
  - the presence of psoriasis,

- and a blood test negative for rheumatoid factor.

Although this criteria set is still used, it does not take account of the fact that psoriatic arthritis can occur without there being current psoriasis on the skin.

More recently the CASPAR criteria have been developed.[11] These consist of the presence of an inflammatory condition in a joint, the spine, or entheses plus at least three points from the following: Current psoriasis (two points); a personal or family history of psoriasis (in the absence of current psoriasis, one point); dactylitis (one point); nail dystrophy (one point); negative rheumatoid factor (one point); radiographic evidence of new bone formation (one point).[12]

- The impact of symptoms and the reduced quality of life in PsA is appropriately described. However, it should also be made clear that PsA can be variable and unpredictable including flares and remissions with possible associated variation in quality of life.[5]
- Not all of the studies cited in the CS found a reduced life expectancy with PsA. The estimate of a loss of three years was based on a Canadian study at the University of Toronto PsA Clinic between 1978 and 2004.[6] This study may not reflect a UK setting and the most up to date management of patients with PsA.

2.2 Critique of company's overview of current service provision

Figure 2.1 shows the current treatment pathway for PsA as described by the company in the submission.[1] The figure also shows the proposed place of ixekizumab in the treatment pathway with ixekizumab being listed as a first-line biological DMARD. Although ixekizumab is licenced for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more non-biological DMARDs, the company aligns ixekizumab with guidance by the National Institute for Health and Care Excellence (NICE) that states that biological DMARDs should be given after failure of two or more conventional non-biological DMARDs. At this point in the pathway, ixekizumab is a competitor to secukinumab, also a IL-17 inhibitor, to the PDE4 drug apremilast and to the TNF-alpha inhibitor drugs, all of which have existing NICE guidance.[13-16]

Ixekizumab is also positioned as a second-line biological DMARD for patients who have not responded adequately or are intolerant to TNF-alpha inhibitor drugs. Ustekinumab, certolizumab and secukinumab are also available for these patients. Ixekizumab is further proposed for those in whom TNF-alpha inhibitor drugs are contraindicated (where ustekinumab and secukinumab are available).[1]

The company states that '*currently available systemic therapies (...) are associated with a number of limitations, such as lack of efficacy, inability to sustain efficacy, side-effects or poor tolerability, and inconvenience or lifestyle compromise. These limitations have led to widespread dissatisfaction with treatments*'.[1] To support these statements, the company cites a multinational survey of 391 dermatologists and 390 rheumatologists in which 30% of their PsA patients are described as using biological DMARDs.[17] The CS also cite a survey of 3,426 patients, 14% of whom are receiving biologic therapy, and 8% a combination of oral and biologic therapy.[18] In this survey, adalimumab and etanercept were the injectable biologics most commonly reported. The company stated that according to this survey 90% of patients with PsA felt there was a need for better therapies.

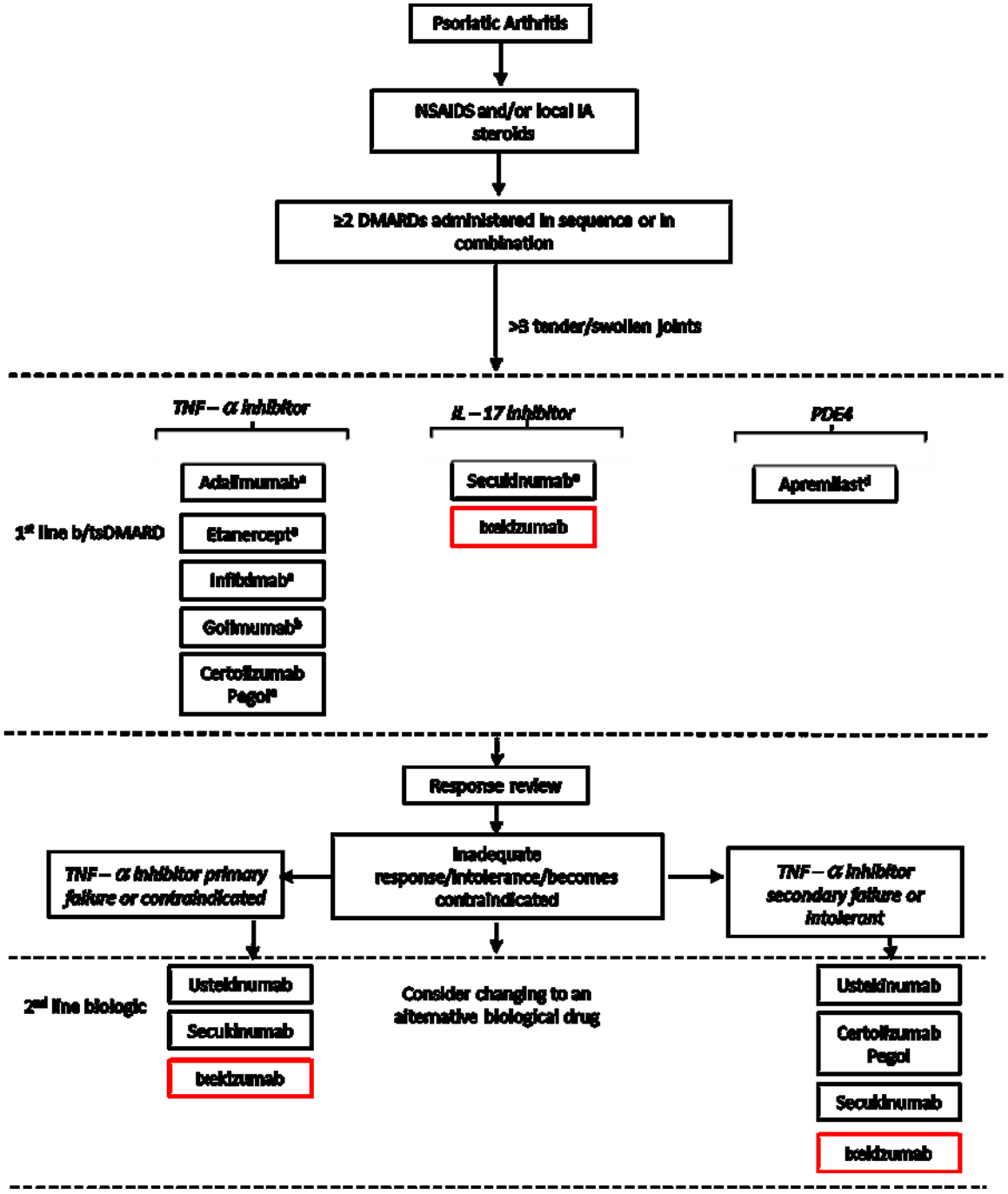
The CS outlines the limitations of the existing biologic therapies including anti-TNF-alpha therapies. A number of studies are cited to illustrate that, although effectiveness has been demonstrated in comparison to placebo, a proportion of patients do not respond adequately and extra-articular symptoms may be inadequately addressed.[1]

The CS states that *'switching to another anti-TNF is a well-established practice in the NHS'*.[1] The company also states that treatment may be less successful with these agents at second line, i.e. *'less than 50% of the patients who achieved an ACR 20, 50 and 70 response after treatment with a TNF-alpha inhibitor in first-line, achieved such a response after receiving treatment with a second-line TNF-alpha inhibitor.*[19]'The average persistence on anti-TNF-alpha therapies in relation to the chronic nature of PsA is highlighted. '*Average survival/persistence of patients with PsA on anti-TNFα therapy is in the range of 2 to 4 years for the first agent and shorter for subsequent anti-TNFα therapies'* based on a literature review.[20]

The company state the unmet need for ixekizumab as providing a new mechanism of action to obtain and sustain efficacy at a similar level to that of the anti-TNF-alpha therapies in both patients naïve to biologic DMARDs as well as those experienced with acceptable safety and minimal disturbance to lifestyle. The CS further state that '*treatments should be able to treat the core joint symptoms of PsA as well as the skin symptoms (psoriasis and nail psoriasis) and the extra-articular PsA symptoms (such as enthesitis and dactilytis)'*.[1]

The CS states that *'ixekizumab is the first monoclonal antibody to block both active forms of IL-17A (IL-17A is expressed in both homodimer and heterodimer forms) with high binding affinity.*[REF CS 64] *It is the second anti IL-17 (and third biologic therapy) to offer an alternative mechanism of action to TNF-α inhibitors'*.[1]

Figure 2.1: Proposed position of ixekizumab within the treatment pathway for patients with PsA based on current NICE recommendations



Source: Section 1.3 of the CS[1]

a = NICE TA199[16]; b = NICE TA220[14]; c = NICE TA340[21]; d = NICE TA433[15]; e = NICE TA445[13]

bDMARD = biologic disease-modifying anti-rheumatic drug; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; IA = intra-articular; IL = interleukin; NICE = National Institute for Health and Care Excellence; NSAID = non-steroidal anti-inflammatory drug; PDE = phosphodiesterase; PsA = psoriatic arthritis; tsDMARD = targeted synthetic disease-modifying anti-rheumatic drugs; TA = technology appraisal; TNF = tumour necrosis actor

ERG comment:

- Ixekizumab represents an additional option for PsA alongside the existing biologic treatments after two or more non-biological approaches have been tried. The need for additional options was highlighted by The British Society for Rheumatology who stated in their submission that '*it is most useful to patients and physicians to have access to more than one agent within the same class as well as different agents targeting different classes'*.[22] They also stated that *'there are now an increasing number of patients who have quite simply run out of options and are left with unremitting symptoms, a very poor quality of life and disease progression'*.[22] This was echoed by the Psoriasis Association who stated that *'as psoriatic arthritis often occurs in young adults, treatments need to be efficacious over a lifetime. It is well documented that treatments can lose efficacy, and so wide availability is vital. Some of the more traditional systemic treatments are limited in their use for younger people wishing to start a family which in turn restricts their treatment options'*.[7]
- In order to be added to the options, the comparable or superior performance of ixekizumab needs to be determined through comparison with all of the relevant biological agents.
- Based on the evidence in the submission and critiqued in this report, the committee will need to consider whether ixekizumab should be used in preference to any of the other agents at first or second line biological treatment.
- Any potential advantage of being the *'first monoclonal antibody to block both active forms of IL-17A'*[1] needs to be proven through a comparison of the two agents, ixekizumab and secukinumab. The committee will need to clarify whether the evidence is sufficient to recommend ixekizumab in place of secukinumab and/or for those who have failed on secukinumab.
- NICE guidance includes stopping rules for the biologic drugs in this pathway, e.g. by stating that etanercept, adalimumab and infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks unless their Psoriasis Area and Severity Index (PASI) 75 response merits continuing treatment.[16] Similar criteria are in place for the other agents although at differing time points (e.g. ustekinumab for example is assessed at 24 weeks). An appropriate stopping rule will be needed for ixekizumab.
- Any comparisons of effectiveness between agents in this pathway should take account of the full range of symptoms that can be experienced in PsA including the core joint symptoms, the skin symptoms and the extra-articular symptoms such as enthesitis and dactilytis. Patient organisations have also highlighted the problem of fatigue.[23]

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3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active psoriatic arthritis whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug therapy.	Adults with active psoriatic arthritis whose disease has not responded adequately to previous DMARD therapy, or have not been able to tolerate or have a contraindication to previous DMARD therapy. Subgroups that should be considered separately are: • Patients whose disease has not responded adequately to at least two previous cDMARD therapies either alone or in combination • Patients whose disease has not responded adequately to one or more bMARD • Patients with concomitant moderate to severe psoriasis for whom the anticipated dosing schedule for ixekizumab would include a q2w induction dosing period and q4w maintenance dosing.	NA
Intervention	Ixekizumab (Taltz®)	Ixekizumab 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) every 4 weeks for patients without concomitant moderate-to-severe psoriasis and Ixekizumab 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,	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks for patients with concomitant moderate-to-severe psoriasis.	
Comparator(s)	For people who have only received one prior non-biological DMARD: • Non-biological DMARDs For people whose disease has not responded adequately to at least two non-biological DMARDs: • bDMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol [subject to ongoing NICE appraisal], secukinumab [subject to ongoing NICE appraisal]) • Apremilast For people whose disease has not responded adequately to non-biological and biological DMARDs, or biological DMARDs are contraindicated: • Ustekinumab • Certolizumab pegol and secukinumab (subject to ongoing NICE appraisal) • Best supportive care.	For people who have failed on two or more prior standard DMARDs (biologic naïve): • TNF-alpha inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) • Secukinumab • Apremilast For people whose disease has not responded adequately to non-biological and biological DMARDs, or bDMARDs are contraindicated: • Ustekinumab • Certolizumab pegol • Secukinumab • Best supportive care.	The positioning of biologic therapy in patients with only one prior standard DMARD is not in line with current NICE pathways or BSR guidance (except in the case of adverse prognostic factors). As noted in the Final Appraisal Determination document for the multiple technology appraisal of secukinumab and certolizumab pegol, the committee questioned whether biologic therapy is established clinical practice in the NHS after failure on only one prior DMARD and which specific group of patients would use a biologic at this stage in the pathway.[13]
Outcomes	The outcome measures to be considered include: • Disease activity • Functional capacity • Disease progression	This submission includes a range of outcome measures to assess the clinical benefit of ixekizumab, including: • Disease activity (ACR 20/ 50/ 70, PsARC, MDA) • Functional capacity (HAQ-DI)	Skin involvement (e.g. PASI response) is a relevant outcome to include in the scope. The following outcomes will be modelled in the economic analysis: • Disease activity, assessed by the PsARC

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Periarticular disease (for example enthesitis, dactylitis) • Mortality • Adverse effects of treatment • Health-related quality of life	• Effect on concomitant skin condition (Psoriasis Area and Severity Index (PASI)) – including PASI 75/90/100 • Other complications of psoriatic arthritis including LEI- enthesitis, NAPSI- nail psoriasis (modified version), LDI- dactylitis, structural progression (mTSS) • Health related quality of life (EQ-5D) • Adverse events will be reported for ixekizumab and comparators based on the results from the clinical studies	• Functional capacity, measured by the HAQ-DI score • Health-related quality of life, measured by EQ-5D and mapped using PASI and HAQ-DI scores Data on the impact of ixekizumab on periarticular disease and disease progression, and the adverse effects of treatment are presented in the submission but not included in the economic analysis due to insufficient comparative data. No biologic treatment for psoriatic arthritis has demonstrated an effect on mortality outcomes in the context of a clinical trial, therefore mortality in the model has been modelled as the application of excess mortality risk associated with PsA to the mortality risk in the general population.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost effectiveness results are expressed as incremental cost per quality-adjusted life year, with a lifetime model horizon, considering costs from an NHS and PSS perspective. The cost of biosimilar etanercept and biosimilar infliximab are taken into consideration in the base-case analysis. Results are presented using the list price for treatments in the base-case due to the confidentiality of the patient access schemes (PAS) for apremilast and secukinumab. The PAS for certolizumab pegol is taken into account.	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. For the comparators the availability and cost of biosimilars should be taken into consideration.		
Subgroups to be considered	If evidence allows the following subgroups will be considered: • the reason for treatment failure (for example due to lack of efficacy, intolerance or adverse events) • Presence or severity of concomitant psoriasis (no psoriasis, mild to moderate psoriasis, moderate to severe psoriasis)	The subgroups of interest in the economic analysis are: • Comorbid psoriasis severity (no psoriasis, mild to moderate psoriasis, moderate to severe psoriasis) • Previous bDMARD experience (bDMARD-naïve, bDMARD-experienced).	
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No equity or equality issues identified.	As per the reference case

Source: Based on Table 1 of the CS[1]

ACR = American College of Rheumatology; ACR 20/ 50/ 70 = at least 20%/ 50%/ 70% improvement in both tender and swollen joint counts; bDMARD = biological disease-modifying anti-rheumatic drug; BSR = British Society for Rheumatology; cDMARD = conventional disease-modifying anti-rheumatic drug; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = European Quality of Life-5 Dimensions; HAQ-DI = Health Assessment Questionnaire-Disability Index; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; MDA = minimal disease activity; mg = milligram; mTSS = modified Total Sharp Score; NA = not applicable; NAPSI = Nail Psoriasis Severity Index; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PAS = Patient Access Scheme; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks

3.1 Population

The population defined in the scope is adults with active psoriatic arthritis whose disease has not responded adequately to previous DMARD drug therapy or for whom DMARDs are not tolerated or contraindicated.[24] The population in the CS is in line with the scope. However, it is important to note that under NICE guidance bDMARDs are given after failure of two or more cDMARDs (see Figure 2.1). While the company aligns ixekizumab with NICE guidance, not all patients meet this criterion in the main trials of the submission (SPIRIT-P1 and P2). In section 2.7 of the CS, the company provides an integrated analysis of [redacted] patients across the two trials meeting NICE criteria. Efficacy of ixekizumab compared to placebo is [redacted] for the outcome of ACR 20.[1] Network meta-analyses (NMA) were performed separately for the bDMARD-naïve and bDMARD-experienced populations as the SPIRIT-P1 and SPIRIT-P2 trials were in different populations based on previous treatment with biologics.

The two main trials in the submission (SPIRIT-P1 and P2) were multinational trials. Across the two trials, [redacted] patients were recruited to [redacted] centres in the UK which represents approximately [redacted] of patients.[25] Comments submitted by the British Society for Rheumatology stated that the trials reflected current UK clinical practice.[22] The company was invited to further address applicability to the UK and their response along with ERG comments on applicability is detailed in sections 4.2.1 and 4.2.2 of this report. The committee will need to decide if it agrees with the company that the SPIRIT trials are sufficiently reflective of a UK patient population.

3.2 Intervention

The intervention (ixekizumab alone or in combination with conventional DMARD) is in line with the scope. In January 2018, it was approved in the EU for the treatment of patients with PsA: '*Ixekizumab, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic (DMARD) therapies'*.[1] Ixekizumab is also licenced and approved by NICE for the treatment of moderate to severe psoriasis (TA442).[24]

Ixekizumab is a biological DMARD, described as '*a recombinant humanised IgG4 monoclonal antibody (mAb) designed and engineered to selectively inhibit interleukin-17A (IL-17A), a pro-inflammatory cytokine'*.[1]However, it is not the first IL-17 agent available for this indication. Secukinumab is licenced and has associated NICE guidance.[26]

Ixekizumab is administered by subcutaneous injection and the dose is dependent on concomitant psoriasis severity. PsA patients without co-morbidity and moderate to severe psoriasis receive an initial dose of 160 mg by subcutaneous injection at week 0 followed by 80 mg every four weeks. Those with concomitant moderate to severe psoriasis receive the initial dose as above then 80 mg at weeks 2, 4, 6, 8, 10 and 12 then maintenance of 80 mg every four weeks. The company states that no additional tests or investigations are required.[1]

In SPIRIT-P1and P2, concomitant medications were permitted alongside ixekizumab. Any implications of this will be discussed in section 4 of this report.

3.3 Comparators

Ixekizumab is an addition to the range of existing DMARDs for PsA. The relevant comparators are presented in Figure 2.1 of this report. The NICE scope indicated the following comparators:

- For people whose disease has not responded adequately to one non-biological disease modifying anti-rheumatic drug
  - Non-biological DMARDs
- For people whose disease has not responded adequately to at least two non-biological DMARDs:
  - Biological DMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, secukinumab)
  - Apremilast
- For people whose disease has not responded adequately to non-biological DMARDs and one or more TNF-alpha inhibitors:
  - Ustekinumab
  - Certolizumab pegol
  - Secukinumab
  - Best supportive care
- For people in whom TNF-alpha inhibitors are contraindicated:
  - Ustekinumab
  - Secukinumab
  - Best supportive care

The company does not present a comparison of ixekizumab with non-biological drugs for people who have not responded to one or more non-biological drugs as this does not reflect the NICE pathway and proposed positioning of ixekizumab. This appears appropriate to the ERG.

All the relevant comparators have been addressed in the submission. However, it is important to realise that the main two trials in the CS compare ixekizumab to placebo rather than to one or more of the active comparators in the scope. Although SPIRIT-P1 also included an active control (adalimumab), the study was not designed to test equivalence or non-inferiority of ixekizumab versus adalimumab.[1] Therefore, there is no direct evidence presented comparing ixekizumab with the comparators in the scope. The evidence in relation to the other DMARDs mentioned in the scope comes from network meta-analyses. This is less reliable than direct comparisons between ixekizumab and other comparators obtained from a direct comparison within one or more RCTs.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- Disease activity
- Functional capacity
- Disease progression
- Periarticular disease (for example enthesitis, tendonitis, dactylitis)
- Mortality
- Adverse effects of treatment
- Health-related quality of life

These outcomes are evaluated in the trials in the submission with the exception of mortality. The company states that *'no biologic treatment for psoriatic arthritis has demonstrated an effect on mortality outcomes in the context of a clinical trial, therefore mortality in the model has been modelled as the application of excess mortality risk associated with PsA to the mortality risk in the general*

population'.[1] The ERG recognises that short-term trials are unlikely to demonstrate any effect of treatment on mortality, should one exist. Having said that, modelling of excess mortality associated with PsA appears reasonable. However the ERG had concerns on the source used to derive the excess mortality which was based on a Canadian study at the University of Toronto PsA Clinic between 1978 and 2004.[6] This study may not reflect a UK setting and the most up to date management of patients with PsA. The ERG considers that the modelled excess mortality was likely high, which would likely induce bias in favour of treatments with high response rates.

The company provided data on periarticular disease, disease progression and adverse events. However, these were not included in the economic analysis due to insufficient comparative data which leads to potential bias in the estimation of HRQoL and cost associated with all treatments.

In relation to disease activity, submissions from Rheumatology Pharmacists UK (RPUK) and the British Society for Rheumatology (BSR) emphasise that PsARC is a more relevant outcome to assess response in clinical practice than ACR measures.[22, 27] PsARC is assessed in the trials in the CS and is used to model disease activity in the economic model.

It should be noted that, as the two main trials in the CS compared ixekizumab to placebo, there is no direct evidence on these effectiveness outcomes of ixekizumab in relation to the other DMARDs. The evidence for comparisons of ixekizumab to other treatments for treatment-emergent adverse events, serious adverse events and discontinuation due to an adverse event was obtained from network meta-analysis provided in the response for request for clarification.[25]

Although not explicitly stated in the NICE scope, the company stated that skin involvement, e.g. PASI response, is a relevant outcome to include in the CS. The ERG believes this to be appropriate, particularly as NICE guidance for other DMARDs allows patients whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at the relevant timepoint to continue treatment if their PASI response merits this.[16]

In summary, relevant outcomes were measured in the trials in the CS which compared ixekizumab with placebo, but comparisons with other treatments are based on indirect treatment comparisons.

3.5 Other relevant factors

The company stated that they '*were unaware of any equality issues that could impact the appraisal of ixekizumab*'.[1]

A confidential patient access scheme (PAS) is provided for ixekizumab. The PAS is a [redacted] providing 80 mg solution for injection in prefilled pen x 2 at [redacted] and an 80 mg solution for injection in prefilled syringe at [redacted].

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify randomised controlled trial (RCT) evidence of ixekizumab and potential relevant comparator treatments for psoriatic arthritis.

4.1.1 Searches

Initial searches were reported for Medline, Medline In-process & Other Non-Indexed Citations, Medline Daily Update, PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). These were undertaken in August 2016 (1990-2016). Update searches were reported for May 2017 (2016-2017). The database host was not reported for the initial searches, Ovid was reported as the host for the update searches. The date the searches were conducted was provided.

Medline and Embase searches included unreferenced randomised controlled trials study design filters. The EBM Reviews CENTRAL search did not include an RCT filter. Medline, Embase and CENTRAL searches were all restricted to English language publications only. Searches of the following trials registers were reported in the appendices of the company submission (section 1.2.1) for 01/01/2016-09/05/2017: clnicaltrials.gov and World Health Organisation (WHO) ICTRP (International Clinical Trials Registry Platform).

Additional searches of the following conferences abstracts were reported: European League Against Rheumatism (EULAR, 2017 only), American College of Rheumatology/Association for Rheumatology Health Professionals (ACR/ARHP, 2016 only) and Asia Pacific Rheumatology Congress (APLAR, not included in the update). However, no details of the conference proceedings search terms, date of searches or results were provided.

The company submission noted that the initial review and update searches were conducted by different third-party vendors.[1] In Appendix D, the company acknowledgment significant mistakes in the Embase, Medline and CENTRAL searches (1990-2016).[28] The mistakes were corrected in the update searches (2016-2017). Unfortunately, the corrected searches were not repeated to cover the date span of the initial searches. The company reported checking whether the flawed initial review searches had missed studies.[28] The cross-checking process involved checking whether relevant included studies from previous systematic reviews (SRs) and network meta-analyses (NMAs) were picked up. The company was satisfied that *'it was deemed to be likely that the initial review captured all relevant studies over the period 1990-2016'*.[1, 28] The process for identifying candidate SRs and NMAs to check the initial review against was not reported in the CS nor appendices. In the clarification response,[25] the company reported selecting SRs and NMAs from the updated RCT search as well as from TA445;[13] independent searches specifically for SRs were not conducted by the company.

ERG comment:

- The main clinical effectiveness searches (1990-2016) contained consequential errors and flaws which will have impacted on retrieval of RCTs. Although the mistakes were corrected in the update searches (2016-2017), corrected searches were not re-run. Relevant studies could have been missed due to these mistakes.
- The company's approach to checking whether studies were missed or not was sub-optimal. Only RCT searches were conducted for the clinical effectiveness review. The company reported in the submission[28] and the clarification response[25] that earlier SRs and NMAs were used to cross-check for missed studies and as a method of validation for the review. As no SR searches were conducted and no SR databases were searched, their approach relied on relevant SRs and NMAs appearing in

- a search limited to randomised controlled trials. Therefore, the ERG did not consider this a robust approach for cross-checking or validation. The ERG believes a more appropriate response to address substantial errors would have been to repeat the corrected searches to ensure the submission was based on a robust systematic review search.
- The ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice.

4.1.2 Inclusion criteria

The eligibility criteria are presented in Table 4.1. All abstracts identified by the searches were reviewed independently by two reviewers and those considered relevant based on the eligibility criteria were then screened for full-text inclusion independently by the same two reviewers. Discrepancies between reviewers at each stage were resolved through discussion or with assistance from a third reviewer.

Table 4.1: Eligibility criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥ 18 years) with active psoriatic arthritis*	Studies not reporting data on adult patients with active PsA, including: • Studies reporting on psoriasis patients only • Studies reporting pooled data for PsA and other conditions • Studies not conducted in paediatric patients (< 18 years)
Interventions	Ixekizumab Biologics: •Adalimumab [Humira®] •Etanercept [Enbrel®] •Golimumab [Simponi®] •Infliximab [Remicade®] •Certolizumab pegol [Cimzia®] •Ustekinumab [Stelara®] •Secukinumab [Cosentyx®] Biosimilars: •Infliximab, etanercept and other biosimilars of the above listed branded biologics Target synthetic DMARDs: •Apremilast [Otezla®] Emerging therapies: •Brodalumab •Tildrakizumab •Abatacept •Tofacitinib •Guselkumab •Clazakizumab •Tocilizumab	Studies not reporting on any of the interventions specified in the inclusion criteria.

Criteria	Inclusion criteria	Exclusion criteria
Comparators	• Placebo (placebo-controlled studies) or best supportive care • Any of the above interventions of interest • Non-biologic approved treatments or cDMARDs as best supportive care or comparators of interventions of interest, including but not limited to: ciclosporin/cyclosporine, methotrexate, leflunomide, and sulfasalazine	Studies where the comparator is none of those specified in the inclusion criteria. Note: Single-arm (i.e. non-controlled) studies will be excluded under the 'Study design' criteria, rather than the 'Comparator' criteria.
Outcomes	Clinical and patient-reported outcomes including disease severity, disease response, and/or disability scores: • American College of Rheumatology 20/50/70 index (ACR20, ACR50, ACR70) • Psoriasis Area and Severity Index (PASI [absolute, % change], PASI 50/75/90/100) • Health Assessment Questionnaire-Disability Index (HAQ-DI) (absolute or mean change from baseline); proportion of patients achieving a change of >0.22 or 0.35) • Psoriatic Arthritis Response Criteria (PsARC) • Enthesitis/dactylitis (e.g. as measured by the Maastricht Ankylosing Spondylitis Enthesitis Score [MASES], or SPARCC or Leeds Enthesitis Index [LEI], Leeds Dactylitis Index-Basic [LDI-B]) • Structural joint outcomes (e.g. mTSS) • Minimal disease activity (Coates criteria for MDA) Drug safety measures: • Adverse events (AE) • Serious and severe adverse events (SAE) • Discontinuation (due to lack of efficacy or due to adverse events)	The study does not contain any of the outcomes of interest specified in the inclusion criteria.
Study designs	• Randomised clinical trials (RCTs) • Cross-over design RCTs[**] • Systematic literature reviews[***]	All other study types, for example, NMAs, non-systematic reviews, retrospective, non-randomised or non-controlled studies, publications that are commentary, editorial, errata, letter, note, or guideline.

Criteria	Inclusion criteria	Exclusion criteria
Language	English language Limit to publications from 1990 to present	• Publication in a language other than English • Publication prior to August 2016 Note: conference abstracts that report same data as a subsequent full-text publication will be marked as duplicates and also excluded.

Source: Based on Table 9 of the CS[1]
Footnote: * The following criteria were not included in the PICOS criteria as they may not be reported on by all studies of interest, and therefore were not used to exclude studies: definition of active PsA as patients having at least 3 tender and 3 swollen joints or at least 5 tender and 5 swollen joints; or as fulfilment of CASPAR criteria classification. ** The expectation was to use information prior to placebo cross-over phase. *** Previous SLRs were identified to validate this SLR, not as a source of data.
ACR = American College of Rheumatology; ACR 20 = at least 20% improvement in both tender and swollen joint counts; ACR 50 = at least 50% improvement in both tender and swollen joint counts; ACR 70 = at least 70% improvement in both tender and swollen joint counts; AE = adverse event; cDMARD = conventional disease-modifying anti-rheumatic drug; CS = company submission; DMARD = Disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; LDI-B = Leeds Dactylitis Index-Basic; LEI = Leeds Enthesitis Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MDA = Minimum Disease Activity; mTSS = modified Total Sharp Score; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; PsA = psoriatic arthritis; PsARC = Psoriasis Area and Severity Index; RCT = randomised controlled trial; SAE = serious adverse event; SLR = systematic literature review; SPARCC = Spondyloarthritis Research Consortium of Canada Enthesitis Index

4.1.3 Critique of data extraction

Data were extracted by two reviewers independently following methods recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[29]

ERG comment: This approach follows recommendations by the Cochrane Handbook.[29]

4.1.4 Quality assessment

The risk of bias of additional studies included in the NMA was assessed using the risk of bias tool from the Cochrane Handbook for the Systematic Reviews of Interventions.[28, 29] Details of how many reviewers performed the assessment were not reported.

ERG comment: The risk of bias was assessed using an established tool. However, it is unclear how many reviewers were involved in the assessment of risk of bias.

4.1.5 Evidence synthesis

A meta-analysis of SPIRIT-P1 and SPIRIT-P2 was not performed as it was not considered appropriate to pool them due to major differences in the patient populations. SPIRIT-P1 was performed in biologic-naïve patients whereas SPIRIT-P2 was performed in biologic-experienced patients. *'As prior bDMARD exposure is a treatment effect modifier, a meta-analysis of the two trials would not have been appropriate'*.[1]

Separate NMA were performed for the biologic-naïve and biologic-experienced populations, further details are provided in section 4.3.

ERG comment: The ERG agrees that is would not have been appropriate to perform a meta-analysis of SPIRIT-P1 and SPIRIT-P2 due to the differences in population. However, it should be noted again that there is no direct evidence of ixekizumab in relation to the other DMARDs, i.e. that all results come from less robust network meta-analyses, as discussed in section 4.3.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Overview of the direct evidence in the submission

The evidence base for the clinical efficacy and safety of ixekizumab in the treatment of psoriatic arthritis following inadequate response to disease modifying ant-rheumatic drugs (DMARDs) consists of two randomised controlled trials (RCTs), as identified by a systematic literature review (SLR), discussed in section 4.1.1 of the ERG report: SPIRIT-P1 and SPIRIT-P2.[1]

The SPIRIT studies are phase III, multicentre, multinational randomised, double-blind, placebo-controlled, parallel group, adult outpatient trials comparing the efficacy and safety of ixekizumab to placebo in two sub-groups of patients: 1) biologic disease-modifying anti-rheumatic drug (bDMARD)-naïve patients (I1F-MC-RHAP, SPIRIT-P1) and 2) tumour necrosis factor (TNF) inhibitor-experienced patients (I1F-MC-RHBE, SPIRIT-P2). In addition, SPIRIT-P1 also included an active control arm (adalimumab). The main methodological features of the SPIRIT trials are summarised in Table 4.2 below.

No direct evidence of ixekizumab in relation to any of the comparators in the scope was presented.

Table 4.2: Overview of RCTs of ixekizumab in the submission

Trial name	SPIRIT-P1 (RHAP)	SPIRIT-P2 (RHBE)
Population	417 adult patients (≥18 years) with active PsA who were bDMARD-naïve	363 adult patients (≥ 18 years) with active PsA who were bDMARD-experienced
Intervention	Ixekizumab 80 mg q2w (n=103) Ixekizumab 80 mg q4w (n=107)	Ixekizumab 80 mg q2w (n=123) Ixekizumab 80 mg q4w (n=122)
Comparator	Placebo (n=106) Adalimumab 40 mg q2w (n=101, not an active comparator)	Placebo (n=118)
Outcomes	Primary outcome: ACR 20 at week 24 Other reported outcomes from the decision problem: • Disease activity (ACR 50/70, PsARC*, MDA) • Functional capacity (HAQ-DI*) • Effect on concomitant skin condition (PASI 75/90/100*) • Other complications of psoriatic arthritis (LEI-enthesitis, NAPSI-nail psoriasis [modified version], LDI-B dactylitis) • Health-related quality of life (EQ-5D*) • Adverse events • Mortality	
	Structural progression (mTSS)	
Trial design	Randomised, double-blind, placebo-controlled, active-controlled, parallel-group study.	Randomised, double-blind, placebo-controlled, parallel-group study.

Trial name	SPIRIT-P1 (RHAP)	SPIRIT-P2 (RHBE)
Duration of trial and trial phases	Double-Blind Treatment Period (week 0-24 – primary endpoint assessment)	
	• Extension Period (week 24-52) • Long-term Extension Period (week 52-156)	• Extension Period (week 24-156)
	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): 3 years	
Settings and locations where the data were collected	114 study sites in 15 countries: Belgium, Bulgaria, Canada, Czech Republic, Estonia, Japan, Spain, France, Great Britain, Mexico, Netherlands, Poland, Russia, Ukraine, United States	109 study sites in 10 countries: Australia, Czech Republic, France, Germany, Italy, Poland, Spain, Taiwan, United Kingdom, and United States

Source: Tables 5 and 8 of the CS[1]
Footnote: * included in economic model
ACR = American College of Rheumatology; ACR 20 = at least 20% improvement in both tender and swollen joint counts; ACR 50 = at least 50% improvement in both tender and swollen joint counts; ACR 70 = at least 70% improvement in both tender and swollen joint counts; bDMARD = biologic disease-modifying anti-rheumatic drugs; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ETV = early termination visit; HAQ-DI = Health Assessment Questionnaire-Disability Index; LDI-B = Leeds Dactylitis Index-Basic; LEI = Leeds Enthesitis Index; MDA = Minimum Disease Activity; mg = milligram; mTSS = modified Total Sharp Score; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; PsA = psoriatic arthritis; PsARC = Psoriasis Area and Severity Index; q2w = once every two weeks; q4w = once every four weeks

Although both trials last up to three years the double-blind period lasts for 24 weeks only. At week 16, patients were classified as responders or non-responders. Responders were those patients who achieved a ≥20% improvement in either tender joint count (TJC) and/or in swollen joint count (SJC) from baseline. All inadequate responders were administered rescue therapy (patient's background therapy) at week 16 which was maintained for the remainder of the treatment period. Patients receiving ixekizumab before week 16 were given rescue therapy while continuing with their same ixekizumab dose regimen. Those who were receiving adalimumab or placebo were re-randomised to receive either ixekizumab 80 mg q2w or q4w (following an eight week wash out period using placebo from weeks 16 to 24 for patients taking adalimumab). At week 24, any remaining patients on placebo or adalimumab were re-randomised to ixekizumab. Further description of the trial design is given in the CS.[1]

Patients receiving cDMARDs at the beginning of the studies were allowed to continue during the double-blind treatment period. However, alteration of the cDMARD dose and/or introduction of a new cDMARD was strongly discouraged unless for safety or used as rescue therapy for inadequate responders at week 16. The investigator could lower or stop the cDMARD if adverse effects could be attributed to it.[1]

ERG comment:

- The evidence is based on two randomised controlled trials which represent the highest level of evidence. However, both trials compare ixekizumab to placebo. No direct evidence is available on ixekizumab in relation to the other comparators in the scope.
- The evidence base includes both those with experience of bDMARDs and those without.
- Outcomes relevant to the scope are presented in the trials.

- The double-blind period is 24 weeks so long-term effectiveness results cannot be determined. The extension periods do, however, provide information on long-term safety.
- At week 16, patients were permitted rescue therapy in case of inadequate response so results up to 16 weeks are more reliable for the comparison between ixekizumab and placebo.
- Both trials were multinational but did include centres in the UK. Across the two trials, [redacted] patients were recruited by [redacted] centres in the UK.[25] This represents approximately [redacted] of patients. Despite the BSR submission[22] stating that the trials reflected current UK clinical practice, this aspect is drawn to the attention of the committee.

4.2.2 Participants in the SPIRIT trials

In both SPIRIT trials, in order to be included patients needed to have an established diagnosis of PsA (of at least six months and meeting the Classification Criteria for Psoriatic Arthritis). They needed to have active PsA defined as at least three of 68 tender and three of 66 swollen joints. Both trials specified that patients had to have active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis. In SPIRIT-P1 and SPIRIT-P2 the main exclusion criteria were related to a history of malignant disease or recent history of infections.

Spirit-P1 required patients to have at least one disease-related joint erosion or a c-reactive protein (CRP) > 6 mg/l (approximately 90% had joint erosions).[1] Any history of biologic treatment for plaque psoriasis or PsA resulted in exclusion from the trial.[1] In SPIRIT P1, 15% of participants who entered the study were cDMARD naïve while 85% had received at least one cDMARD.[25]

Spirit P-2 required patients to have been previously treated with a TNF alpha inhibitor and to have had an inadequate response to one or two TNF alpha inhibitors or to be intolerant to them. In Spirit-P2 patients needed to have been previously treated with one or more cDMARDs (cf. Table 6 of the CS[1]).

Table 9 of the CS showing patient demographics had some errors which were brought to the company's attention and corrections were supplied in response to clarification.[25] The amended table is reproduced in Table 4.3.

Table 4.3: Participant demographics in the SPIRIT trial

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	Placebo	ADA40 q2w	IXE80 q4w	IXE80 q2w	Total	Placebo	IXE80 q4w	IXE80 q2w	Total
	n=106	n=101	n=107	n=103	n=417	n=118	n=122	n=123	n=363
Patient demographics									
Age, mean years (SD)	50.6 (12.3)	48.6 (12.4)	49.1 (10.1)	49.8 (12.6)	49.5 (11.9)	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)	51.9 (12.0)
Male, n (%)	48 (45.3)	51 (50.5)	45 (42.1)	48 (46.6)	192 (46.0)	56 (47.5)	63 (51.6)	50 (40.7)	169 (46.6)
Race, n (%)									
White	99 (93.4)	95 (94.1)	102 (95.3)	96 (93.2)	392 (94.0)	108 (91.5)	111 (91.0)	113 (91.9)	332 (91.5)**
Asian	5 (4.7)	3 (3.0)	2 (1.9)	5 (4.9)	15 (3.6)	7 (5.9)	7 (5.7)	7 (5.7)	21 (5.8)**
Other	2 (1.9)*	3 (3.0)*	3 (2.8)*	2 (1.9)*	10 (2.6)*	3 (2.5)	4 (3.3)	2 (1.6)	9 (2.5)**
Number of patients by region, n (%)									
Europe	76 (71.7)	73 (72.3)	80 (74.8)	77 (74.8)	306 (73.4)	50 (42.4)	49 (40.2)	50 (40.7)	149 (41.0)
Rest of the world	30 (28.3)	28 (27.7)	27 (25.2)	26 (25.2)	111 (26.6)	68 (57.6)	73 (59.8)	73 (59.3)	214 (59.0)
United Kingdom	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight category, n (%)									
< 80 kg	44 (41.5)	33 (32.7)	43 (40.2)	54 (52.4)	174 (41.7)	38 (32.2)	45 (36.9)	55 (44.7)	138 (38.0)
≥ 80 to < 100 kg	45 (42.5)	36 (35.6)	43 (40.2)	34 (33.0)	158 (37.9)	47 (39.8)	41 (33.6)	43 (35.0)	131 (36.1)
≥ 100 kg	17 (16.0)	32 (31.7)	21 (19.6)	15 (14.6)	85 (20.4)	33 (28.0)	36 (29.5)	25 (20.3)	94 (25.9)
Mean BMI, kg/m^2 (SD)	29.2 (6.3)	32.1 (11.4)	30.2 (8.4)	28.6 (6.6)	30.0 (8.5)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)	30.9 (7.2)
Baseline characteristics									
Time since PsA diagnosis, mean years (SD)	6.3 (6.9)	6.9 (7.5)	6.2 (6.4)	7.2 (8.0)	6.7 (7.2)	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)	10.0 (8.2)
Time since PsA onset, mean years (SD)	10.4 (8.8)	9.2 (7.3)	10.0 (9.5)	10.8 (10.8)	10.1 (9.3)	11.1 (8.5)	13.8 (10.6)	11.5 (7.5)	12.2 (9.0)

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	Placebo	ADA40 q2w	IXE80 q4w	IXE80 q2w	Total	Placebo	IXE80 q4w	IXE80 q2w	Total
	n=106	n=101	n=107	n=103	n=417	n=118	n=122	n=123	n=363
Previous non-biologic systemic agent, n (%)	67 (63.2)	64 (63.4)	63 (58.9)	72 (69.9)	266 (63.8)	90 (76.3)	95 (77.9)	103 (83.7)	288 (79.3)
Previous methotrexate	45 (42.5)	43 (42.6)	37 (34.6)	45 (43.7)	170 (40.8)	69 (58.5)	69 (56.6)	72 (58.5)	210 (57.9)
Previous sulfasalazine	20 (18.9)	26 (25.7)	19 (17.8)	30 (29.1)	95 (22.8)	31 (26.3)	38 (31.1)	29 (23.6)	98 (27.0)
Previous leflunomide	13 (12.3)	15 (14.9)	19 (17.8)	10 (9.7)	57 (13.7)	25 (21.2)	26 (21.3)	29 (23.6)	80 (22.0)
Previous apremilast	-	-	-	-	-	5 (4.2)	8 (6.6)	3 (2.4)	16 (4.4)
Current methotrexate use, n (%)	59 (55.7)	57 (56.4)	57 (53.3)	53 (51.5)	226 (54.2)	40 (33.9)	48 (39.3)	61 (49.6)	149 (41.0)
Past cDMARD use, n (%)	24 (22.6)	20 (19.8)	22 (20.6)	23 (22.3)	89 (21.3)	66 (55.9)	62 (50.8)	50 (40.7)	178 (49.0)
Current cDMARD use, n (%)	69 (65.1)	67 (66.3)	68 (63.6)	63 (61.2)	267 (64.0)	52 (44.1)	60 (49.2)	73 (59.3)	185 (51.0)
Previous biologic agent, n (%)	-	-	-	-	-	118 (100)	122 (100)	123 (100)	363 (100)
Prior TNFi experience, n (%)									
Inadequate responder to 1 TNFi	-	-	-	-	-	68 (57.6)	71 (58.2)	65 (52.8)	204 (56.2)
Inadequate responder to 2 TNFi	-	-	-	-	-	41 (34.7)	41 (33.6)	46 (37.4)	128 (35.3)
Intolerance to a TNFi	-	-	-	-	-	9 (7.6)	10 (8.2)	12 (9.8)	31 (8.5)
DAS28-CRP, mean (SD)	4.9 (1.0)	4.9 (1.0)	5.0 (1.0)	5.0 (1.1)	4.9 (1.0)	5.0 (1.1)	5.1 (1.1)	5.1 (1.1)	5.1 (1.1)
CRP (mg/l), mean (SD)	15.1 (23.6)	13.2 (19.1)	12.8 (16.4)	15.1 (25.9)	14.1 (21.5)	12.1 (19.6)	17.0 (27.5)	13.5 (26.1)	14.2 (24.7)
CRP category >6 mg/l, n (%)	65 (61.3)	62 (61.4)	69 (64.5)	54 (52.4)	250 (60)	57 (49.1)	60 (50.4)	53 (43.1)	170 (47.5)
Van der Heijde modified total Sharp score, mean (SD)[30]	17.6 (28.6)	15.9 (27.4)	19.2 (32.7)	15.2 (28.9)	17.0 (29.4)	-	-	-	-
SPARCC total score, mean (SD)	NR	NR	NR	NR	NR	5.7 (4.38)	5.6 (3.98)	6.1 (4.30)	5.8 (4.21)
Patients with erosions, n (%)	93 (98.9)	91 (95.8)	93 (93.0)	94 (95.9)	371 (95.9)	NR	NR	NR	NR
Tender joint count 68 joints, mean (SD)	19.2 (13.0)	19.3 (13.0)	20.5 (13.7)	21.5 (14.1)	20.1 (13.4)	23.0 (16.2)	22.0 (14.1)	25.0 (17.3)	23.4 (15.9)

Demographic parameter	SPIRIT-P1					SPIRIT-P2			
	Placebo	ADA40 q2w	IXE80 q4w	IXE80 q2w	Total	Placebo	IXE80 q4w	IXE80 q2w	Total
	n=106	n=101	n=107	n=103	n=417	n=118	n=122	n=123	n=363
Swollen joint count 66 joints, mean (SD)	10.6 (7.3)	9.9 (6.5)	11.4 (8.2)	12.1 (7.2)	11.0 (7.4)	10.3 (7.4)	13.1 (11.2)	13.5 (11.5)	12.3 (10.3)
HAQ-DI total score, mean (SD)	1.2 (0.6)	1.1 (0.6)	1.2 (0.5)	1.2 (0.6)	1.2 (0.6)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)
Current Psoriasis, n (%)	102 (96.2)	97 (96.0)	100 (93.5)	95 (92.2)	394 (94.5)	108 (91.5)	118 (96.7)	113 (91.9)	339 (93.4)
Percentage of BSA for patients who have baseline plaque psoriasis, mean (SD)	14.4 (20.2)	14.8 (19.2)	15.1 (16.3)	12.0 (15.6)	14.1 (17.9)	9.0 (12.7)	12.5 (17.4)	11.6 (18.6)	11.0 (16.4)
BSA ≥ 3%, n (%)	67 (67.7)	68 (72.3)	73 (73.0)	59 (64.8)	267 (69.5)	67 (62.6)	68 (61.8)	68 (63.0)	203 (62.5)
PASI score in patients ≥3% BSA, mean (SD)	6.2 (7.5)	5.5 (6.5)	6.9 (6.6)	6.0 (7.0)	6.1 (6.9)	7.1 (7.1)	9.3 (9.1)	8.8 (10.3)	8.4 (8.9)
Moderate to severe psoriasis as defined as PASI > 12, sPGA ≥ 3 and BSA ≥ 10, n (%)	16 (16.2)	8 (8.5)	17 (17.0)	12 (13.2)	53 (13.8)	11 (9.3)	15 (12.3)	12 (9.8)	38 (10.5)
Current enthesitis, n (%)	57 (53.8)	56 (55.4)	70 (65.4)	59 (57.3)	242 (58.0)	69 (58.5)[a]	68 (55.7)[a]	84 (68.3)[a]	221 (60.9)[a]
LEI score, mean (SD)	2.9 (1.7)	3.0 (1.6)	2.7 (1.6)	3.1 (1.8)	2.9 (1.7)	2.9 (1.7)	2.9 (1.4)	3.0 (1.7)	2.9 (1.6)
Current dactylitis, n (%)	39 (36.8)	23 (22.8)	54 (50.5)	41 (39.8)	157 (37.6)	14 (11.9)[b]	28 (23.0)[b]	20 (16.3)[b]	62 (17.1)[b]
LDI score, mean (SD)	46.2 (65.5)	93.9 (111.9)	58.1 (96.7)	40.6 (54.6)	55.8 (83.6)	37.3 (25.2)	31.5 (33.8)	53.9 (37.6)	40.1 (34.3)

Source: Based on Table 9 of the CS[1] and Table 6 of the response to request for clarification[25]

Footnotes: [a] Defined as LEI > 0; [b] Defined as LDI-B score > 0; [*] Derived from Mease et al, 2017[31]; [**] Derived from Nash et al, 2017[32]

ADA = adalimumab; BMI = body mass index; BSA = body surface area; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = c-reactive protein; DAS28-CRP = disease activity score 28 diarthrodial joint count based on c-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; IXE = ixekizumab; kg = kilogram; LEI = Leeds Enthesitis Index; PASI = Psoriasis Area and Severity Index; NR = not reported; PsA = psoriatic arthritis; q2w = once every two weeks; q4w = once every four weeks; SD = standard deviation, SPARCC = Spondyloarthritis Research Consortium of Canada Enthesitis Index; sPGA = static physician's global assessment; TNFi = tumour necrosis factor inhibitor

The mean age of patients in SPIRIT-P1 was 49.5 and 51.9 years in SPIRIT-P2. Just under half were male (SPIRIT-P1: 46.0% and SPIRIT-P2: 46.6%). Most patients across the two trials were white (SPIRIT-P1: 94% and SPIRIT-P2: 91.5%). In total, 3.6% of the patients in SPIRIT-P1 and 5.8% in SPIRIT-P2 were Asian. The SPIRIT-P1 study was conducted with the majority of patients from Europe (73.4%) whereas in SPIRIT-P2 41% were from Europe.

Mean BMI in SPIRIT-P1 was 30.0 (SD 8.5) and 30.9 (SD 7.2) in SPIRIT-P2. The mean disease duration (time since PsA diagnosis) was 7.2 years in SPIRIT-P1 and 8.2 years in SPIRIT-P2. Current psoriasis occurred in 94.5% of patients in SPIRIT-P1 and in 93.4% of patients in SPIRIT-P2. Moderate to severe psoriasis was found in 13.8% of SPIRIT-P1 and 10.5% of SPIRIT-P2 patients. In SPIRIT-P1 58% had current enthesitis and 37.6% had current dactylitis. In SPIRIT-P2 the corresponding figures were 60.9% and 17.1%).[1]

ERG comment:

- Approximately 85% of the participants in SPIRIT-P1 had received a cDMARD which is normally given before a bDMARD in clinical practice so 15% of the patients in SPIRIT-P1 are not relevant to the population in the scope.
- Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. A separate analysis of the NICE ITT population is provided in the CS based on [redacted] patients across the two trials.[1]
- Non-white participants are underrepresented across the two trials.
- Mean BMI in the SPIRIT trials is within the obese classification so patients in the trials may be more overweight than those seen in practice.
- The ERG asked the company to clarify whether patients included in those trials are representative of UK clinical practice. The company replied that they had sourced real world data to assess the representativeness of patients in the SPIRIT trials for UK practice.[25] In the Adelphi Psoriatic Arthritis Disease Specific Programme (DSP), a total of [redacted] patient record forms were completed by [redacted] rheumatologists and [redacted] UK dermatologists. Of these patients, [redacted] were bDMARD-naïve and [redacted] bDMARD experienced (based on the Adelphi Psoriatic Arthritis DSP; as cited in the Clarification response.[25] The company also compared the patients to a recently published UK study from The Health Improvement Network (THIN).[8]
- The company stated that patients in SPIRIT-P1 had higher baseline CRP and a greater number of tender and swollen joints than patients in the Adelphi study therefore '*at least the same level of ACR response rates would be expected to be achieved in UK practice as was demonstrated by SPIRIT-P1*'.[25]This is an assumption made by the company.
- The ERG noted that mean age and proportion of males was similar in the SPIRIT-P1 trial and the UK Adelphi study (biological-naïve) and THIN database studies. However, BMI did appear to be a little higher in SPIRIT-P1. The UK PsA patients in Adelphi DSP had slightly higher rates of prior conventional synthetic DMARD (csDMARD) use ([redacted] of UK PSA bio-naive patients).
- The ERG noted that mean age was similar in the SPIRIT-P2 trial and the UK Adelphi study (bio-experienced). The proportion of males was slightly higher ([redacted] in Adelphi vs. 46.6% in Spirit-P2). Again, BMI did appear to be a little higher in SPIRIT-P2. The company stated that '*The rate of prior csDMARD use is consistent in SPIRIT-P2 with the Adelphi DSP dataset. 77.5% of bio-experienced patients randomized to IXE80MGQ4W received prior csDMARD use compared to [redacted] of bio-experienced patients in the Adelphi DSP dataset.*'[25]
- Patients in SPIRIT-P2 generally had more severe disease at baseline than those bio-experienced patients treated in UK clinical practice as captured by Adelphi DSP. SPIRIT-P2 included a

- population with higher baseline CRP scores, a greater proportion of patients with baseline CRP >6 mg/dl (47.5% vs [redacted]) and a greater number of tender joints at baseline (23.4 (SD 15.9) vs. [redacted] (SD [redacted])).
- In summary, the committee will need to decide, based on the factors highlighted by the ERG and the comparisons with the UK sample, whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice.

4.2.3 Quality assessment of the SPIRIT trials

The quality of the SPIRIT trials was assessed by the company in the CS with further details of the rating of quality criteria in the CS appendices.[28] Elements assessed were randomisation, allocation concealment, comparability of groups, blinding of care providers, patients and outcome assessors and drop out, selective reporting of outcomes and use of intention to treat analysis and appropriate methods for dealing with missing data. Table 4.4 provides an overview of the quality assessment of the SPIRIT RCTs from the point of view of the company and the ERG.

Table 4.4: SPIRIT-P1 and P2 study quality

Quality dimension	SPIRIT-P1 CS	SPIRIT-P1 ERG	SPIRIT-P2 CS	SPIRIT-P2 ERG	ERG comment
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Patients were randomised using a computer-generated random sequence using an interactive voice response system (IVRS).
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	However, in SPIRIT-P2 greater proportions of patients in the ixekizumab 80 mg q2w group were using methotrexate at baseline, compared to patients in the placebo group (49.6% versus 33.9%). Methotrexate use was not different between the ixekizumab 80 mg q4w and placebo groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Patients and study site personnel were blinded to study treatment until after all patients had discontinued from treatment or completed week 24. Unblinding did not occur until the reporting database was locked for the week 24 statistical analysis.
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	None identified
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes*	Yes*	No	No	The authors stated that the Itch Numeric Rating Scale was implemented to assess itching in SPIRIT-P1 but was not reported by Mease et al., 2017.[31] Results for this scale are going to be reported in a paper currently under development (and were in the CSR).
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	Efficacy and health outcome analyses were conducted according to the treatment to which all randomised patients were assigned i.e. ITT population. NRI and mBOCF methods were used to account for missing data.

Quality dimension	SPIRIT-P1 CS	SPIRIT-P1 ERG	SPIRIT-P2 CS	SPIRIT-P2 ERG	ERG comment
Did the authors of the study publication declare any conflicts of interest?	Yes	Unclear	Yes	Unclear	Unclear which study publication is being referenced.

Source: Based on table 12 of the CS[1] and table 37 of the CS appendices[28]
Footnote: * Itch NRS was a gated secondary endpoint in SPIRIT-P1, however, statistical testing was not performed as the prior gated endpoint was not significant.
CS = company submission; CSR = clinical study report; ERG = evidence review group; ITT = intention-to-treat; IVRS = interactive voice response system; mBOCF = modified baseline observation carried forward; NRI = non-responder imputation; q2w = once every two weeks; q4w = once every four weeks

ERG comment:

- The ERG agrees with the company's assessment of the quality of the SPIRIT trials. Both are well conducted randomised, blinded trials.
- The quality comments refer only to the 24-week double blind period of the trial, not to the open label extension period.

4.2.4 Statistical analysis of the SPIRIT trials

Efficacy analyses of both SPIRIT trials were performed for the ITT population and patients were analysed according to the randomised treatment even if they did not take that treatment, did not receive the correct treatment or did not follow the protocol. Only data collected up to week 16 were included in the analyses for patients who were inadequate responders at week 16. A gatekeeping statistical testing strategy was used for the analysis of the primary and major secondary outcomes with testing being performed in a pre-defined order to minimise multiple comparisons.

The primary outcome in both trials was the proportion of patients achieving an ACR 20 response at week 24. This was compared between each ixekizumab arm and placebo using logistic regression analysis adjusting for geographic region and cDMARD experience (naïve, past or current use) at baseline in SPIRIT-P1 and for geographic region and TNFi experience (inadequate response to one, two, or intolerant) at baseline in SPIRIT-P2. Results were reported as odds ratios (OR) with 95% confidence intervals (CI) and p-values. Missing data were imputed using non-responder imputation with non-responders defined as patients not meeting the clinical response criteria, being eligible for rescue therapy at week 16, having missing clinical response data, discontinuing from the trial prior to week 24, or not having at least one post-baseline assessment. Other binary outcomes (PsARC at weeks 12 and 24; PASI 75, 90 and 100 at week 12; ACR 20 at week 12; and ACR 50 and 70 at weeks 12 and 24) were analysed using the same methods.

Continuous outcomes such as the change from baseline to weeks 12 and 24 in HAQ-DI and mTSS as well as the change from baseline to week 12 in LEI (for patients with enthesitis at baseline) and itch (for patients with baseline psoriatic lesions involving $\geq$ 3% BSA) were analysed using a mixed-effect repeated measures model (MMRM) which included treatment, geographic region, baseline score, the treatment-by-visit interaction and cDMARD use at baseline (for SPIRIT-P1) or TNFi use at baseline (for SPIRIT-P2). As this model accounted for data being missing at random, missing data were not imputed.

Subgroup analyses were performed using a logistic regression model containing treatment, the relevant subgroup and the treatment-by-subgroup interaction, the interaction was tested using a significance level of 0.10. Differences between treatments were analysed within each subgroup category using Fisher's exact test regardless of whether or not the interaction term was statistically significant. Subgroup analyses were performed for concomitant methotrexate use (as a post-hoc analysis), gender, age, concomitant cDMARD therapy at baseline, cDMARD experience at baseline, prior TNFi experience, baseline disease severity, previous therapy for PsA and duration of PsA (all pre-specified analyses), see section 4.2.5. A further subgroup analysis was used to evaluate the efficacy of ixekizumab in those patients who would be eligible for bDMARD treatment under current NICE criteria.

4.2.5 Efficacy results of the SPIRIT trials

The main results of the SPIRIT trials, as presented in the CS, are given in Table 4.5. Efficacy analyses were performed using the ITT population. The primary outcome in both SPIRIT trials was ACR 20

response rates at week 24. In both SPIRIT studies, significantly more patients achieved an ACR 20 response with ixekizumab compared with placebo (SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 62.1%, placebo 30.2%; SPIRIT-P2: IXE 80 q4w 53.3%, IXE 80 q2w 48.0%, placebo 19.5%; $p<0.001$ for all comparisons to placebo). In the SPIRIT-P1 trial, patients treated with adalimumab had similar response rates to the ixekizumab arms. Ixekizumab was also found to be superior to placebo for ACR 20 at week 12 and for ACR 50 and 70 at 12 and 24 weeks, see Table 4.5.

In both SPIRIT-P1 and P2 trials, the percentage of patients who achieved a PsARC response at week 12 as well as week 24 were statistically significantly greater for both ixekizumab groups compared to placebo in all cases (Week 12 – SPIRIT-P1: IXE 80 q4w 55.1%, IXE 80 q2w 61.2%, placebo 34.0%; SPIRIT-P2: IXE 80 q4w 50.0%, IXE 80 q2w 52.0%, placebo 23.7%. Week 24 – SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 66.0%, placebo 32.1%; SPIRIT-P2: IXE 80 q4w 55.7%, IXE 80 q2w 47.2%, placebo 20.3%), see Table 4.5.

In terms of quality of life at week 12, patients in the two ixekizumab groups achieved significantly greater mean change from baseline in HAQ-DI total scores in both SPIRIT trials, see Table 4.5.

The company stated that '*statistically significant differences for the ixekizumab 80 mg Q4W and Q2W versus placebo were observed for all major secondary endpoints in SPIRIT-P1 with the exception of the change from baseline to week 12 in LEI ($p > .25$ for each comparison) and the change from baseline to week 12 in itch NRS*'.[1] A summary of further results relevant to the NICE scope is given below in Table 4.6.

Table 4.5: Main results of the SPIRIT trials

	SPIRIT-P1				SPIRIT-P2		
Endpoint	**Placebo n=106**	**ADA40 q2w n=101**	**IXE80 q4w n=107**	**IXE80 q2w n=103**	**Placebo n=118**	**IXE80 q4w n=122**	**IXE80 q2w n=123**
ACR 20 response rate at week 24							
ACR 20, n (%)	32 (30.2)	58 (57.4)	62 (57.9)	64 (62.1)	23 (19.5)	65 (53.3)	59 (48.0)
OR (95% CI) p-value	-	3.16 (1.78, 5.60) <0.001	3.24 (1.84, 5.72) <0.001	3.88 (2.18, 6.91) <0.001	-	4.74 (2.65, 8.48) <0.001	3.79 (2.12, 6.78) <0.001
PsARC response rate at week 12							
n (%)	36 (34.0%)	59 (58.4%)	59 (55.1%)	63 (61.2%)	28 (23.7%)	61 (50.0%)	64 (52.0%)
OR (95%CI) p-value	-	2.8 (1.59, 5.02) <0.001	2.5 (1.41, 4.34) 0.002	3.2 (1.81, 5.71) <0.001	-	3.26 (1.87, 5.69) <0.001	3.47 (1.99, 6.05) <0.001
PsARC response rate at week 24							
n (%)	34 (32.1%)	59 (58.4%)	62 (57.9%)	68 (66.0%)	24 (20.3%)	68 (55.7%)	58 (47.2%)
OR (95%CI) p-value	-	3.0 (1.70, 5.35) <0.001	3.0 (1.69, 5.22) <0.001	(2.36, 7.57) <0.001	-	5.0 (2.81, 8.90) <0.001	3.55 (1.99, 6.32) <0.001
Response rate at week 12							
PASI 75							
PASI 75, n (%)	5 (7.5)	23 (33.8)	55 (75.3)	41 (69.5)	7 (10.4)	39 (57.4)	42 (61.8)
OR (95%CI) p-value	-	6.3 (2.2, 17.95) <0.001	38.8 (13.36, 112.72) <0.001	29.1 (9.87, 85.53) <0.001	-	14.03 (5.28, 37.27) <0.001	16.67 (6.28, 44.24) <0.001
PASI 90							
PASI 90, n (%)	1 (1.5)	15 (22.1)	38 (52.1)	34 (57.6)	4 (6.0)	26 (38.2)	29 (42.6)
OR (95%CI) p-value	-	18.5 (2.36, 144.84) 0.006	71.6 (9.40, 545.52) <0.001	91.8 (11.86, 710.43) <0.001	-	10.52 (3.36, 32.95) NA	17.96 (5.32, 60.62) <0.001

PASI 100							
PASI 100, n (%)	1 (1.5)	10 (14.7)	23 (31.5)	24 (40.7)	4 (6.0)	13 (19.1)	16 (23.5)
OR (95%CI) p-value	-	10.9 (1.35, 88.49) 0.025	29.7 (3.86, 228.18) 0.001	46.1 (5.94, 357.57) <0.001	-	3.82 (1.16, 12.55) NA	5.87 (1.78, 19.32) 0.004
ACR response rates at week 12							
ACR 20							
ACR 20, n (%)	33 (31.1)	52 (51.5)	61 (57.0)	62 (60.2)	26 (22.0)	61 (50.0)	59 (48.0)
OR (95%CI) p-value	-	2.4 (1.34, 4.17) 0.003	2.9 (1.66, 5.14) <0.001	3.3 (1.88, 5.89) <0.001	-	3.56 (2.02, 6.26) <0.001	3.28 (1.85, 5.79) <0.001
ACR 50							
ACR 50, n (%)	5 (4.7)	30 (29.7)	36 (33.6)	41 (39.8)	4 (3.4)	38 (31.1)	41 (33.3)
OR (95%CI) p-value	-	8.6 (3.19, 23.35) <0.001	10.3 (3.83, 27.48) <0.001	13.4 (5.01, 35.77) <0.001	-	14.61 (4.82, 44.28) <0.001	14.58 (4.98, 42.68) <0.001
ACR 70							
ACR 70, n (%)	0	18 (17.8)	16 (15.0)	17 (16.5)	2 (1.7)	18 (14.8)	13 (10.6)
OR (95%CI) p-value	-	NA	NA	NA	-	11.9 (2.47, 57.41) 0.002	7.46 (1.63, 34.22) NA
ACR response rates at week 24							
ACR 50							
ACR 50, n (%)	16 (15.1)	39 (38.6)	43 (40.2)	48 (46.6)	6 (5.1)	43 (35.2)	41 (33.3)
OR (95%CI) p-value	-	3.6 (1.83, 6.94) <0.001	3.8 (1.97, 7.38) <0.001	5.0 (2.57, 9.64) <0.001	-	10.83 (4.31, 27.23) <0.001	9.31 (3.75, 23.13) <0.001
ACR 70							
ACR 70, n (%)	6 (5.7)	26 (25.7)	25 (23.4)	35 (34.0)	0 (0.0)	27 (22.1)	15 (12.2)
OR (95%CI) p-value	-	5.8 (2.27, 14.79) <0.001	5.1 (2.00, 13.09) <0.001	8.7 (3.46, 21.80) <0.001	-	NA	NA

HAQ-DI Change from baseline to week 12							
Patients in model	n=100	n=95	n=96	n=95	n=102	n=114	n=113
Endpoint (LSM) Change (SE)	-0.13 (0.05)	-0.35 (0.05)	-0.37 (0.05)	-0.47 (0.05)	-0.1 (0.06)	-0.4 (0.06)	-0.4 (0.06)
LSM Difference (95% CI)	-	-0.22 (-0.35, -0.09)	-0.24 (-0.36, -0.12)	-0.34 (-0.47, -0.21)	-	-0.3 (-0.5, -0.2)	-0.3 (-0.4, -0.1)
p-value	-	<0.001	<0.001	<0.001	-	<0.001	<0.001

Source: Based on Tables 13-18, of the CS[1]

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 HAQ-DI

ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; IXE = ixekizumab; LSM = least squares mean; NA = not available; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SE = standard error; q2w = once every two weeks; q4w = once every four weeks

Table 4.6: Further results of the SPIRIT trials

	SPIRIT-P1				SPIRIT-P2		
Endpoint	**Placebo n=106**	**ADA40 q2w n=101**	**IXE80 q4w n=107**	**IXE80 q2w n=103**	**Placebo n=118**	**IXE80 q4w n=122**	**IXE80 q2w n=123**
mTSS from baseline to week 24 change (SE)	n = 61	n = 83	n = 82	n = 85	NA	NA	NA
	0.49 (0.09)	0.10 (0.09)	0.17 (0.08)	0.08 (0.08)	NA	NA	NA
Minimal disease activity at week 24	n = 106	n = 101	n = 107	n = 103	n = 118	n = 122	n = 123
	16 (15.1)	32 (31.7)	32 (29.9)	42 (40.8)	4 (3.4)	34 (27.9)	29 (23.6)
		OR = 2.61 (1.32 to 5.14)	OR = 2.42 (1.23 to 4.75)	OR = 3.93 (2.03 to 7.64)		OR = 11.58 (3.91 to 34.30)	OR = 8.89 (3.01 to 26.27)
Proportion of patients achieving complete dactylitis resolution at week 24	n = 28	n = 18	n = 39	n = 26	n = 14	n = 28	n = 20
	7 (25.0)	14 (77.8)	31 (79.5)	20 (76.9)	3 (21.4)	21 (75.0)	10 (50.0)
		OR = 10.3 (2.51 to 42.6)	OR = 12.3 (3.79 to 40.1)	OR = 10.0 (2.80 to 36.0)		OR = 16.59 (2.43 to 113.25)	OR = 6.20 (0.92 to 41.76)
Proportion of patients with complete enthesitis resolution at week 24	n = 57	n = 54	n = 68	n = 57	n = 69	n = 68	n = 84
	11 (19.3)	18 (33.3)	29 (42.6)	22 (38.6)	15 (21.7)	24 (35.3)	26 (31.0)
		OR = 2.23 (0.93 to 5.36)	OR = 3.23 (1.42 to 7.35)	OR = 2.66 (1.13 to 6.25)		OR = 2.01 (0.93 to 4.34)	OR = 1.57 (0.74 to 3.34)
Proportion of patients achieving psoriasis nail resolution at week 24	n = 74	n = 71	n = 70	n = 74	n = 73	n = 89	n = 74
	14 (18.9)	28 (39.4)	18 (25.7)	27 (36.5)	5 (6.8)	18 (20.2)	22 (29.7)
		OR = 2.8 (1.32 to 5.98)	OR = 1.50 (0.67 to 3.29)	OR = 2.5 (1.18 to 5.34)		OR = 3.67 (1.26 to 10.65)	OR = 7.33 (2.44 to 21.96)

Source: Based on Appendix P of the CS[28]

ADA = adalimumab; CS = company submission; IXE = ixekizumab; mTSS = modified Total Sharp Score; NA = not available; OR = odds ratio; SE = standard error; q2w = once every two weeks; q4w = once every four weeks

For both SPIRIT studies, subgroup analyses were conducted for the ACR 20 response rate at week 24 (ITT population). A range of subgroups were investigated including demographic characteristics such as gender and age, geographic regions, use of conventional DMARDs, prior TNFi use, baseline severity, duration of PsA and presence of bone erosion.[28] The company found that efficacy was shown '*regardless of age, race, baseline BMI, geographic region, baseline CRP, previous PsA therapy status, concomitant DMARD therapy (current use at baseline), cDMARD experience at baseline, duration since PsA onset, in both SPIRIT studies'*.[1]

The company noted a statistically significant interaction (p=0.01) between treatment and subgroup in the baseline weight subgroup in SPIRIT-P1 where there was a greater difference between ixekizumab and placebo for patients weighing between 80 and 100 kg compared to those weighing less than 80 kg, and there were no significant between treatment differences for patients weighing more than 100 kg. For SPIRIT-P2 there was a statistically significant interaction for the gender subgroup (p=0.008) although the size of the difference was not clinically significant. More males than females had an ACR 20 response at 24 weeks with ixekizumab.

The company conducted further post-hoc subgroup analysis based on concomitant methotrexate use. Treatment by subgroup interaction (concomitant methotrexate versus no concomitant methotrexate) was not significant for ACR 20 response (Table 4.7).[1]

As not all participants in the SPIRIT trials would have been eligible for biological therapy under current NICE criteria, the company conducted a subgroup analysis using an integrated set of patients from SPIRIT-P1 and P2 who met the NICE criteria. The total number of patients available for analysis was [redacted]. [redacted] of patients who received ixekizumab 80 mg q4w or q2w achieved an ACR 20 response at week 24 compared to placebo ([redacted] and [redacted] vs. [redacted] respectively).[1]

Table 4.7: Subgroup results of the SPIRIT trials – ACR response rate at week 24

	SPIRIT-P1					SPIRIT-P2			
Endpoint	**p-value interaction[a]**	**Placebo n=106 n (%)**	**ADA40 q2w n=101 n (%)**	**IXE80 q4w n=107 n (%)**	**IXE80 q2w n=103 n (%)**	**p-value interaction[a]**	**Placebo n=118 n (%)**	**IXE80 q4w n=122 n (%)**	**IXE80 q2w n=123 n (%)**
Gender									
Male	0.436	16 (33.3)	36 (70.6)	28 (62.2)[b]	34 (70.8)[b]	0.008	7 (12.5%)	39 (61.9%)	31 (62.0%)
Female		16 (27.6)	22 (44.0)[c]	34 (54.8)[b]	30 (54.5)[c]		16 (25.8%)	26 (44.1%)	28 (38.4%)
Age									
< 65 years	0.883	30 (32.3)	54 (60.7)[c]	61 (60.4)[c]	58 (65.2)[c]	NA	18 (17.0%)	49 (52.1%)	51 (50.5%)
≥ 65 and < 75 years		2 (15.4)	4 (36.4)	1 (16.7)	5 (50.0)		5 (45.5%)	16 (59.3%)	7 (35.0%)
≥75 years		0	0	0	1 (33.3)		0 (0.0%)	0 (0.0%)	1 (50.0%)
Race									
American Indian or Alaska Native	0.992	1 (50.0)	2 (66.7)	1 (50.0)	2 (100.0)	NA		-	-
Asian		0	2 (66.7)	1 (50.0)	4 (80.0)		0 (0.0%)	4 (57.1%)	6 (85.7%)
Black or African American		0	0	0	0		0 (0.0%)	1 (100.0%)	0 (0.0%)
Native Hawaiian or other Pacific Islander		0	0	0	0		0 (0.0%)	0 (0.0%)	0 (0.0%)
White		31 (31.3)	54 (56.8)[c]	59 (57.8)[c]	58 (60.4)[c]		22 (20.4%)	59 (53.2%)	52 (46.0%)
Multiple		0	0	1 (100.0)	0		1 (50.0%)	1 (50.0%)	0 (0.0%)
Ethnicity									
Hispanic or Latino	NA	NA	NA	NA	NA	NA	2 (18.2%)	5 (45.5%)	4 (30.8%)

Not Hispanic or Latino		NA	NA	NA	NA		21 (19.8%)	59 (54.1%)	54 (49.5%)
Not Reported		NA	NA	NA	NA		0 (0.0%)	1 (50.0%)	1 (100.0%)
Baseline weight									
< 80 kg	0.010[b]	17 (38.6)	19 (57.6)	24 (55.8)	36 (66.7)[b]	0.431	9 (23.7%)	21 (46.7%)	21 (38.2%)
≥ 80 kg and < 100 kg		8 (17.8)	17 (47.2)[b]	30 (69.8)[c]	22 (64.7)[c]		8 (17.0%)	25 (61.0%)	26 (60.5%)
≥ 100 kg		7 (41.2)	22 (68.8)	8 (38.1)	6 (40.0)		6 (18.2%)	19 (52.8%)	12 (48.0%)
Baseline BMI									
Underweight	0.864	0	1 (100.0)	0	2 (100.0)	NA	0	0 (0.0%)	0
Normal		10 (43.5)	10 (62.5)	18 (66.7)	21 (63.6)		3 (17.6%)	12 (54.5%)	16 (51.6%)
Overweight		11 (24.4)	17 (53.1)[d]	18 (60.0)[b]	19 (65.5)[c]		8 (17.8%)	19 (51.4%)	19 (46.3%)
Obese		8 (25.8)	22 (56.4)	17 (51.5)[d]	20 (60.6)[b]		10 (23.3%)	30 (58.8%)	21 (48.8%)
Extreme obese		3 (50.0)	8 (61.5)	7 (53.8)	1 (20.0)		2 (15.4%)	4 (36.4%)	2 (33.3%)
Geographic region									
Europe	0.156	11 (36.7)	11 (39.3)	15 (55.6)	16 (61.5)	NA	10 (20.0%)	26 (53.1%)	22 (44.0%)
United States		NA	NA	NA	NA		13 (21.7%)	33 (50.8%)	29 (46.0%)
Rest of the world		21 (27.6)	47 (64.4)[c]	47 (58.8)[c]	48 (62.3)[c]		0 (0.0%)	6 (75.0%)	8 (80.0%)
Baseline CRP									
≤ 6 mg/l	0.274	14 (34.1)	21 (53.8)	18 (47.4)	26 (53.1)	0.083	15 (25.4%)	27 (45.8%)	35 (50.0%)
> 6 mg/l		18 (27.7)	37 (59.7)[c]	44 (63.8)[c]	38 (70.4)[c]		8 (14.0%)	36 (60.0%)	24 (45.3%)
Previous PsA therapy status									
Yes	0.949	22 (30.1)	38 (55.9)[b]	42 (59.2)[c]	48 (61.5)[c]				
No		10 (30.3)	20 (60.6)[d]	20 (55.6)	16 (64.0)[d]				
Concomitant DMARD therapy (current use at baseline)									
Yes	0.321	22 (31.9)	43 (64.2)[c]	38 (55.9)[b]	39 (61.9)[c]	0.511	12 (23.1%)	30 (50.0%)	34 (46.6%)

No		10 (27.0)	15 (44.1)	24 (61.5)[b]	25 (62.5)[b]		11 (16.7%)	35 (56.5%)	25 (50.0%)
Concomitant methotrexate (current use at baseline)[e]									
Yes	0.199	18 (30.5)	38 (66.7)[c]	31 (54.4)[d]	33 (62.3)[c]	NA	7 (17.5)	14 (50.0)[b]	31 (50.8)[c]
No		14 (29.8)	20 (45.5)	31 (62.0)[b]	31 (62.0)[b]		16 (20.5)	41 (55.4)[c]	28 (45.2)[b]
Conventional DMARD experience at baseline									
Current use at baseline	0.505	22 (31.9)	43 (64.2)[c]	38 (55.9)[b]	39 (61.9)[c]	NA	NA	NA	NA
Past use at baseline		7 (29.2)	10 (50.0)	16 (72.7)[b]	14 (60.9)[d]		NA	NA	NA
DMARD naïve		3 (23.1)	5 (35.7)	8 (47.1)	11 (64.7)[d]		NA	NA	NA
Prior TNFi experience									
Inadequate responder to 1 TNFi	NA	NA	NA	NA	NA	0.519	12 (17.6%)	39 (54.9%)	28 (43.1%)
Inadequate responder to 2 TNFi		NA	NA	NA	NA		7 (17.1%)	21 (51.2%)	24 (52.2%)
Intolerance to a TNFi		NA	NA	NA	NA		4 (44.4%)	5 (50.0%)	7 (58.3%)
Duration since PsA onset									
0 to < 2 years	0.415	5 (27.8)	8 (53.3)	8 (57.1)	7 (50.0)	NA	NA	NA	NA
≥ 2 to < 5 years		5 (38.5)	13 (59.1)	11 (45.8)	12 (44.4)	0.374	7 (26.9%)	15 (62.5%)	12 (42.9%)
≥ 5 years		22 (29.3)	37 (57.8)[c]	43 (62.3)[c]	45 (72.6)[c]		16 (17.4%)	50 (51.0%)	47 (49.5%)
Tobacco current use at baseline									
Yes	NA	NA	NA	NA	NA	0.987	6 (25.0%)	15 (60.0%)	14 (53.8%)
No		NA	NA	NA	NA		17 (18.1%)	50 (51.5%)	45 (46.4%)

Baseline percentage of BSA									
< 3%	NA	NA	NA	NA	NA	0.638	9 (18.0%)	25 (54.3%)	21 (42.0%)
≥ 3%		NA	NA	NA	NA		14 (20.9%)	34 (50.0%)	34 (50.0%)
Moderate to severe psoriasis									
Yes	NA	NA	NA	NA	NA	0.913	2 (18.2%)	9 (60.0%)	6 (50.0%)
No		NA	NA	NA	NA		21 (19.6%)	56 (52.3%)	53 (47.7%)
Current enthesitis									
Yes	NA	NA	NA	NA	NA	0.657	17 (20.0%)	46 (51.7%)	49 (49.5%)
No		NA	NA	NA	NA		6 (18.2%)	19 (57.6%)	10 (41.7%)
Baseline LDI									
Basic group: = 0	NA	NA	NA	NA	NA	0.889	21 (20.2%)	50 (53.2%)	50 (48.5%)
Basic group: > 0		NA	NA	NA	NA		2 (14.3%)	15 (53.6%)	9 (45.0%)

Source: Figures 5 and 6 of the CS[1]; Tables 38 and 39 of the CS appendix[28]

Footnote: [a] A logistic regression analysis with treatment, subgroup and the interaction of treatment by subgroup included as factors, and the treatment by subgroup interaction is tested at the 10% significance level. [b] $p<0.01$ versus placebo; [c] $p\leq0.001$ versus placebo; [d] $p<0.05$ versus placebo; [e] post-hoc analysis. NB: If no group within the subgroup is <10% of the total population, only summary statistics are provided for that subgroup (that is, no inferential testing and p-value is presented as NA). Footnotes b to d only reported for SPIRIT-P1 and post-hoc analysis of SPIRIT-P2.

ADA = adalimumab; BMI = body mass index; BSA = body surface area; CRP = c-reactive protein; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; IXE = ixekizumab; kg = kilogram; LDI = Leeds Dactylitis Index; mg = milligram; NA = not available; PsA = psoriatic arthritis; q2w = once every two weeks; q4w = once every four weeks; TNFi = Tumour necrosis factor inhibitor

ERG comment:

- Both trials demonstrated superiority of ixekizumab in relation to placebo on outcomes of importance to patients. However, when interpreting 24 week results it should be noted that patients who were identified as inadequate responders at week 16 were required to modify their concomitant medication by adjusting the dose of existing medication(s) and/or introduction of new medication(s). The company stated that '*Modifications made at week 16 must have remained in place and unchanged throughout the remainder of the double-blind period of the study. The following medications were eligible for modification: NSAIDs and opiate analgesics, cDMARDs, and oral corticosteroids. Additionally, one intra-articular injection of a corticosteroid was permitted for Inadequate Responders*'.[1]However, only data of non-responders up to 16 weeks were included.
- The company demonstrated efficacy of ixekizumab in relation to placebo for a population reflective of NICE current guidance on use of bDMARDs after failure of two cDMARDs. However, this analysis was based on [redacted] patients across both trials so percentages of responders should be treated with some caution.

4.2.6 Safety results of the SPIRIT trials

Safety data were obtained from 416 patients (including 209 using ixekizumab) who took at least one dose of study drug in SPIRIT-P1 and by 363 patients (including 247 using ixekizumab) in SPIRIT-P2. Data on adverse events are presented in the CS for the 24-week double blind period of the two SPIRIT trials (see Table 4.8) and for the extension period (up to week 52). The company presented data on study drug discontinuation, adverse events, serious adverse events and discontinuations due to AEs. A serious adverse event (SAE) was defined as any AE '*that resulted in one of the following outcomes: death, initial or prolonged inpatient hospitalisation, a life-threatening experience (immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, or any other outcome considered significant by the investigator for any other reason*'.[1] Adverse events of special interest were also gathered and the main ones as presented by the company are listed in Table 4.8.

Patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials (SPIRIT-P1: IXE 80 q4w 66.4%, IXE 80 q2w 65.7%, adalimumab 64.4%, placebo 47.2%; SPIRIT-P2: IXE 80 q4w 68%, IXE 80 q2w 73.2%, placebo 64.4%). In SPIRIT-P1, the differences between both ixekizumab groups and placebo were statistically significant. Similarly, regarding AEs possibly related to the study drug, numbers were higher in both ixekizumab groups compared to placebo in both SPIRIT trials (SPIRIT-P1: IXE 80 q4w 29.9%, IXE 80 q2w 36.3%, adalimumab 20.8%, placebo 11.3%; SPIRIT-P2: IXE 80 q4w 28.7%, IXE 80 q2w 40.7%, placebo 24.6%). SPIRIT-P1 has a reference adalimumab arm and it can be observed that occurrence of adverse events was similar in the adalimumab group to the ixekizumab groups although fewer appeared to be attributable to the drug, see Table 4.8.

The company commented that adverse events across the two SPIRIT trials were mainly of mild or moderate severity and it can be seen from Table 4.8 that SAEs were relatively uncommon (SPIRIT-P1: IXE 80 q4w 5.6%, IXE 80 q2w 2.9%, adalimumab 5.0%, placebo 1.9%; SPIRIT-P2: IXE 80 q4w 2.5%, IXE 80 q2w 6.5%, placebo 3.4%). There were no deaths across the two trials in the double-blind periods. The proportion of patients who discontinued medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab and placebo groups.

The most frequently reported AEs were infections which were comparable across groups (25.7% of all patients in SPIRIT-P1 and 35.5% in SPIRIT-P2). Injection site reactions were statistically significantly

more common with ixekizumab than placebo in both, SPIRIT-P1 (IXE 80 q4w 12.1%, IXE 80 q2w 15.7%, adalimumab 2.0%, placebo 0%) and SPIRIT-P2 (IXE 80 q4w 11.5%, IXE 80 q2w 23.6%, placebo 4.2%).

A total of 381 patients in SPIRIT-P1 and 310 in SPIRIT-P2 entered the extension phase of the trials (up to week 52). As there is no placebo comparison at this stage, it is most useful to examine if the pattern of events seen in the double-blind phase continues in the extension phase. In SPIRIT-P1 in those receiving IXE 80 q4w throughout, the incidence of AEs was 55.7% and in those receiving IXE 80 q2w throughout the incidence of AEs was 56.3% compared to 66.4% and 65.7% up to week 24. In SPIRIT-P2 in those receiving IXE 80 q4w, the incidence of AEs was 71.2% and in those receiving IXE 80 q2w the incidence of AEs was 63.6% compared to 68% and 73.2% up to week 24. The company reported that most events continued to be mild or moderate.[1] Infections and injection site reactions continued to be the most frequently reported events. The company further commented that the safety profile of ixekizumab up to two years of treatment in SPIRIT-P1was similar to that obtained in the double-blind period. In SPIRIT-P2, one death caused by cardiorespiratory arrest was reported in the group randomised to placebo then to IXE 80 q2w. This event was reported in detail in the CSR supplied by the company and was not considered to be study-drug related.[33]

In response to the request for clarification, results for a network meta-analysis of adverse events were presented, see section 4.3 for details.[25]

Table 4.8: Overview of AEs in SPIRIT P1 and P2 – double blind period

	SPIRIT-P1				SPIRIT-P2		
Endpoint	**Placebo** (n=106), n (%)	**Adalimumab** (n=101), n (%)	**IXE80 q4w** (n=107), n (%)	**IXE80 q2w** (n=102), n (%)	**PBO** (n=118), n (%)	**IXE80 q4w** (n=122), n (%)	**IXE80 q2w** (n=123), n (%)
Patients with ≥1 TEAE	50 (47.2)	65 (64.4)	71 (66.4)	67 (65.7)	76 (64.4)	83 (68.0)	90 (73.2)
Discontinuations from study drug due to AE	2 (1.9)	2 (2.0)	2 (1.9)	4 (3.9)	6 (5.1)	5 (4.1)	8 (6.5)
Deaths	0	0	0	0	0	0	0
SAEs	2 (1.9)	5 (5.0)	6 (5.6)	3 (2.9)	4 (3.4)	3 (2.5)	8 (6.5)
TEAEs possibly related to study	12 (11.3)	21 (20.8)	32 (29.9)	37 (36.3)	29 (24.6)	35 (28.7)	50 (40.7)
Treatment-emergent AEs of Special Interest							
Cytopenias	6 (5.7)	4 (4.0)	1 (0.9)	4 (3.9)	0	0	0
Hepatic	7 (6.6)	13 (12.9)	5 (4.7)	9 (8.8)	2 (1.7)	2 (1.6)	5 (4.1)
Infection	27 (25.5)	26 (25.7)	30 (28.0)	24 (23.5)	35 (29.7)	47 (38.5)	47 (38.2)
Injection-site reactions	5 (4.7)	6 (5.9)	26 (24.3)	27 (26.5)	5 (4.2)	14 (11.5)	29 (23.6)
Allergic reactions / Hypersensitives	3 (2.8)	5 (5.0)	2 (1.9)	5 (4.9)	6 (5.1)	13 (10.7)	14 (11.4)
Cerebrocardiovascular events	0	3 (3.0)	0	0	2 (1.7)	0	0
Malignancies	1 (0.9)	1 (1.0)	0	0	0	2 (1.6)	0
Depression	0	1 (1.0)	0	0	3 (2.5)	2 (1.6)	2 (1.6)

Source: Tables 27 and 29 of the CS[1]

AE = adverse event; IXE = ixekizumab; q2w = once every two weeks; q4w = once every four weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

ERG comment:

- In total, 456 patients have been exposed to ixekizumab across the two SPIRIT trials. This has revealed an increased but manageable set of adverse events when compared to placebo.
- Safety is evaluated in a double-blind manner for just 24 weeks. However, the long-term extension phases of the trials (up to two years available in SPIRIT-P1) add weight to the evidence of an acceptable safety profile in a population of patients with psoriatic arthritis.
- The increased incidence of infection with ixekizumab compared to placebo is noted. The Summary of Product Characteristics (SmPC) for ixekizumab notes that it '*should be used with caution in patients with clinically important chronic infection. If such an infection develops, monitor carefully and discontinue Taltz if the patient is not responding to standard therapy or the infection becomes serious. Taltz should not be resumed until the infection resolves. Taltz must not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of Taltz in patients with latent TB*'.[34] Patients will need to be made aware of the increased risk of infections.
- Including both psoriatic arthritis trials and trials of plaque psoriasis, the SmPC notes that a total of 7,339 patients have been treated with ixekizumab representing 13,645.6 years of exposure. The SmPC notes that serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. Cases of new or exacerbations of Crohn's disease and ulcerative colitis have also been reported. Caution is advised when prescribing ixekizumab to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, and that patients should be monitored closely. Furthermore, ixekizumab should not be used with live vaccines.[34] Regarding the SPIRIT trials, it was noted that injection site reactions were statistically significantly more common in ixekizumab groups in comparison to placebo.[34]
- The only direct safety comparisons, as for effectiveness comparisons, are between placebo and ixekizumab. However, SPIRIT-P1 has a reference adalimumab arm and it can be observed that occurrence of adverse events was similar in the adalimumab group to the ixekizumab groups although fewer of the adalimumab events appeared to be attributable to the drug. Additional safety comparisons between treatments are reported in the NMA results in section 4.3.

4.2.7 Ongoing trials

The CS mentioned two ongoing trials.[1] The first (SPIRIT-P3) has a dosage which is not in line with the licence, i.e. ixekizumab 80 mg q2w was given to all patients irrespective of psoriasis severity. Hence no further description of the trial was given in the CS. The second ongoing trial (SPIRIT-H2H) was described. SPIRIT-H2H was started in August 2017, is currently recruiting patients and is due to complete in April 2019. This randomised, open label trial will compare ixekizumab to adalimumab with 275 bDMARD naïve patients in each arm.[1]

ERG comment:

- Neither of the two ongoing trials at their current stage would have informed the submission. The ERG notes that SPIRIT-H2H will provide a direct comparison with adalimumab which is not available in the current submission.

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

As SPIRIT-P1 and SPIRIT-P2 were in different patient populations separate Bayesian network meta-analyses (NMAs) were performed for each population to compare ixekizumab with relevant comparators. One analysis was performed for the biologic-naïve patient population and another for the

biologic-experienced patient population. Trials for the comparator treatments were identified through a systematic review as described in section 4.1 of this report.

The outcomes included in the NMA were:

- Joint response measured by the proportion of patients achieving PsARC response
- Functional capacity measured by the absolute change from baseline in HAQ-DI score conditional on achieving PsARC response
- Skin response measured by PASI 50/75/90/100

Additional NMA results were provided in the clarification response for ACR 20, 50 and 70 responses and adverse events.[25]

NMAs were performed using Bayesian methods following the guidance provided by the NICE Decision Support Unit Technical Support Document series.[35] Data for each treatment group were modelled using an arm-based likelihood. Bayesian models were performed in JAGS via R for the PsARC and PASI outcomes, and in a Lilly analysis tool based on R and OpenBUGs for change in HAQ-DI conditional on PsARC response.

PsARC response was modelled using a binomial likelihood model with a logit link and PASI 50/75/90/100 was modelled using multinomial probit model using conditional binomial likelihood. In the multinomial model, it is assumed that the treatment effect on the probit scale is the same for all four PASI outcomes so information can be borrowed from different PASI outcomes even if a particular study does not report one of the PASI outcomes. For both outcomes the primary analysis used 12-week results for ixekizumab, 16-week results were included in a sensitivity analysis. The Bayesian model used vague priors of normal (0, 10000) for trial baselines and treatment effects and uniform (0, 5) for binomial, multinomial and continuous standard deviations and multinomial categories. Three chains and a burn-in period of 30,000 runs were used with an additional 30,000 runs and a thinning parameter of 2 used to obtain parameter estimates.

Continuous outcomes such as the change from baseline in HAQ-DI were analysed using a normal model with an identity link. Three chains and a burn-in period of 10,000 runs were used with an additional 20,000 runs used to obtain parameter estimates.

Meta-regression controlling for baseline risk by including the response on placebo as a covariate were also performed for PsARC and PASI outcomes for the biologic-naïve analysis. There were insufficient studies available to perform these analyses for the biologic-experienced population.

For all analyses both fixed and random effects models were run and model fit was compared with the Deviance Information Criterion (DIC), the model with the lowest DIC was considered the best fit after accounting for the number of model parameters and good convergence with little autocorrelation. If the difference in DIC was less than five points, or the network was small or there were convergence difficulties then the fixed effect model was preferred. As many networks had edges consisting of only one study, it was difficult to accurately estimate between study heterogeneity in the random effects models. Fixed effect model results were presented and used in the economic model. Random effects model results were provided in the clarification response[25]

4.3.1 Biologic-naïve population

Details of the trials included in the NMA for the biologic-naïve population are provided in Table 4.9. The network diagram of trial evidence for the PsARC and PASI outcomes is shown in Figure 4.1 and the network diagram for the change from baseline in HAQ-DI is shown in Figure 4.2.

The fixed effect NMA results for PsARC response between 12 and 16 weeks are shown in Table 4.10. These show that the estimated probability of achieving a PsARC response was [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w compared to [redacted] for placebo, both ixekizumab results were significantly greater than placebo. However, the probability of a PsARC response with ixekizumab 80 mg was [redacted] than for all other treatments except [redacted]. [redacted] had the greatest probability of a PsARC response at [redacted] and [redacted] respectively. Results using 16-week ixekizumab results were similar with an estimated probability of a PsARC response of [redacted] (95% credible interval (CrI) [redacted]) for ixekizumab 80 mg q2w and [redacted] (95% CrI [redacted]) for ixekizumab 80 mg q4w.

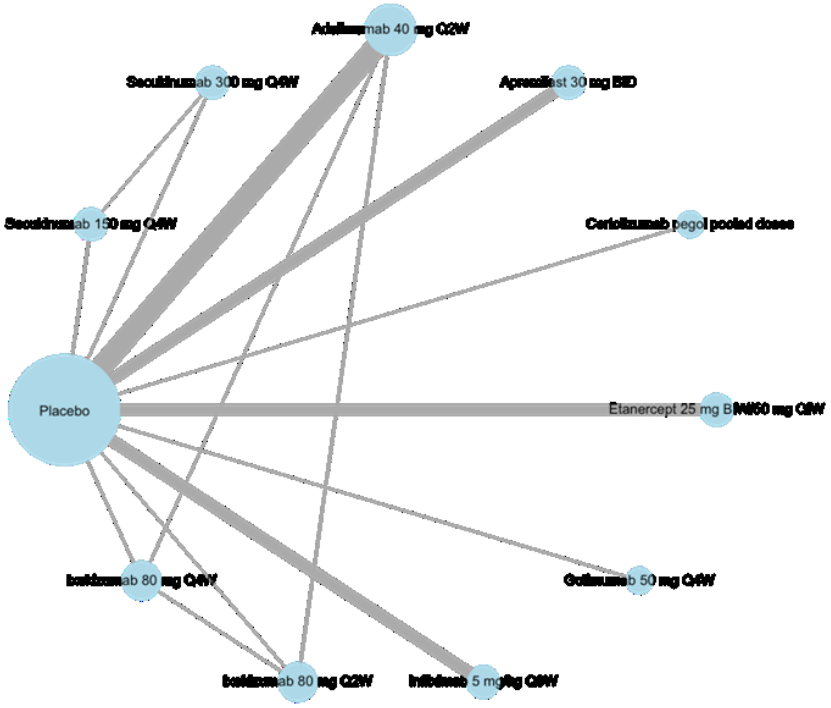
Table 4.9: Trials included in NMA for the bDMARD-naïve population

Trial	First author, year	Treatment arm	Time (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
ADEPT	Mease 2005[36]	Adalimumab 40 mg q2w	12	Yes	Yes	Yes	Yes	No	Yes
ADEPT	Mease 2005[36]	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Secukinumab 150 mg q4w	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Secukinumab 300 mg q4w	12	Yes	Yes	Yes	Yes	No	Yes
Genovese 2007	Genovese 2007[38]	Adalimumab 40 mg q2w	12	Yes	No	No	No	No	Yes
Genovese 2007	Genovese 2007[38]	Placebo	12	Yes	No	No	No	No	Yes
GO-REVEAL	Kavanaugh 2009[39]	Golimumab 50 mg q4w	14	Yes	Yes	Yes	Yes	No	Yes
GO-REVEAL	Kavanaugh 2009[39]	Placebo	14	Yes	Yes	Yes	Yes	No	Yes
IMPACT	Antoni 2005[40]	Infliximab 5 mg/kg q8w	16	Yes	Yes	Yes	Yes	No	Yes
IMPACT	Antoni 2005[40]	Placebo	16	Yes	Yes	Yes	Yes	No	Yes
IMPACT 2	Antoni 2005[41]	Infliximab 5 mg/kg q8w	14	Yes	Yes	Yes	Yes	No	Yes
IMPACT 2	Antoni 2005[41]	Placebo	14	Yes	Yes	Yes	Yes	No	Yes
Mease 2000	Mease 2000[42]	Etanercept 25 mg biw/50 mg qiw	12	Yes	Yes	Yes	No	No	Yes
Mease 2000	Mease 2000[42]	Placebo	12	Yes	Yes	Yes	No	No	Yes
Mease 2004	Mease 2004[43]	Etanercept 25 mg biw/50 mg qiw	12	Yes	No	No	No	No	Yes
Mease 2004	Mease 2004[43]	Placebo	12	Yes	No	No	No	No	Yes
OPAL-BROADEN	Mease 2016[44]	Adalimumab 40 mg q2w	12	No	No	Yes	No	No	Yes
OPAL-BROADEN	Mease 2016[44]	Placebo	12	No	No	Yes	No	No	Yes
PALACE 1*	Kavanaugh 2014[45]	Apremilast 30 mg bid	16	Yes	Yes	Yes	No	No	Yes
PALACE 1*	Kavanaugh 2014[45]	Placebo	16	Yes	Yes	Yes	No	No	Yes
PALACE 2*	Cutolo 2016[46]	Apremilast 30 mg bid	16	Yes	Yes	Yes	No	No	Yes

Trial	First author, year	Treatment arm	Time (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
PALACE 2*	Cutolo 2016[46]	Placebo	16	Yes	Yes	Yes	No	No	Yes
PALACE 3	Edwards 2016[47]	Apremilast 30 mg bid	16	No	Yes	Yes	No	No	Yes
PALACE 3	Edwards 2016[47]	Placebo	16	No	Yes	Yes	No	No	Yes
RAPID-PsA*	Mease 2014[48]	Certolizumab pegol pooled doses	12	Yes	Yes	Yes	Yes	No	No
RAPID-PsA*	Mease 2014[48]	Placebo	12	Yes	Yes	Yes	Yes	No	No
SPIRIT-P1	Eli Lilly and Company[49, 50]	Adalimumab 40 mg q2w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q2w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q4w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Placebo	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Adalimumab 40 mg q2w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q2w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Ixekizumab 80 mg q4w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P1	Eli Lilly and Company[49, 50]	Placebo	16	Yes	No	Yes	Yes	Yes	Yes

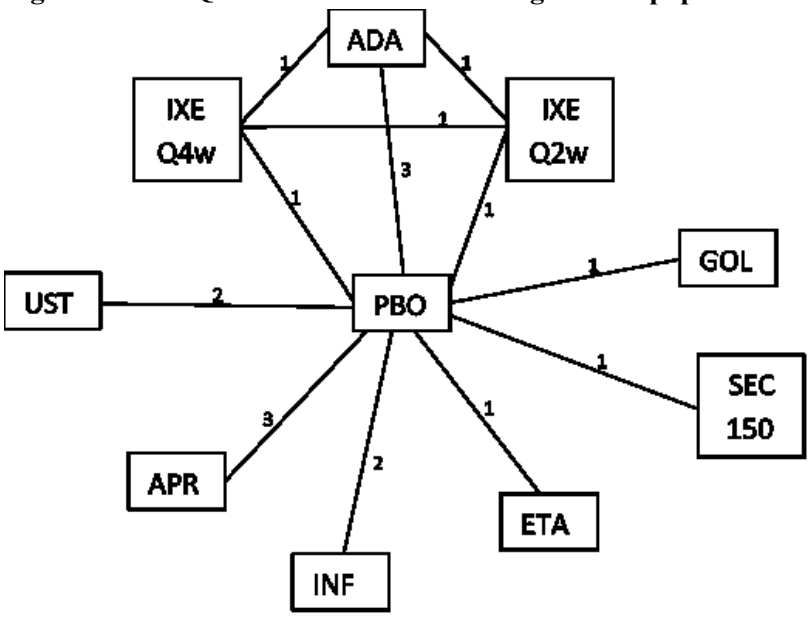
Source: Based on Table 20 of the CS[1]
Footnote: * Outcomes were not reported for bDMARD-naive subgroup at the response assessment time point specified in NICE guidance therefore overall population data are used
bDMARD = biologic disease-modifying anti-rheumatic drug; bid = twice daily; biw = twice weekly; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; kg = kilogram; mg = milligram; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; qiw = once weekly

Figure 4.1: PsARC and PASI network for the biologic-naïve population



Source: Based on Figure 7 of the CS[1]
bid = twice daily; CS = company submission; kg = kilogram; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; qiw = once weekly
Circle size is proportional to the number of patients per treatment, line width is proportional to the number of studies per pairwise comparison of treatments.

Figure 4.2: HAQ-DI network for the biologic-naïve population



Source: Based on Figure 4 of the CS[1]
ADA = adalimumab; APR = apremilast; ETA = etanercept; GOL = golimumab; INF = infliximab; IXE = ixekizumab; PBO = placebo; q2w = once every two weeks; q4w = once every four weeks; SEC = secukinumab; UST = ustekinumab

Table 4.10: PsARC response for the biologic-naïve population

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]
Apremilast 30 mg bid	[redacted]
Certolizumab pegol pooled doses	[redacted]
Etanercept 25 mg biw/50 mg qiw	[redacted]
Golimumab 50 mg q4w	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Secukinumab 150 mg q4w	[redacted]
Secukinumab 300 mg q4w	[redacted]

Source: Based on Table 21 of the of the CS[1]
bid = twice daily; biw = twice weekly; CrI = credible interval; CS = company submission; mg = milligram; PsARC = Psoriatic Arthritis Response Criteria; qiw = once weekly; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

The fixed effect NMA results for PASI response are shown in Table 4.11. These show that for ixekizumab 80 mg q2w the estimated probability of achieving a PASI 50 response was [redacted], [redacted] for PASI 75, [redacted] for PASI 90 and [redacted] for PASI 100. For ixekizumab 80 mg q4w these results were [redacted] for PASI 50, [redacted] for PASI 75, [redacted] for PASI 90 and [redacted] for PASI 100. [redacted] had the highest overall probability of achieving each PASI response. Results using 16-week ixekizumab results were similar.

Table 4.11: PASI response for the biologic-naïve population

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg q2w	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30 mg bid	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg biw/ 50 mg qiw	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab 50 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg q8w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	PASI 50 (95% CrI)	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Secukinumab 150 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 22 of the of the CS[1]
bid = twice daily; biw = twice weekly; CrI = credible interval; CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; qiw = once weekly; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

The fixed effect NMA results for ACR response are shown in Table 4.12. These show that for ixekizumab 80 mg q2w the estimated probability of achieving an ACR 20 response was [redacted] an ACR 50 response was [redacted] and an ACR 70 response was [redacted]. For ixekizumab 80 mg q4w, the estimated probability of achieving an ACR 20 response was [redacted] an ACR 50 response was [redacted] and an ACR 70 response was [redacted]. [redacted] had the highest overall probability of achieving each ACR response.

Table 4.12: ACR response for the biologic-naïve population

Treatment	ACR20 (95% CrI)	ACR50 (95% CrI)	ACR70 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg q2w	[redacted]	[redacted]	[redacted]
Apremilast 30 mg bid	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]
Etanercept 25 mg biw/ 50 mg qiw	[redacted]	[redacted]	[redacted]
Golimumab 50 mg q4w	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg q8w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg q4w	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg q4w	[redacted]	[redacted]	[redacted]

Source: Based on Table 8 of the response to request for clarification[25]
ACR = American College of Rheumatology; ACR 20 = At least 20% improvement in both tender and swollen joint counts; ACR 50 = At least 50% improvement in both tender and swollen joint counts; ACR 70 = At least 70% improvement in both tender and swollen joint counts; bid = twice daily; biw = twice weekly; CrI = credible interval; mg = milligram; qiw = once weekly; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

The fixed effect NMA results for the change from baseline in HAQ-DI score conditional on PsARC response are shown in Table 4.13. These show that in general patients who achieved a PsARC response had a greater reduction (improvement) in HAQ-DI compared to those patients who did not achieve a PsARC response. For PsARC responders, the mean change for ixekizumab 80 mg q2w was [redacted] and for ixekizumab 80 mg q4w it was [redacted] both of which were [redacted]. The most effective treatment was [redacted] with an estimated mean change from baseline in HAQ-DI of [redacted].

For PsARC non-responders, the treatments with the greatest improvement in HAQ-DI were [redacted] (mean change [redacted]) and [redacted] (mean change [redacted]) followed by [redacted] (mean change [redacted]). [redacted].

Table 4.13: Change from baseline in HAQ-DI

Treatment	Mean change from baseline – PsARC responders	95% CrI	Mean change from baseline – PsARC non-responders	95% CrI
Placebo	[redacted]	[redacted]	[redacted]	
Ixekizumab q4w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab q2w	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 23 of the of the CS[1]
CrI = credible interval; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks

4.3.2 Biologic-experienced population

The trials used in the NMA for the biologic-experienced population are summarised in Table 4.14. The network diagram of trial evidence for PsARC and PASI outcomes is shown in Figure 4.3 and the network including additional evidence for secukinumab and certolizumab pegol (pooled doses) is shown in Figure 4.4. These networks were smaller than for the biologic-naïve population, i.e. mostly containing five or fewer studies.

Table 4.14: Trials included in NMA for the biologic-experienced population

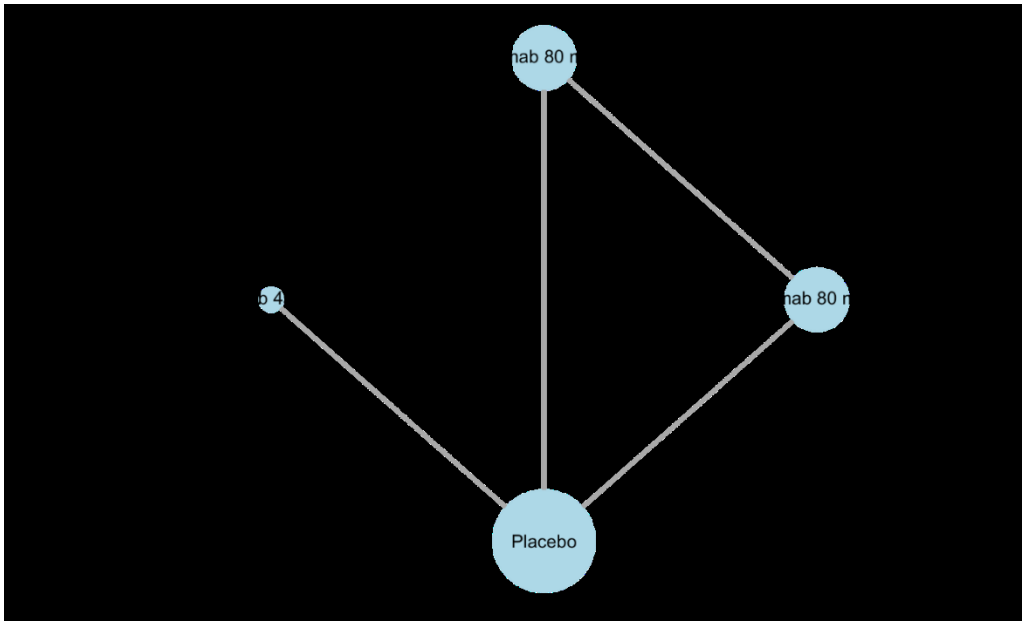
Trial	First author, year	Treatment arm	Timepoint (weeks)	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	HAQ-DI
PSUMMIT 2	Ritchlin 2014[51]	Placebo	24	Yes	No	Yes	No	No	Yes
PSUMMIT 2	Ritchlin 2014[51]	Ustekinumab 45 mg q12w	24	Yes	No	Yes	No	No	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q2w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q4w	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Placebo	12	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q2w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Ixekizumab 80 mg q4w	16	Yes	No	Yes	Yes	Yes	Yes
SPIRIT-P2	Nash 2017[32]	Placebo	16	Yes	No	Yes	Yes	Yes	Yes
FUTURE 2*	Thom 2016[37]	Placebo	12	Yes	Yes	Yes	Yes	No	Yes
FUTURE 2*	Thom 2016[37]	Secukinumab 300 mg q4w	12	Yes	Yes	Yes	Yes	No	Yes
RAPID-PsA	Mease 2014[48]	Certolizumab pegol pooled doses	12	Yes	Yes	Yes	Yes	No	No
RAPID-PsA	Mease 2014[48]	Placebo	12	Yes	Yes	Yes	Yes	No	No

Source: Based on Table 24 of the CS[1]

Footnote: * Outcomes were not reported for bDMARD-experienced subgroup at the response assessment time point specified in NICE guidance therefore overall population data are used

bid = twice daily; biw = twice weekly; CS = company submission; HAQ-DI = Health Assessment Questionnaire-Disability Index; kg = kilogram; mg = milligram; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly

Figure 4.3: PsARC and PASI network for the biologic-experienced population

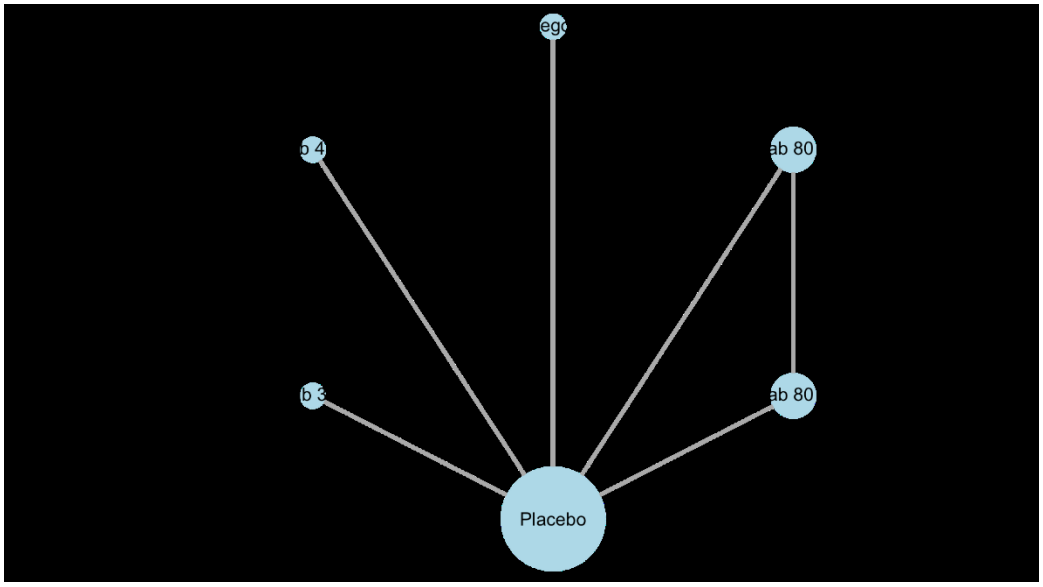


Source: Based on Figure 8 of the CS[1]

CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

Circle size is proportional to the number of patients per treatment, line width is proportional to the number of studies per pairwise comparison of treatments.

Figure 4.4: PsARC and PASI network for the biologic-experienced population, sensitivity analysis including secukinumab and certolizumab pegol pooled doses



Source: Based on Figure 9 of the CS[1]

CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

Circle size is proportional to the number of patients per treatment, line width is proportional to the number of studies per pairwise comparison of treatments.

The fixed effect NMA results for PsARC response are shown in Table 4.15 for the base-case analysis and Table 4.16 for the sensitivity analysis including overall population data for secukinumab and certolizumab pooled doses. These show that the estimated probabilities of achieving a PsARC response were [redacted] for ixekizumab 80 mg q2w [redacted] and ixekizumab 80 mg q4w [redacted] both of which were [redacted].

When overall population data (for both biologic-naïve and experienced patients) were included for secukinumab and certolizumab pooled doses the estimated proportions achieving a PsARC response were [redacted] for ixekizumab at [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w both of which were [redacted]. [redacted] had the greatest probability of PsARC response at [redacted]

Table 4.15: PsARC response for the biologic-experienced population

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]

Source: Based on Table 25 of the CS[1]
CS = company submission; mg = milligram; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

Table 4.16: PsARC response for the biologic-experienced population including secukinumab and certolizumab pegol (pooled doses)

Treatment	PsARC (95% CrI)
Placebo	[redacted]
Certolizumab pegol pooled doses	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Secukinumab 300 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]

Source: Based on Table 29 of the CS appendices[28]
Note: Posterior median (95% credible interval). Mixed biologic naive and experienced population for the following treatments: Apremilast 30 mg bid, Certolizumab pegol pooled doses, Placebo, Secukinumab 150 mg q4w, Secukinumab 300 mg q4w
bid = twice daily; CrI = credible interval; CS = company submission; mg = milligram; PsARC =Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

The fixed effect NMA results for PASI response are shown in Table 4.17 for the base-case analysis and Table 4.18 for the sensitivity analysis including overall population data for secukinumab and certolizumab pooled doses. These show that the estimated probabilities of achieving each PASI response were [redacted] for ixekizumab 80 mg q2w than ixekizumab 80 mg q4w but overall [redacted] had the greatest estimated probability of each PASI response.

When overall population data (for both biologic-naïve and experienced patients) were included for secukinumab and certolizumab pooled doses, the treatment with the greatest probability of each PASI response was [redacted] followed by [redacted].

Table 4.17: PASI response for the biologic-experienced population

Treatment	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg q12w	[redacted]	[redacted]	[redacted]

Source: Based on Table 26 of the CS[1]
Note: PASI 50 data were not included in the dataset as it was not reported by these studies.
CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

Table 4.18: PASI response for the biologic-experienced population including secukinumab and certolizumab pegol (pooled doses)

Treatment	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg q12w	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg q12w	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 32 of the CS appendices[28]
bid = twice daily; CrI = credible interval; CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

The fixed effect NMA results for ACR response are shown in Table 4.19 These show that ixekizumab 80 mg q4w had the [redacted] of achieving an ACR 20 response [redacted] an ACR 50 response [redacted] and an ACR 70 response [redacted] which were [redacted] than the response with [redacted] but not [redacted] or [redacted]

Table 4.19: ACR response for the biologic-experienced population

Treatment	ACR 20	ACR 50	ACR 70
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg q12w	[redacted]	[redacted]	[redacted]

Source: Based on Table 9 of the response to request for clarification[25]
ACR = American College of Rheumatology; ACR 20 = At least 20% improvement in both tender and swollen joint counts; ACR 50 = At least 50% improvement in both tender and swollen joint counts; ACR 70 = At least 70% improvement in both tender and swollen joint counts; CrI = credible interval; CS = company submission; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

4.3.3 Adverse events

Additional NMAs of treatment-emergent adverse events (TEAE), serious adverse events (SAE) and discontinuation due to adverse events (DAE) were performed in response to the clarification letter and the results were provided in the clarification response [25].

NMA results for TEAE are shown in Table 4.20 and show that the estimated probabilities of a TEAE were [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w. Adalimumab 40 mg had the [redacted] of a TEAE at [redacted] and placebo the [redacted]

Table 4.20: Conditional probabilities of experiencing a TEAE

Treatment	TEAEs
Adalimumab 40 mg q2w	[redacted]
Certolizumab pegol pooled doses	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Placebo	[redacted]

Source: Based on Table 10 of the response to request for clarification[25]
CrI = credible interval; CS = company submission; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks; TEAE = treatment-emergent adverse event

NMA results for SAE are shown in Table 4.21 and show that the estimated probability of a SAE was [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w. Secukinumab 300 mg had the [redacted] of a SAE at [redacted] and golimumab 50 mg the [redacted] but for most treatments the SAE rate was [redacted].

Table 4.21: Conditional probabilities of experiencing a SAE

Treatment	SAEs
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]

Apremilast 30 mg bid	[redacted]
Certolizumab pegol pooled doses	[redacted]
Etanercept 25 mg biw/50 mg qiw	[redacted]
Golimumab 50 mg q4w	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Secukinumab 150 mg q4w	[redacted]
Secukinumab 300 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]
Ustekinumab 90 mg q12w	[redacted]
Source: Based on Table 11 of the response to request for clarification[25] bid = twice daily; biw = twice weekly; CS = company submission; kg = kilogram; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly; SAE = serious adverse event	

NMA results for DAE are shown in Table 4.22 and show that the estimated probabilities of discontinuing due to an AE were [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w. Certolizumab pegol (pooled doses) had the [redacted] and ustekinumab 45 mg [redacted]

Table 4.22: Conditional probabilities of experiencing a DAE

Treatment	DAEs
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]
Apremilast 30 mg bid	[redacted]
Certolizumab pegol pooled doses	[redacted]
Golimumab 50 mg q4w	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]
Ustekinumab 90 mg q12w	[redacted]
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]
Apremilast 30 mg bid	[redacted]
Source: Based on Table 12 of the response to request for clarification[25] bid = twice daily; biw = twice weekly; CS = company submission; DAE = discontinuation due to adverse event; kg = kilogram; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly	

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

- The NMA used standard Bayesian analysis methods as recommended in the NICE Decision Support Unit (DSU) Technical Support Documents 2.[35] The data and programs used for the PsARC, PASI and change in HAQ-DI were supplied by the company and checked by the ERG.

- Due to the small size of most networks and the fact that many edges only contained a single trial, fixed effect models were used in the submission and economic model. Results from random effects models were also supplied in the clarification response and reviewed by the ERG. The ERG considers the NMA analysis methods and the presentation of fixed effect results to be appropriate, given the small size of many of the networks and little difference in fit between fixed and random effects models.
- Additional NMA results were provided in the clarification response for other outcomes including ACR response and adverse events (treatment-emergent, serious and discontinuation due to adverse events). However, the ERG did not have the associated data so these NMA results could not be verified.
- The ERG could verify the results for the PsARC and PASI outcomes. However, for change in HAQ-DI for PsARC responders and non-responders the results from the NMA for ixekizumab q2w and q4w produced by the ERG did not match those provided by the company. Results for other treatments from the same model could be reproduced but not those for ixekizumab. As there was only one study providing input data for ixekizumab in the dataset provided by the company the model estimates should have been similar to the study estimates. For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data. For PsARC non-responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data.
- Potential limitations of the NMA analyses are:
  - The use of different timepoints, including 12, 14, 16, and 24 weeks although sensitivity analyses replacing ixekizumab week 12 data with week 16 data showed little impact on the results.
  - As stated in the CS, the networks may have contained undetectable heterogeneity and inconsistency which could not be evaluated in some of the smaller networks so the treatment effects from the fixed effects models may be too precise.
  - To include other key comparators (apremilast, secukinumab and certolizumab pegol), trial data were included for the full population (rather than only biologic-naïve or biologic-experienced). *"If prior biologic exposure is an effect modifier for these treatments, the NMA results will not be representative of the treatment effect in a pure biologic-naïve/experienced population"* (section 2.9.3 of the CS[1]).
  - As the NMA analyses are based on indirect comparisons they are a weaker source of evidence than direct treatment comparisons obtained within a RCT and need to be treated with caution given the potential for clinical and statistical heterogeneity.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As described in section 4.1.1, the ERG did not consider the company's explanation of cross-checking recall of their flawed RCT searches adequate. The company checked recall of their searches against included studies in SRs, NMAs and health technology assessments (HTAs) also picked up in the RCT searches. Specific searches for SRs, NMAs and HTAs were not carried out nor were searches of SR or HTA databases conducted.

Therefore, the ERG conducted independent rapid appraisal searches to retrieve systematic reviews, meta-analyses and HTAs, searching the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), KSR Evidence, and Embase (Ovid). The ERG screened the rapid appraisal results and checked included

studies against the company submission. Full details of the independent rapid appraisal are presented in Appendix 1.

The ERG identified eight relevant publications, including SLRs, NMA and HTA reports.[52-59] These were checked for relevant primary studies potentially missed in the CS. Screening the results of the rapid appraisal searches, the ERG did not identify any study missed in the CS. However, the ERG identified one randomised study (Atteneo et al. 2010[60]) which has been excluded at the full paper review stage and was labelled as excluded for "Study design".[28] As detailed in section 4.1.1, the ERG believes that the appropriate response to address the substantial errors in the CS searches would have been to repeat the corrected searches to ensure the submission was based on a robust systematic review search. It should be noted that no full search was conducted by the ERG due to the limited time available for the assessment, i.e. not identifying relevant studies in the rapid appraisal should not be seen as evidence of absence of relevant studies missed in the CS.

4.6 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for ixekizumab and its comparators in patients with PsA as per the NICE scope. The company presented direct evidence from two RCTs, SPIRIT-P1 and SPIRIT-P2 that compared ixekizumab to placebo in adults with PsA. No direct evidence was presented for ixekizumab in relation to any of the other comparators in the NICE scope.

SPIRIT-P1 was conducted in biological DMARD naïve patients whilst SPIRIT-P2 was conducted in those with experience of biological DMARDs. SPIRIT-P1 included 417 patients and SPIRIT-P2 363 patients and both were well conducted, multinational trials. Across the two trials approximately [redacted] of patients were from the UK. Both trials demonstrated superiority of ixekizumab in relation to placebo on outcomes of importance to patients such as ACR criteria and PSARC measures during the double-blind phase of the trial up to 24 weeks. The company also provided more limited evidence on the efficacy of ixekizumab in relation to placebo for a population reflective of NICE current guidance on use of bDMARDs.

In total, 456 patients have been exposed to ixekizumab across the two SPIRIT trials. Data on adverse events are presented in the CS for the 24-week double blind period of the two SPIRIT trials and for the extension period (up to week 52). In the double-blind treatment phase patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials. Adverse events across the two SPIRIT trials were mainly of mild or moderate severity. There were no deaths across the two trials in the double-blind periods. The proportion of patients who discontinued medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab and placebo groups. The most frequently reported AEs were infections which were comparable across groups. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials. The only direct safety comparisons, as for effectiveness comparisons, are between placebo and ixekizumab. However, SPIRIT-P1 has a reference adalimumab arm and it can be observed that occurrence of adverse events was similar in the adalimumab group to the ixekizumab groups although fewer of the adalimumab events appeared to be attributable to the drug.

Ixekizumab represents an additional option for PsA alongside the existing biologic treatments after two or more non-biological approaches have been tried. The need for additional options has been highlighted by patient and professional organisations. However, in order to be added to the options or indeed to be used preferentially over another agent, the comparable or superior performance of ixekizumab needs to be investigated through comparison with all of the relevant biological agents. In this submission, in the absence of trials directly comparing active treatments the company has

conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, PASI 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, ixekizumab [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted], with [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders and [redacted] were the most effect treatments.

There was less evidence for bMARD-experienced patients (fewer than five trials in most analyses) and ixekizumab was [redacted] ustekinumab for PsARC response. For PASI response, ustekinumab [redacted] ixekizumab.

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response [redacted]. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

A literature review was conducted to identify relevant cost effectiveness studies and HTA appraisals in psoriatic arthritis. Two separate strands of searching were conducted to identify: cost effectiveness models, and model inputs. All searches were presented in Appendix G.[28]

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission. For both strands, initial searches were reported for PubMed, Embase, Health Technology Assessment Database (HTA via Centre for Reviews and Dissemination (CRD)) and the Health Economic Evaluations Database (HEED via Wiley), and were undertaken in November 2014 (2000-2014). Update searches were reported for June 2017 (2000-2017). Additional update searches for both strands were also undertaken in Medline via Ovid. The database hosts were reported for all initial searches. The date the searches were conducted was provided, though the date span of the databases searched was not given for all searches. Website searches of 11 key HTA agencies were also performed. For these searches, date of initial search and update search was reported, together with search terms and Uniform Resource Locators (URLs).

Searches for cost effectiveness analysis review

A SLR was conducted to identify cost effectiveness evaluations. Strategies were presented in the submission appendices,[28] and further information was provided in the clarification response.[25]

PubMed, Medline, Embase and HTA searches included unreferenced costs and economic evaluation study design filters. Although the company stated that the NHS Economic Evaluation Database (NHS EED) was searched, the search results clearly indicated the resource had not been searched.

Extensive restriction to focus (RTF) was applied to the indexing within the cost facet for the cost effectiveness model (CEM) Embase and Medline searches, where only Major subject indexing headings were retrieved. Extensive use of RTF may be overly restrictive and impair sensitivity of the searches. Current best practice recommendations[61, 62] caution against use of RTF in more than two concepts, which may have impaired performance of the CS CEM search strategies.

Searches for model inputs

A SLR was conducted to identify health-related quality of life studies. PubMed, Medline, Embase and HTA searches included unreferenced filters to identify quality of life and utilities. Although the company stated that the NHS EED was searched, the search results clearly indicated the resource had not been searched.[1, 28]

The initial model input searches focussed on quality of life and HRQoL studies. When the model input searches were updated and re-run in 2017, additional terms for health utilities were added. The company's clarification response reported that the results of the update search were deduplicated against the initial search results using Endnote reference management software.[25]

Unfortunately, the additional utilities terms in the update searches included incorrect truncation. The company attempted to use Ovid truncation commands through the PubMed search for all free-text terms. It was also noted that several Ovid MeSH commands were reproduced in this PubMed search, therefore the relevant PubMed MeSH terms were not searched for. These truncation and MeSH errors were not found in the initial PubMed search for model inputs. Consequently, the ERG did not think the

PubMed update search worked as intended and would have been much improved by applying the correct database syntax for PubMed, in PubMed.

The model inputs searches in Embase showed that extensive RTF was applied to the Quality of life/HRQoL, cost, and UK/Europe components. The Medline model inputs searches showed that extensive RTF was applied to the Quality of life/HRQoL, and cost components. Extensive use of RTF may be overly restrictive and impair sensitivity of the searches. As noted with the CEM searches above, use of extensive RTF in more than two concepts may have impaired performance of the CS model input search strategies.

The inclusion criteria presented in Table 40 (page 152 of the CS appendices[28]) stated that languages other than English, French, German, Italian and Spanish would be excluded. As current best practice states that *'whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'*, the ERG was concerned about potential introduction of language bias.[63] The inclusion criteria for CEM studies published as abstracts was inconsistently applied between the initial review (2000-2014) and the update review (2014-2017). CEM abstracts were excluded from the initial review but were not excluded from the update review.

All the cost effectiveness searches were limited by date from 2000-2017/06. Potentially studies may have been missed due to the date restriction but the impact of this is difficult to assess.

Website searches of 11 key HTA agencies were also performed. For these searches, date of initial search and update search, search terms, number of records retrieved and URLs were all reported in the clarification response.[64]

ERG comment:

- The ERG noted the for both CEM and model inputs Medline and Embase searches used extensive focused MeSH and Emtree indexing terms which may have adversely affect recall of the search strategies. When RTF is applied to subject indexing terms, only Major subject indexing headings are retrieved. The ERG considered the extensive use of RTF overly restrictive and potentially impairing recall of possibly relevant references and did not consider the extensive implementation of RTF in the Embase and Medline searches adequately sensitive for this systematic review.
- The CEM and model inputs searches of the HTA database involved application of cost and HRQoL/utilities filters respectively. The ERG considered this inappropriate and unnecessary, as an HTA search for psoriatic arthritis retrieved only 36 records (date of search: 22.3.18). As the submission stated health technology assessments were of interest, it was not necessary to limit a database solely comprising of HTAs in this way.
- The CEM search of the HEED database included application of cost filter terms. As HEED was a database specifically of economic evaluations, it was inappropriate and unnecessary for the company to restrict the search with terms for costs and health economics. The HEED search for model inputs included only psoriatic arthritis and retrieved 42 records. Therefore, it would have preferable and quicker to use that population-only search for the CEM review as well.
- The ERG thought it was possible potentially relevant economic evaluations might have been overlooked by failing to conduct a search of NHS EED. An ERG test search of NHS EED retrieved 17 unique economic studies not retrieved by the company's HTA search (see Appendix 1). This omission was of particular concern in light of the strategy restrictions applied

to the HTA and HEED searches. It is possible that relevant evidence may have been missed as a consequence.

- The CEM PubMed search contained a typographical error in the MeSH indexing for Markov Chains, which impaired retrieval of references reporting use of Markov Chains analysis.
- Typographical errors, incorrect truncation and database syntax mistakes were noted in several of the cost effectiveness PubMed searches.

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.1.

Table 5.1: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with PsA	Studies with paediatric-only populations were excluded.
Intervention	Conventional systemic DMARD (methotrexate, sulfasalazine, gold salts and leflunomide)† Novel targeted synthetic DMARDs (apremilast and tofacitinib) Biologic DMARD (adalimumab, etanercept, certolizumab pegol, golimumab, infliximab, brodalumab†, ustekinumab and secukinumab‡)	Treatments not listed in the inclusion criteria Updated review: treatments not listed and conventional systemic DMARDs
Comparator	Any comparator	None
Outcomes	QALY-based outcome measure	CEMs without outcome measures based on QALYs
Study design	CEMs, HTA appraisals of relevant CEMs. In the original review, only full publications for studies focusing on CEMs were included. The updated review did not exclude CEMs that were published as abstracts.	Languages other than English, French, German, Italian and Spanish were excluded. Studies published before January 1st 2000 were excluded

Source: Based on Table 40 of Appendix J of the CS appendices[28]
Footnote: † Conventional systemic DMARDs and brodalumab were not treatments of interest in the updated review. ‡ Secukinumab was added as a treatment of interest in the updated review.
CEM = cost effectiveness model; CS = company submission, DMARD = disease-modifying anti-rheumatic drug, HTA = health technology assessment; QALY = quality-adjusted life year

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. However, the ERG disagrees that searching for QALY-based outcomes only does fully capture the search for HRQoL and cost and resource use studies.

5.1.3 Included/excluded studies in the cost effectiveness review

The searches related to CEA resulted in six peer-reviewed CEM publications and two CEMs published in abstract form. Furthermore, seven HTA appraisals from the NICE website and another six submissions to other HTA agencies (All Wales Medicines Strategy Group (AWMSG), Canadian Agency for Drugs and Technologies in Health (CADTH), the Australian Pharmaceutical Benefits Advisory Committee (PBAC), Scottish Medicines Consortium (SMC), and the Swedish Dental and Pharmaceutical Benefits Board (TLV)) were identified.

In total, 37 studies reporting utility values for patients with PsA were identified in the initial review and 13 additional studies were identified in the updated review. Seven studies reported relevant EQ-5D utility values.[65-71]

The searches for costs and resource use studies resulted in two published studies in the initial review[8, 72] and three additional studies (all abstracts)[73-75] were identified in the updated review. Methodology, results and applicability of these studies are provided in appendix I of the CS.

ERG comment: The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria. The company conducted a *de novo* economic analysis and used the second revision of the York model as its foundation, in accordance with several of the identified CEMs.

5.1.4 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness studies but no specific conclusion was formulated. No specific conclusion has been formulated for the studies included in the resource use and costs review.

ERG comment: Eligibility criteria were suitable for the SLR on cost effectiveness studies. However, outcome criteria were considered not specific enough to capture all relevant HRQoL as well as cost and resource use studies. The company based their *de novo* analysis on the approach of the revised York model.

The cost effectiveness searches in the company's clarification response were all documented and reproducible. However, there were a number of inconsistencies and mistakes which impaired performance of the cost effectiveness and model input searches.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Markov state-transition model using a treatment sequencing approach.	To assess the cost effectiveness of ixekizumab versus other recommended treatments in the treatment of PsA.	Chapter 3.2
States and events	Health states include: - Trial period - Continued treatment period - BSC - Death These health states are based on response assessed using the PsARC (transition from trial period health state to continued treatment health state), and utilities and costs are valued based on corresponding HAQ-DI and PASI scores.	The model structure is similar to that of the York model[13] which has been used in subsequent NICE submissions.	Chapter 3.2.2

	Approach	Source/Justification	Signpost (location in CS)
Comparators	B/tsDMARDs. B/tsDMARD-naïve patient population: - Adalimumab - Apremilast - Certolizumab pegol - Etanercept - Golimumab - Infliximab - Secukinumab B/tsDMARD-experienced patient population: - Ustekinumab - BSC	These comparators were recommended by NICE. Certolizumab pegol and secukinumab in the b/tsDMARD-experienced population were not considered in the company's base-case, which was justified based on the absence of studies on these treatments in that specific population.	Chapter 3.2.3
Population	Six subgroups are analysed separately. Patients are divided into three concomitant psoriasis severity levels and in each psoriasis severity level the following prior treatment experience is considered: - b/tsDMARD-naïve patients - b/tsDMARD-experienced patients	The licence wording of "one or more DMARD therapies" covers a broader patient population than the patient populations that have met NICE criteria for eligibility for b/tsDMARD therapy, i.e. patients who have not responded adequately to at least 2 cDMARDs.	Chapter 3.2.1
Treatment effectiveness	Based on PsARC response the proportion of responders to treatment (eligible for treatment continuation) is determined. Patients who do not achieve response enter the trial period for the next active treatment in the sequence or BSC (always last treatment in the sequence). Treatment discontinuation risk due to any cause is assumed to be treatment independent and constant over time. Upon discontinuation, patients revert to their baseline HAQ-DI and PASI scores. Change from baseline HAQ-DI is treatment specific and conditional on PsARC response.	In line with previous TAs.	Chapter 3.3
Adverse events	The impact of adverse events of treatments on HRQoL and costs are not explicitly incorporated in the model.	It was assumed that adverse events were captured only to the extent that they affect the initial response and the long-term withdrawal rates.	Chapter 3.4.4 and 3.5.3

	Approach	Source/Justification	Signpost (location in CS)
Health related QoL	Health utilities were assessed from patients in the SPIRIT trials using the EQ-5D-5L and were mapped to the EQ-5D-3L. The utility data subsequently informed a utility algorithm corresponding to HAQ-DI and PASI scores.	In line with previous TAs.	Chapter 3.4.5
Resource utilisation and costs	The following costs and resource use categories were considered in the company cost effectiveness model: - Acquisition costs of b/tsDMARDs - Treatment administration - Monitoring and tests - Disease management: HAQ-DI and PASI related costs	In line with recent NICE TAs of treatments in PsA. Costs were sourced from the NHS[76], MIMS[77], PSSRU[78] and published literature.	Chapter 3.5
Discount rates	Discount of 3.5% for utilities and costs	As per NICE reference case[79]	Chapter 3.2.2
Subgroups	The six subgroups considered in the economic analysis were stratified by prior treatment with b/tsDMARDs and the presence and extent of concomitant psoriasis. Severity thresholds for psoriasis were: - No psoriasis - Mild-to-moderate psoriasis: BSA≥3% and PASI≤10 - Moderate-to-severe psoriasis: BSA>3% and PASI>10	In line with NICE scope.	Chapter 3.9
Sensitivity analysis	Both DSA and PSA are performed, as well as scenario analyses.		Chapter 3.8

BSA = body surface area; BSC = best supportive care; CS = company submission; DMARD = disease-modifying anti-rheumatic drug; bDMARD = biologic disease-modifying anti-rheumatic drug; b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; DSA = deterministic sensitivity analysis; HAQ-DI = Health Assessment Questionnaire-Disability Index; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PSA = probabilistic sensitivity analysis; PsARC = Psoriatic Arthritis Response Criteria; PSSRU = Personal Social Services Research Unit; TA = technology appraisal

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: 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	Yes	
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	Not all possible treatment sequences were considered. Not all comparators were included in the base-case analyses for b/tsDMARD-experienced patients (excluded: certolizumab pegol, secukinumab). The costs of methotrexate as a concomitant treatment were not included in any of the analyses while it is stated in the scope.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	
Synthesis of evidence in outcomes	Systematic review	Partly	SLR and NMA, but not on all relevant outcomes as identified in the scope.
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	

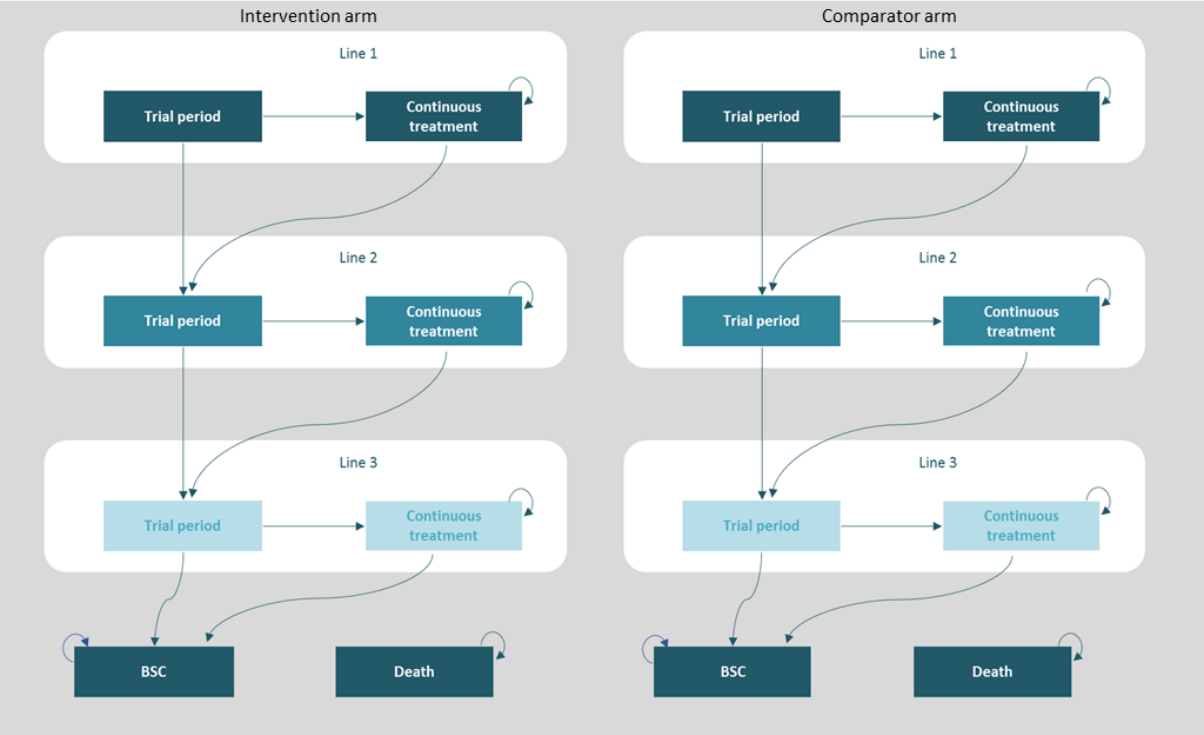
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Yes	

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review

5.2.2 Model structure

The company developed a de novo Markov state-transition model in Visual Basic for Applications (VBA) with a Microsoft Excel interface. The model structure was mainly informed by the 2016 update of the York model (so-called "revised York model") and included treatment sequences, i.e. patients could receive multiple treatments in sequences (Figure 5.1).[26] The choice of this model structure was informed by expert opinions, as stated in the company submission. The original version of the York model (2011) was used for the TAs of ustekinumab[21] and golimumab[14] and the 2016 update of the York model was used for the multiple TA of secukinumab and certolizumab pegol.[26] Treatment effectiveness was determined by PsARC response, PASI score, and HAQ-DI score. PsARC was used to determine treatment response in the base-case analysis while PASI (in the presence of concomitant psoriasis) and HAQ-DI scores were used to determine resource use and costs, and health state utility values. In the current assessment, additional PASI response thresholds (PASI 50, PASI 90 and PASI 100) were added to the 2016 version of the York model. These alternative PASI response thresholds are used in sensitivity analyses in which alternative response criteria, based on a combination of PASI 50, PASI 90, or PASI 100 response and PsARC response, are used.

Figure 5.1: Model structure



Source: Based on Figure 10 of the CS[1]
Note: Arrows denote possible transitions. Transition to death is possible from all treatment states but not presented for simplicity.
BSC = best supportive care

The model structure consisted of the following treatment states: the trial period, the continued treatment period, BSC, and death. Patients entered the model in the first trial period. Trial periods were composed of tunnel states (i.e. 3-6 tunnel states) and lasted for 12-24 weeks, depending on the treatment received. From the start of the trial period, patients experienced a PASI and HAQ-DI score improvement based on PsARC response (theoretically assessed at the end of the trial period) and the treatment received. At the end of the trial period, PsARC response was assessed.

Patients responding to treatment, based on PsARC response, transited to the continued treatment period and maintained their abovementioned improvement in PASI and HAQ-DI scores. PASI and HAQ-DI scores remained constant during the continued treatment period until treatment discontinuation. Non-responders at the end of the trial period discontinued treatment. Upon treatment discontinuation, patients reverted to their baseline PASI and HAQ-DI scores and switched to the next active treatment in the sequence (i.e. next trial period) or BSC. BSC was the last treatment option after patients had been treated with all active treatments in the sequence. BSC was composed of a mix of cDMARDs and palliative care but no further detail on treatments composing BSC was provided. The effectiveness of BSC was assumed to be equal to the effectiveness of placebo.

Patients could die in all health states. Mortality rates based on the general UK population were adjusted using a standardised mortality ratio (SMR) of 1.36 to represent the excess mortality associated with PsA.[6] The cycle length was one month and no half-cycle correction was applied because the cycle length was considered to be sufficiently short. The cost effectiveness model does not include the HRQoL and economic consequences of adverse events.

ERG comment: The main concerns of the ERG related to the model structure are: a) the use of the PsARC response to determine the transition to the treatment continuation state, b) the instantaneous PASI and HAQ-DI improvement in the trial period states, c) the assumption that psoriasis does not progress over time, d) the non-inclusion of adverse events in the cost effectiveness model, e) the unclear definition of BSC, f) the cycle length of the model.

a) The main concern of the ERG concerning the model structure is the use of PsARC response to determine treatment effectiveness, for two reasons:
   Firstly, the ERG acknowledges that this measure is commonly used to assess response in the PsA patient population. However, in health state transition models, the use of a relative measure to define health states may violate the assumption that patients in a health state are similar in terms of HRQoL and resource use consumption. In order to explore whether this assumption was violated in the current assessment, the ERG requested of the company to show that patients achieving (or not) PsARC response were homogeneous in terms of disease severity, utility gain, and resource use and costs.[80] The company provided an overview of baseline patient characteristics for PsARC responders and non-responders at 12 weeks but this did not allow for investigation of whether these patient populations are homogenous after (non-)response. Hence, the treatment continuation state may potentially be populated with a heterogeneous patient population.
   Secondly, the use of PsARC response only to determine treatment continuation may not be representative of UK clinical practice. In peripheral spondyloarthritis, patients achieving PASI 75 response but no PsARC response may continue treatment based on dermatologist assessment. Consequently, the use of PsARC response only to determine treatment continuation does potentially underestimate the proportion of patients continuing treatment after the trial period.[81] The company incorporated a scenario in which treatment continuation was based on the probability of achieving both PsARC and PASI 75 response. This approach is also not representative of UK clinical practice and the estimated probabilities used in this scenario were not obtained from an NMA (rather calculation based on the correlation between PsARC and PASI).
   Despite the abovementioned issues, the company approach of using the PsARC response only to determine treatment continuation is consistent with the 2016 York model. Moreover, both approaches (using PsARC response only or a combination of PsARC and PASI 75 responses) are likely not to be completely representative of UK clinical practice and there is probably no better alternative evidence to estimate the probabilities of continuing treatment. Therefore, the ERG used the same approach as the company in its base-case analysis, i.e. treatment continuation is based on PsARC response only.
b) The company incorporated an instantaneous PASI and HAQ-DI improvement at the beginning of the trial period (i.e. before PsARC response assessment) without justifying why this would be the most appropriate assumption.[1, 25, 28] This assumption potentially increases health benefits obtained with treatment with long trial periods, which are apremilast (16 weeks), ustekinumab (24 weeks) and secukinumab (16 weeks).
c) The company assumed no changes in baseline psoriasis over time. This assumption is in line with previous assessments in psoriasis and psoriatic arthritis.[15, 16, 26] However, the company acknowledges that psoriasis is a heterogeneous disease with an unpredictable natural history and that there is no evidence to support this assumption.[25] The company further explains that if psoriasis would progress over time, this would likely happen in the BSC state, which would potentially increase the cost effectiveness of treatments with high PsARC response rate. The ERG agrees with this claim.
d) The HRQoL and economic consequences of adverse events were not included in the cost effectiveness model which leads to biased estimates of HRQoL and economic consequences of

treatments for PsA in the current assessment. The ERG considers that adverse events should be incorporated in the cost effectiveness model since discontinuation rates due to adverse events differ between treatments. More details on this issue are provided in section 5.2.7.

e) Since BSC was not accurately described in the CS, the ERG requested the company to provide a definition of BSC. The company responded that BSC was composed of *"physiotherapy, NSAIDs, local glucocorticoid injections and cDMARDs"*, based on UK clinical expert opinion.[25] No details were provided on the expert opinion elicitation methods and results, and the company did not provide the proportion of patients who may receive each of the above-mentioned treatment as part of BSC. Hence, the ERG is not able to assess whether BSC is representative of the UK context, and whether the effectiveness and the costs associated with BSC in the cost effectiveness model are valid.

f) The company used a cycle length of one month while the trial periods of treatments vary between 12 and 24 weeks, which are modelled as tunnel states (three to six tunnel states). Hence, trial periods are modelled as periods of 3 to 6 months (13 to 26 weeks). Health benefits associated with the trial periods are thus potentially overestimated and resources used are distributed over a longer period of time than would be the case in clinical practice.

5.2.3 Population

Ixekizumab, with or without methotrexate, was granted marketing authorisation by the EMA for the treatment of active PsA in adults who have responded inadequately to, or who are intolerant to, one or more DMARD therapies.[34] This population is broader than the population of interest for the current decision problem, as defined by NICE guidance. According to the NICE guidance, only patients with an inadequate response to at least two cDMARDs become eligible for b/tsDMARDs in the UK.[13] However, the SPIRIT-P1 trial included patients who did not receive cDMARDs and SPIRIT-P2 included patients who were treated with one or more cDMARDs.

The cost effectiveness model discriminates between six subgroups based on the presence and severity of concomitant psoriasis and whether patients had been treated with another b/tsDMARD before ixekizumab. The severity of psoriasis was defined as follows: a) no psoriasis, b) mild-to-moderate psoriasis (BSA≥3% and PASI≤10), and c) moderate-to-severe psoriasis (BSA>3% and PASI>10). Table 5.4 presents the baseline PASI and HAQ-DI scores of each subgroup. The baseline age of the population was 51 years.

Table 5.4: Baseline PASI and HAQ-DI scores for each subgroup included in the cost effectiveness model

	b/tsDMARD-naive	b/tsDMARD-experienced
No psoriasis	Baseline PASI = 0 Baseline HAQ-DI = 1.17	Baseline PASI = 0 Baseline HAQ-DI =1.39
Mild-to-moderate psoriasis	Baseline PASI = 3.9 Baseline HAQ-DI = 1.17	Baseline PASI = 3.7 Baseline HAQ-DI = 1.2
Moderate-to-severe psoriasis	Baseline PASI = 20.4 Baseline HAQ-DI = 1.19	Baseline PASI = 23.4 Baseline HAQ-DI = 1.16

Source: Based on Table 36 in the CS[1], SPIRIT-P1 CSR[50] and SPIRIT-P2 CSR[33]
b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; CS = company submission; CSR = clinical study report, HAQ-DI = Health Assessment Questionnaire-Disability Index; PASI = Psoriasis Area and Severity Index

ERG comment: Issues concerning the patient population included in the current assessment are: a) the representativeness of the patient population from the SPIRIT trial programme for the current decision

problem, b) the choice of cut-off values to determine psoriasis severity, c) the different baseline PASI scores compared to the previous TA.

a) Concerns on the patient representativeness of the patient population from the SPIRIT trial programme and its impact on the relevance and validity of the NMA results to the UK context are expressed in section 4.2.2 of this report. Since the same patient characteristics and the NMA results have been used directly in the cost effectiveness model, these concerns also apply to the cost effectiveness analysis (and results) performed by the company.
b) The subgroups based on the presence and severity of psoriasis were only briefly described in the CS. The ERG requested more detail on the definitions of these subgroups in its clarification letter.[80] The company responded that the definitions used to derive these three subpopulations were based on the definitions used for the SPIRIT trials.[25] "No psoriasis" meant that "*the joint symptoms of these patients may be recognised as psoriatic arthritis due to family history or personal history of psoriasis or psoriatic nail symptoms.*" The ERG presumes that "no psoriasis" patients were the ones without psoriasis or with a BSA<10% and/or static physician's global assessment (sPGA) <3. Mild-to-moderate psoriasis was defined as PASI<12, sPGA≥3 and BSA≥10%, and moderate-to-severe psoriasis as PASI≥12 and sPGA≥3 and BSA≥10%. These definitions, based on the SPIRIT trials, do not align with the York model in which mild-to-moderate psoriasis is defined as a BSA≥3% and PASI score ≤10, and moderate-to-severe psoriasis as a BSA≥3% and PASI>10. Baseline PASI scores when using each definition are provided in Table 5.5. The York model definitions lead to a higher baseline PASI score in the mild-to-moderate psoriasis subgroup but to a lower baseline PASI score in the moderate-to-severe psoriasis subgroup.[25]

Table 5.5: Comparison of mean PASI scores (SD) at baseline in model subgroups

Source	b/tsDMARD-naive		b/tsDMARD-experienced	
	Mild-to-moderate psoriasis	Moderate-to-severe psoriasis	Mild-to-moderate psoriasis	Moderate-to-severe psoriasis
SPIRIT trial definition	3.9 (3.2)	20.4 (6.9)	3.7 (3.3)	20.4 (10.0)
York model definition	4.5 (2.6)	18.3 (7.1)	4.2 (2.5)	20.0 (10.0)

Source: Based on Table 45 of the response to the request for clarification[25]
b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; PASI = Psoriasis Area and Severity Index; SD = standard deviation

c) The ERG requested that the company explain the differences in baseline PASI scores between the current and previous appraisals because baseline PASI scores in the current assessment are noticeably higher in the moderate-to-severe psoriasis subgroup than in the 2016 York model.[26] As emphasised by the company, higher baseline PASI scores lead to higher absolute PASI reduction when achieving PASI 75 response.[25] The company did not provide an explanation for these discrepancies but stated that the influence of the baseline PASI score on the cost effectiveness results is expected to be minimal, without providing evidence to support this statement. The ERG used baseline PASI scores from the revised York model in a scenario analysis to assess the impact of this assumption on the results. Baseline PASI scores in that appraisal were 7.3 for the mild-to-moderate psoriasis subgroup and 12.5 for the moderate-to-severe psoriasis subgroup.[26]

5.2.4 Interventions and comparators

The cost effectiveness of ixekizumab, once every two weeks (q2w) or once every four weeks (q4w), is assessed against each b/tsDMARDs recommended by NICE for patients with PsA whose disease has not responded to two prior cDMARDs. All treatment sequences of the intervention began with ixekizumab while comparator treatment sequences began with another b/tsDMARDs. Dosing regimens and stopping rules (determining the length of the trial period) of each treatment are based on NICE guidance (Table 5.6). The length of the trial period for ixekizumab was set to 12 weeks in the company base-case analysis while the SmPC for ixekizumab advises that treatment should be discontinued in patients who did not show response after 16 to 20 weeks of treatment.[34] The company justified the use of the 12-week trial period stating that this was done to align with the stopping rules of other TNF-alpha inhibitors, however, the ERG is concerned that this may not be appropriate. The company provided results of a scenario analysis using a 16-week trial period for ixekizumab, which, in most cases, produced ICERs slightly less favourable for ixekizumab.

A treatment sequencing approach was adopted by the company. Hence, patients switched to a subsequent b/tsDMARD when they stopped responding to their first active treatment in the model. The company states that this approach is reflective of clinical practice in the UK and was adopted in the 2016 York model.[26] Tables 39 and 40 of the CS present the different treatment sequences included in the cost effectiveness model for the b/tsDMARD-naïve and b/tsDMARD-experienced subgroups, stratified by psoriasis severity.[1] Treatment sequences for b/tsDMARD-naïve patients were composed of two b/tsDMARD treatments, ustekinumab being the second-line treatment in all sequences, and then BSC while treatment sequences for b/tsDMARDs-experienced included one b/tsDMARD treatment before BSC. The CS does not describe how the treatment sequences have been selected.

Table 5.6: Treatments doses and length of trial period

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
Ixekizumab q2w	If patient has concomitant moderate-to-severe psoriasis, 80 mg every two weeks for 12 weeks, following a 160 mg starting dose in the trial period; thereafter 80 mg every 4 weeks	NA	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	Base case: 12 Sensitivity analysis: 16	8	13	18
Ixekizumab q4w	80 mg every four weeks, following a 160 mg starting dose.	NA	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.	Base case: 12 Sensitivity analysis: 16	5	13	15
Adalimumab	Injection, 40 mg administered every other week	Adalimumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[16]	Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period[82]	12	6	26	26
Apremilast	Oral tablet, 30 mg twice daily after an initial titration schedule: Day 1: 10 mg qd; Day 2: 10 mg bid; Day 3: 10 mg AM, 20 mg	Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate	If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered[83]	16	223	730	725

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
	PM; Day 4: 20 mg biw; Day 5: 20 mg AM, 30 mg PM	response using the PsARC[15]					
Certolizumab pegol 200 mg q2w	Injection, loading dose 40 mg at weeks 0,2 and 4; 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered	Certolizumab pegol should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[13]	Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment[84]	12	10	26	29
Etanercept 50 mg qiw	Injection, 50mg once weekly	Etanercept should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[16]	Treatment should be discontinued in patients who show no response after 12 weeks[85]	12	12	52	52
Golimumab 50mg	Injection, 50 mg once a month	Golimumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[14]	Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within 12 to 14 weeks of treatment (after 3-4 doses)[86]	12	3	12	12
Infliximab	By intravenous infusion, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks	Infliximab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks[16]	If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given[87]	12	3	6.5	8
Ustekinumab 45 mg	Injection, body-weight <100 kg, initially 45 mg, then 45 mg	Ustekinumab should be discontinued in people whose PsA has	Consideration should be given to discontinuing treatment in patients who have shown no	24	3	4.33	5

Treatment	Dosing instructions	Stopping rule - NICE	Stopping rule - SmPC	Model trial period (weeks)	Trial period doses	Annual doses	Year 1 doses
	4 weeks after initial dose, then 45 mg every 12 weeks	not shown an adequate response using the PsARC at 24 weeks[21]	response up to 28 weeks of treatment[85]				
Secukinumab 150 mg	Injection of 150mg at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4 for b/tsDMARD-naïve patients without concomitant moderate-to-severe psoriasis	Secukinumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 16 weeks[13]	Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment[88]	16	7	13	16
Secukinumab 300 mg	Dose of 300mg (two 150 mg injections) at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4 for TNF-naïve patients with concomitant moderate-to-severe psoriasis or patients with prior exposure to TNF-alpha inhibitors	Secukinumab should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 16 weeks[13]	Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment[88]	16	7	13	16

Source: Based on Table 38 of the CS[1]
biw = twice weekly; b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; CS = company submission; kg = kilogram; NA = not available; mg = milligram; NICE = National Institute for Health and Care Excellence; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; qd = once daily; qiw = once weekly; SmPC = Summary of Product Characteristics

ERG comment: The ERG is concerned about a) the selection of the treatment sequences included in the cost effectiveness model, and b) the non-inclusion of comparators included in the NICE scope.

a) The CS does not provide justification for the selection of the treatment sequences included in the cost effectiveness model, besides that these were included in the York model.[26] In its response to clarification question B8, the company states that the treatment sequences are informed by NICE recommendations and the license of treatments.[25] The company explains that, for b/tsDMARDs-naïve patients, all sequences consider ustekinumab as second-line treatment because it is recommended after TNF-alpha inhibitors failure in this population. The company acknowledges that secukinumab and certolizumab pegol are also recommended as second-line treatment but that only ustekinumab has been considered as second-line treatment to facilitate the comparison across all treatment sequences. In addition, the company states that the treatment sequences included in the current assessment are not exhaustive in the UK context.[25] The ERG explored alternative treatment sequences in its analyses, considering secukinumab and certolizumab pegol as second-line treatments.
   The CS does not explain why treatment sequences are restricted to a maximum of two b/tsDMARDs, i.e. two b/tsDMARDs followed by BSC in the b/tsDMARD-naïve subgroup and one b/tsDMARD followed by BSC in the b/tsDMARD-experienced subgroup. In its response to the clarification letter, the company states that this assumption was similar to the approach used in the 2016 York model and is supported by the Adelphi DSP real-world dataset in which only [redacted] of patients received three or more b/tsDMARD treatments. However, no details were provided on this dataset (years during which patients were included, patient characteristics, study design and analyses). The ERG was thus not able to judge the credibility of the argument that [redacted] use three or more DMARDs.
b) Certolizumab pegol and secukinumab are listed in the NICE final scope as comparators in the b/tsDMARD-experienced subgroup[89] but these treatments were not included in the company base-case analyses concerning this population. Additionally, the scope states that b/tsDMARDs may be administered with or without methotrexate. Hence, the ERG requested the company to include these comparators in its base-case analyses. The company did not include methotrexate, justified by stating that its acquisition costs were low and the clinical outcomes of studies included in the SLR were not reported separately for patients who did or did not receive concomitant methotrexate. The effectiveness of methotrexate is however indirectly included in the effectiveness estimates because a proportion of patients in SPIRIT and other trials included in the NMA received concomitant methotrexate.[31, 32, 36, 38, 40] The ERG agrees with the company that including the acquisition costs of methotrexate would not dramatically influence the cost effectiveness results.
   The company justified their decision to not include certolizumab pegol and secukinumab in the base-case analyses for the b/tsDMARD-experienced subgroup by stating that there was no study identified in the SLR which provided separate effectiveness estimates for b/tsDMARD-naïve and b/tsDMARD-experienced patients receiving these treatments. The identified studies provide effectiveness estimates for a mixed population of b/tsDMARD-naïve and b/tsDMARD-experienced patients treated with certolizumab pegol and secukinumab. These studies were used in the CS to estimate the effectiveness of these treatments in the b/tsDMARD-naïve subgroup. The company therefore assumed, in the b/tsDMARD-naïve subgroup, that the effectiveness of certolizumab pegol and secukinumab is equal in b/tsDMARD-experienced and b/tsDMARD-naïve patients. This contradicts its argument of not using the same evidence to estimate the effectiveness of certolizumab pegol and secukinumab in the b/tsDMARD-experienced subgroup because the studies do not provide estimates for b/tsDMARD-naïve and b/tsDMARD-experienced patients separately.

The ERG included both certolizumab pegol and secukinumab in its base-case analysis, by using the treatment effectiveness estimates obtained from the extended NMA for the b/tsDMARD-experienced subgroup. The extended NMA also has the advantage of providing the PASI 50 outcome which is needed for the calculation of change in PASI scores (see section 5.2.6 for more details on this issue).

5.2.5 Perspective, time horizon and discounting

The analysis takes a NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The company claim to have adopted a 40-year time horizon.[1]

ERG comment: In the CS, the company states a 40-year time horizon was used, however, the model continues until patients reach the age of 99 (less than 1% of patients are still alive). This was considered to represent a lifetime time horizon. The approach is in concordance with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness in the economic model is informed by PsARC, HAQ-DI and PASI, all sourced from the NMA described in section 4.3 of this report (section 2.9 of the CS).[1] PsARC and PASI are estimated separately for patients with and without prior b/tsDMARD exposure while HAQ-DI is estimated in patients without prior b/tsDMARD exposure (due to lack of evidence).

PsARC

The PsARC is a PsA-specific composite responder index and based on four items related to joint tenderness, joint swelling, patient global assessment and physician global assessment. Response is achieved if improvements in two out of four items is obtained, of which at least one is related to the joint tenderness or swelling score (≥30% improvement), and no item has worsened.[90]

In the economic model, after the trial period, treatment is continued for patients classified as responders based on PsARC while treatment is discontinued for PsARC non-responders. The company argues that this is consistent with current UK practice (by referring to the NICE Pathway for musculoskeletal conditions[91]) and with cost effectiveness studies identified in the SLR. Patients who continue treatment (i.e. PsARC responders) are assumed to maintain their improvement(s) in joint and/or skin outcomes until treatment discontinuation.

Treatment discontinuation

A constant annual treatment discontinuation of 16.5%[92] (i.e. 1.49% per model cycle of one month) is applied to the continued treatment state and represents treatment discontinuation due to any cause. The company argued that in absence of alternative data, the same treatment discontinuation rate is applied for all treatments and treatment lines.[1]

HAQ-DI

The HAQ-DI (range 0-3) considers the amount of difficulty patients have in performing the following activities[93]:

1. dressing and grooming
2. arising
3. eating
4. walking
5. hygiene
6. reach

7. grip
8. common daily activities

The baseline HAQ-DI scores used in the model are reported in Table 5.4. The change from baseline HAQ-DI is assumed to be dependent on treatment and PsARC response and used to estimate utility and costs. Moreover, it is assumed that the change from baseline HAQ-DI occurs instantly after initiating treatment (in the trial period) and that patients maintain this improvement until treatment discontinuation. After active treatment discontinuation, patients receive BSC and the HAQ-DI score is assumed to immediately rebound to its baseline value. HAQ-DI then progresses at a rate equivalent to the natural history progression (annual deterioration of 0.072[14]) until it plateaus at the maximum value of the HAQ-DI scale (i.e. 3).

PASI

The PASI provides a quantitative assessment of psoriasis lesion burden. This is calculated based on the amount of BSA involved and degree of severity of erythema, induration, and scale, weighted by body part. [90]

The baseline PASI scores used in the model are reported in Table 5.4. Similar to the changes in HAQ-DI, the change from baseline PASI is assumed to be dependent on treatment and PsARC response and used to estimate utility and costs. Moreover, it is assumed that the change from baseline PASI occurs instantly after initiating treatment (in the trial period) and that patients maintain this improvement until treatment discontinuation. After active treatment discontinuation, patients receive BSC and the PASI score is assumed to immediately rebound to its baseline value. In contrast with HAQ-DI scores (for which natural history progression is incorporated), the baseline PASI scores were assumed to be constant over time. The company stated that this assumption was made in the absence of data to model otherwise.

For PsARC responders, the reduction in PASI (i.e. improvement) compared with baseline PASI was assumed to be 75% (i.e. assuming all PsARC responders would have PASI 75). The PsARC non-responders were assumed to have either PASI 50 (i.e. reduction in baseline PASI by 50%) or no reduction in baseline PASI (see CS Table 42 for the calculation details).[1]

Mortality

Mortality was independent of health states patients were in. It was calculated based on background mortality increased by a standardised mortality ratio (SMR) of 1.36[6] to reflect disease-related mortality.

ERG comment: The ERG's concerns relate to a) the lack of information provided on treatment effectiveness parameters used in the economic model (in CS section 3.3[1]); b) the calculation of change in PASI depending on PsARC response; c) assumptions regarding natural progression of HAQ-DI after active treatment discontinuation; d) the SMR of 1.36 applied to reflect disease-related mortality; e) the assumption of no treatment response for BSC (after active treatment discontinuation); f) assuming treatment discontinuation to be equal for all b/tsDMARD treatments (and independent of treatment line) and g) the estimated HAQ-DI for ixekizumab q4w.

a) The "Clinical parameters and variables" section of the CS (Section 3.3) does not provide an overview of the parameters and variables used in the model. However, in response to clarification question B12, the company provided a transition matrix to illustrate the transitions probabilities used in the model, see Table 5.7.[25] In addition to the transition matrix, the ERG retrieved an overview of PsARC and PASI response per treatment (different for the b/tsDMARD-naïve and experienced populations) and an overview of HAQ-DI reduction per treatment (identical for the

b/tsDMARD-naïve and experienced populations) from the economic model submitted by the company (provided in Tables Table 5.8 and Table 5.9).

b) The ERG identified an inconsistency between the calculation of change in PASI depending on PsARC response in the economic model and the calculation methods reported in Table 42 of the CS.[1] Although the formulae reported in CS Table 42 lack justification (e.g. that all PsARC responders would have PASI 75), the ERG adjusted the calculation of change in PASI in the model to be consistent with CS Table 42. Related to this, the ERG noted that the NMA used in the CS base-case for the b/tsDMARD-experienced population did not provide estimates for PASI 50 (see Table 5.8). Therefore, the ERG preferred to use the NMA including secukinumab and certolizumab pegol for the b/tsDMARD-experienced population as these did have estimates for PASI 50 needed to estimate the calculation of change in PASI (Table 5.8). See ERG comments in section 5.2.4 for further details regarding the ERG's preference of the NMA including secukinumab and certolizumab pegol. In case PASI 50 estimates were missing, the company presumably assumed 0% PASI 50, likely benefiting treatments with higher PsARC response.

c) After active treatment discontinuation, patients receive BSC and their HAQ-DI score immediately rebounds to its baseline value and subsequently progresses using an annual deterioration of 0.072 until the maximum value of the HAQ-DI scale (i.e. 3). Although the ERG requested more detail regarding this calculation (clarification question B6d), it remains unclear to the ERG whether this linear deterioration is plausible, or whether a multiplicative progression factor would have been more plausible, for instance.[25, 80] This assumption of linear deterioration is consistent with the York model.[13] It should however be noted that if, in fact, the annual deterioration were non-linear and decreased over time, the assumption made by the company is likely benefiting treatments with a higher PsARC.

d) The SMR of 1.36[6] used by to company to increase background mortality and reflect disease related mortality seems an overestimation of the actual mortality in this population as this SMR was derived from the period between 1978 and 2004. If only the subset analysis with a follow-up period between 1996-2004 was to be considered, the SMR would be 1.05 (95% CI 0.79 to 1.41).[6] The ERG prefers to adopt the SMR of 1.05 in its base-case given it is based on more recent data (and the SMR seems to have declined over time).[6]

e) Once patients transit to BSC, positioned after discontinuation of active treatment in the model, the PASI and HAQ-DI immediately rebound to its baseline value. This implicitly assumes no treatment effect of BSC (regarding PASI and HAQ-DI). In response to clarification question B9, the company indicates that for BSC *"a combination of physiotherapy, NSAIDs, local glucocorticoid injections and cDMARDs may be used"*.[25] Although the assumption of no treatment effect can be questioned, it does not seem unreasonable to assume that the treatment response to BSC in that setting, i.e. after failure on two b/tsDMARD therapies, will be modest. Moreover, the ERG acknowledges that the evidence on BSC after failing two lines of b/tsDMARD treatment is likely scarce.

f) Treatment discontinuation was assumed to be equal for all b/tsDMARD treatments (independent of treatment line). This assumption (although consistent with the York model) is questionable, given that all-cause treatment discontinuation might differ substantially between treatments (see clarification response Table 50).[25]

g) As discussed in section 4.4 of this report, the reduction in HAQ-DI scores (retrieved from the NMA) for ixekizumab q4w (both responders and non-responders) seems inconsistent with the trial data. Therefore, the ERG preferred to use the reduction in HAQ-DI scores from the trial for ixekizumab q4w, this would be [redacted] and [redacted] for responders and non-responders respectively.

Table 5.7: Overview of transition probabilities in sequencing approach

	Treatment 1 trial period month 1	**Treatment 1 trial period month 2**	**Treatment 1 trial period month 3/4**	**Treatment 1 continued treatment period**	**Treatment 2 trial period month 1**	**Treatment 2 trial period month 2**	**Treatment 2 trial period month 3/4**	**Treatment 1 continued treatment period**	**BSC**	**Death**
Treatment 1 trial period month 1	NA	1-(mortality risk)	NA	NA	NA	NA	NA	NA	NA	Mortality risk
Treatment 1 trial period month 2	NA	NA	1-(mortality risk)	NA	NA	NA	NA	NA	NA	Mortality risk
Treatment 1 trial period month 3/4	NA	NA	NA	PsARC response rate	1-PsARC response-(mortality risk)	NA	NA	NA	NA	Mortality risk
Treatment 1 continued treatment period	NA	NA	NA	1-(mortality risk)- 1.49%	1.49%	NA	NA	NA	NA	Mortality risk
Treatment 2 trial period month 1	NA	NA	NA	NA	NA	1-(mortality risk)	NA	NA	NA	Mortality risk
Treatment 2 trial period month 2	NA	NA	NA	NA	NA	NA	1-(mortality rate)	NA	NA	Mortality risk
Treatment 2 trial	NA	NA	NA	NA	NA	NA	NA	PsARC response rate	1-PsARC response-	Mortality risk

	Treatment 1 trial period month 1	**Treatment 1 trial period month 2**	**Treatment 1 trial period month 3/4**	**Treatment 1 continued treatment period**	**Treatment 2 trial period month 1**	**Treatment 2 trial period month 2**	**Treatment 2 trial period month 3/4**	**Treatment 1 continued treatment period**	**BSC**	**Death**
period month 3/4									(mortality risk)	
Treatment 2 continued treatment period	NA	NA	NA	NA	NA	NA	NA	1-(mortality risk)-1.49%	1.49%	Mortality risk
BSC	NA	NA	NA	NA	NA	NA	NA	NA	1-(mortality risk)	Mortality risk
Death	NA	NA	NA	NA	NA	NA	NA	NA	NA	1

Source: Based on Table 49 of the response to the request for clarification[25]
BSC = best supportive care; NA = not available; PsARC = Psoriatic Arthritis Response Criteria

Table 5.8: PsARC and PASI response

Name	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	Absolute PASI score[a]			
						Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
						Responders	Non-responders	Responders	Non-responders
b/tsDMARD-naive population									
Ixekizumab q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biosimilar etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biosimilar infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b/tsDMARD-experienced population									
Ixekizumab q2w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]
Ixekizumab q4w	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]
Ustekinumab	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]
BSC	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[c]	[redacted]	[c]

Name	PsARC	PASI 50	PASI 75	PASI 90	PASI 100	Absolute PASI score[a]			
						Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
						Responders	Non-responders	Responders	Non-responders
b/tsDMARD-experienced population (including secukinumab and certolizumab pegol)									
Ixekizumab q2w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Retrieved from the economic model[94]

Notes: [a] These values are calculated by the ERG based on the formulae provided in CS Table 42.[1] The absolute PsARC and PASI response for BSC represents the response for BSC as comparator (i.e. not BSC as treatment state after discontinuation of active treatment, here the baseline PASI is assumed). [b] Ustekinumab data for the b/tsDMARD-naïve population was retrieved from the b/tsDMARD-experienced population. This was presumably assumed given Ustekinumab was only provided as the second treatment sequence. [c] It is unclear how this is calculated in the model given PASI50 is missing.

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supporting care; mg = milligram; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks

Table 5.9: HAQ-DI reduction compared with baseline (retrieved from the economic model)

Name	HAQ-DI reduction	
	Responders	Non-responders
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Biosimilar etanercept	[redacted]	[redacted]
Biosimilar infliximab	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Ixekizumab q2w	[redacted]	[redacted]
Ixekizumab q4w	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]

Source: Retrieved from the economic model[94]
BSC = best supporting care; HAQ-DI = Health Assessment Questionnaire-Disability Index; mg = milligram; q2w = once every two weeks; q4w = once every four weeks

5.2.7 Adverse events

No adverse events are considered in the economic model. The company argued that adverse events are implicitly captured to the extent that they affect the initial response and the long-term treatment discontinuation rates.

ERG comment: The ERG believes the justification provided by the company stating that adverse events are implicitly captured by the long-term withdrawal rates is flawed, given that these withdrawal rates are assumed to be identical for all treatments. Furthermore, the scope identified adverse events as relevant outcomes for this appraisal. The ERG believes that not incorporating adverse events is a substantial weakness of the economic model, particularly given that treatment discontinuation due to adverse events might differ between treatments, as was shown in response to clarification question A8 (see section 4.3.3, Table 4.22).[25]

5.2.8 Health-related quality of life

According to the CS, the SLR identified seven studies reporting UK relevant utility values. Out of these, the company considered only one study to be consistent with the NICE reference case and to be appropriate for the CEA model (Saad et al, 2010[71]). However, according to the company, this study, and the others, were not used in the health economic model because *"the studies identified in the HRQoL review reported only health state utility values"*.[1]

Instead, the company used the data from the SPIRIT trials in which the EQ-5D-5L questionnaire was administered to patients at baseline and week 12. The data collected from these studies were then analysed separately, to reflect the differences in terms of functional disability and skin involvement between the two populations of b/tsDMARD-naïve (utility derived from SPIRIT-P1) and b/tsDMARD-experienced (utility derived from SPIRIT-P2) patients. Consistent with the NICE reference case, health state utility values were obtained from the responses to the EQ-5D-5L using a hybrid of time-trade-off (TTO) and discrete choice experiments (DCE) on a representative sample from England. The

company did not impute missing values and justified this stating that the proportions of patients with missing EQ-5D score were small (20/417 in SPIRIT-P1 and 32/331 in SPIRIT-P2). In the CS, no further information was provided as to how these EQ-5D data were used.

In line with NICE's position statement on EQ-5D-5L data, the obtained data were mapped to EQ-5D-3L using the indirect mapping approach according to van Hout et al. 2012.[95] The EQ-5D-5L utility values were used in a scenario analysis.

The company used these EQ-5D-3L (5L in scenario analysis) data to establish a relationship between patients' HAQ-DI and PASI scores and HRQoL using an ordinary least squares regression model that had previously been used in the York models and was considered by the company to provide a better goodness-of-fit than alternative specifications of the model, e.g. including an interaction term between HAQ-DI and PASI and including adjustments for age and gender. Thus, the model specification only includes an intercept and coefficients for HAQ-DI and PASI scores, as shown in equation 1, with coefficients reported in Table 5.10:

Equation 1 – Utility regression model

$$Utility = \beta_0 - \beta_{HAQ} * HAQ - \beta_{PASI} * PASI$$

Table 5.10: Coefficients of linear regression of utility versus HAQ-DI and PASI

	Intercept		HAQ-DI		PASI	
Source	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
b/tsDMARD-naïve: SPIRIT-P1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b/tsDMARD-experienced: SPIRIT-P2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 43 of the CS[1]
b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; PASI = Psoriasis Area and Severity Index; SE = standard error

The company did not incorporate the HRQoL associated with adverse events in their health economic model. The company justified this by stating that the HRQoL impact of AEs was also not modelled in other economic models submitted to HTA agencies. The company stated that the impact of AEs was captured only to the extent that they affect the initial response and the long-term withdrawal rates.

A summary of all utility values used in the cost effectiveness analysis is provided in Table 5.11.

Table 5.11: Summary of utility values used for CEA

State	Utility value (PsARC responders)	Utility value (PsARC non-responders)	Reference in company submission	Justification
b/tsDMARD-naïve, no psoriasis				
Trial period	0.624		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.744	0.624	Table 21, Table 22, Table 23,	Derived from treatment-specific response rates in the
ADA	0.717	0.647		

State	Utility value (PsARC responders)	Utility value (PsARC non-responders)	Reference in company submission	Justification
APR	0.693	0.641	Table 36, Equation 2	biologic-naïve NMA and from baseline HAQ-DI score
CZP	0.702	0.637		
ETA	0.750	0.662		
GOL	0.702	0.637		
INF	0.756	0.661		
SEC 150	0.735	0.652		
b/tsDMARD-naïve, mild-moderate psoriasis				
Trial period	0.605		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.739	0.613	Table 21, Table 22, Table 23, Table 36, Equation 2	Derived from treatment-specific response rates in the biologic-naïve NMA and from baseline PASI and HAQ-DI scores
ADA	0.709	0.629		
APR	0.683	0.622		
CZP	0.692	0.618		
ETA	0.736	0.642		
GOL	0.694	0.619		
INF	0.750	0.649		
SEC 150	0.729	0.639		
b/tsDMARD -naïve, moderate-severe psoriasis				
Trial period	0.518		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q2w	0.716	0.600	Table 21, Table 22, Table 23, Table 36, Equation 2	Derived from treatment-specific response rates in the biologic-naïve NMA and from baseline PASI and HAQ-DI scores
ADA	0.669	0.550		
APR	0.638	0.539		
CZP	0.642	0.533		
ETA	0.675	0.556		
GOL	0.657	0.539		
INF	0.723	0.596		
SEC 300	0.701	0.590		
b/tsDMARD -experienced, no psoriasis				
Trial period	0.589		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.763	0.634	Table 23, Table 25, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline HAQ-DI score
UST	0.737	0.675		

State	Utility value (PsARC responders)	Utility value (PsARC non-responders)	Reference in company submission	Justification
b/tsDMARD -experienced, mild-moderate psoriasis				
Trial period	0.577		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q4w	0.711	0.586	Table 23, Table 25, Table 26, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline PASI scores, which determines the severity of psoriasis.
UST	0.683	0.637		
b/tsDMARD -experienced, moderate-severe psoriasis				
Trial period	0.310		Table 36, Equation 2	Baseline utility at start of trial period
Continued treatment period				
IXE q2w+q4w	0.497	0.422	Table 23, Table 25, Table 26, Equation 2	Derived from treatment-specific response rates in the biologic-experienced NMA and from baseline PASI scores, which determines the severity of psoriasis.
UST	0.453	0.493		
BSC	Point estimate NA	NA	NA	HAQ-DI progresses each cycle according to natural history in BSC
Death	0	NA	NA	No utility assigned in death state

Source: Based on Table 44 of the CS[1]
ADA = adalimumab; APR = apremilast; b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; CEA = cost effectiveness analysis, CS = company submission; CZP = certolizumab pegol; ETA = etanercept; GOL = golimumab; HAQ-DI = Health Assessment Questionnaire-Disability Index; INF = infliximab; IXE = ixekizumab; NA = not available; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; q2w = once every two weeks; q4w = once every four weeks; SEC = secukinumab; UST = ustekinumab

ERG comment: The ERG's concerns related to a) the omission of alternative utility values from the literature without clear justification, b) the methods used for analysing the SPIRIT HRQoL observations, c) the use of utility values unadjusted to the general population age-related utilities, and d) the fact that the HRQoL impact of AEs is not incorporated.

a) The company identified seven studies reporting UK utility values. None of these were used in the base-case CEA or scenarios and the justification provided by the company was that *"the studies identified in the HRQoL review reported only health state utility values"*.[1] The company furthermore stated that *"the model followed the approach of the 2016 York model by modelling utility as a function of HAQ and PASI"*.[1] The ERG was concerned that important studies to inform HRQoL might have been excluded and checked the company's Appendix H[28] to verify that the company's decision not to use the identified HRQoL studies was appropriate. Apart from Saad et

al. 2010,[71] the other six studies were deemed irrelevant because they did not report utility values according to disease severity or functional status. The ERG agrees with the company on this. Utilities reported in Saad et al. 2010 were SF-6D scores based on the SF-36 questionnaire which was administered every six months in a cohort of 596 PsA patients starting to receive anti-TNF therapies in the UK setting. The baseline HAQ-DI score in this population was higher than in the population considered in this appraisal (1.88 instead of 1.18 in the b/tsDMARD-naive group, i.e. the SPIRIT-P1 population). SF-6D scores and HAQ-DI scores were reported for baseline, six months, 12 months and 18 months follow-up. SF-6D scores were also available for different treatments (etanercept, infliximab and adalimumab) but differences between these groups were very small. PASI scores were not reported. Given that, in the CS, utility values were modelled in relationship with HAQ-DI and PASI, the use of this study was indeed limited. The company's approach of using HRQoL data from their pivotal trials was therefore deemed reasonable.

b) The ERG had two concerns with regards to the analysis of HRQoL data from the SPIRIT trial programme. Firstly, no imputation method was applied in case of missing information on EQ-5D, thereby assuming that HRQoL data were missing completely at random. In their response to clarification question B16.a), the company justified this by having examined the data for, and not found, a pattern in the potential association between missing information and study- and patient-related characteristics.[25] No further information on this exercise was provided and the ERG therefore considers the non-imputation of missing data as a limitation. In a scenario, the company used the "Last observation carried forward" (LOCF) approach to impute missing data. This approach would address missing values only for those patients that had filled in the EQ-5D questionnaire at baseline and therefore might not address all missing information. Furthermore, the LOCF method is rarely appropriate and usually creates biased results.[96] The differences in the resulting regressions are shown in the equations below. Since the number of missing values was small in the SPIRIT trials and the LOCF method for imputation is generally not recommended, the ERG did not pursue this scenario further.

   Secondly, utility values were obtained using only the week 12 measurements, thus excluding baseline observations. The use of a mixed model for repeated measures could have facilitated accounting for baseline EQ-5D values and other factors but this was not explored by the company. In response to clarification question B16.b), the company stated that a mixed effects model for repeated measures would not have been appropriate because it would reduce the variability around EQ-5D.[25] The ERG considers that it may have been better to use all available data, potentially by estimating 12-week EQ-5D with baseline EQ-5D as a covariate. However, the ERG did not consider this a major issue.

c) In the CS model, utilities were not adjusted for general population utilities. This was addressed in response to clarification question B17.[25] The results of this scenario show that this adjustment has only a minor impact on cost effectiveness analysis results. The ERG prefers this and uses this adjustment in its base-case.

d) The HRQoL impact of AEs was not incorporated in the company's analysis. Due to the differing AE profiles of the different treatments (see section 5.2.7), which could have a significant impact on HRQoL, this is considered a major limitation.

5.2.9 Resources and costs

In Appendix I, the company stated that five studies reporting cost and resource use in the population of interest were identified through the SLR and its update.[28] One of these was deemed clearly not applicable to clinical practice in England and the applicability to clinical practice in England was considered unclear in the four other studies. Of these four studies only the study by Poole et al. (2010)[72]

was used to inform a scenario analysis. Other than this, the company used sources that were also used in the revised York model used in the previous TA by Corbett et al. 2017.[26]

Drug acquisition costs

Drug acquisition costs for b/tsDMARDs were sourced from the online version of the Monthly Index of Medical Specialities (MIMS)[77] and are shown in Table 5.12. Ixekizumab is provided with a confidential simple discount patient access scheme (PAS). Secukinumab and apremilast are also provided with a PAS, but list prices were used for these two comparators in the CS model as these PAS prices were not publicly available. Certolizumab pegol and ustekinumab are recommended by NICE with complex PAS schemes in place, which require the manufacturer of certolizumab pegol to provide the first 12 weeks of treatment free of cost; and the high dose of ustekinumab (90 mg) needed for people who weigh more than 100 kg is provided at the same total cost as the low dose (45 mg). Both of these schemes are incorporated in the present CEA. The cost of infliximab was calculated based on the weight-based dosing, and the weight for this was obtained from the SPIRIT trial programme. For infliximab and etanercept, biosimilar prices are used in the base-case model and branded prices are used in a sensitivity analysis.

Table 5.12: Drug acquisition costs

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (trial period)	Total annual cost (continued treatment)	Source
IXE q2w	1	80 mg	£1,125	£1,125	£9,000	£14,625	List price: MIMS 2017[77]
IXE q4w	1	80 mg	£1,125	£1,125	£5,625	£14,625	List price: MIMS 2017[77]
IXE q2w	1	80 mg	[redacted]	[redacted]	[redacted]	[redacted]	PAS price
IXE q4w	1	80 mg	[redacted]	[redacted]	[redacted]	[redacted]	PAS price
ADA	2	40 mg/ 0.8 ml	£704.28	£352.14	£2,112.84	£9,155.64	MIMS 2017[77]
APR*	56	30 mg	£550.00	£9.82	£2,190.18	£7,150.00	MIMS 2017[77]
CZP†	2	200 mg	£715.00	£357.50	£0†	£9,295.00	MIMS 2017 [77]; NICE FAD TA445 [13]
ETA (Enbrel)	4	50 mg	£715.00	£178.75	£2,145.00	£9,295.00	MIMS 2017[77]
ETA biosimilar (Benepali)	4	50 mg	£656.00	£164.00	£1,968.00	£8,528.00	MIMS 2017[77]
GOL	1	50 mg	£762.97	£762.97	£2,288.91	£9,155.64	MIMS 2017[77]
INF (Remicade)‡	1	100 mg	£419.62	£2,056.40	£6,169.21	£13,366.63	MIMS 2017[77]
INF biosimilar (Remsima) ‡	1	100 mg	£377.00	£1,847.54	£5,542.62	£12,009.01	MIMS 2017[77]
SEC 150 mg*	2	150 mg	£1218.78	£609.39	£4,265.73	£7,922.07	MIMS 2017[77]

Items	Pack size	Dose strength	Pack cost	Cost per dose	Total cost (trial period)	Total annual cost (continued treatment)	Source
SEC 300 mg*	2	150 mg	£1218.78	£1,218.78	£8,531.46	£15,844.14	MIMS 2017[77]
UST 45	1	45 mg	£2,147.00	£2,147.00	£4,294.00	£9,303.67	MIMS 2017[77]

Source: Based on Table 45 of the CS[1]
Footnote: * List price used in model due to confidential discount PAS; † CZP is associated with a PAS that provides the first 12 weeks of treatment free; ‡Infliximab dose based on a baseline weight of 87.02 kg
ADA = adalimumab; APR = apremilast; CZP = certolizumab pegol; ETA = etanercept; GOL = golimumab; INF = infliximab; IXE = ixekizumab; mg = milligram; ml = millilitre; MIMS = Monthly Index of Medical Specialities; q2w = once every two weeks; q4w = once every four weeks; SEC = secukinumab; UST = ustekinumab

Drug administration costs

All therapies of interest are administered as a subcutaneous (SC) injection with the exception of oral apremilast, and infliximab, which is administered via intravenous (IV) infusion. Patients who received SC injections incurred administration costs only for one hour nurse training for self-administration in the trial period and no further administration costs in the continued treatment period. Patients who received infliximab incurred an IV infusion cost three times in the trial period and an average of 6.5 times each year they remained on treatment. No administration costs were applied to oral administration of apremilast.

The cost of administration was obtained from the PSSRU Unit Costs of Health and Social Care 2016[78] and the NHS Reference Costs 2015-16[76] and is shown in Table 5.13.

Table 5.13: Drug administration costs

Administration method	Admin cost	Admin: trial period	Annual admin	Total cost: trial period	Total annual cost	Source
SC self-injection: a hour-long nurse training sessions	£43.00	1	0	£108.00	£0.00	PSSRU, Unit Costs of Health and Social Care 2016, section 10, cost per hour of Nurse in GP practice[78]
IV infusion, outpatient procedure	£236.19	3	6.5	£291.24	£631.02	NHS Reference Cost 2015-2016, Deliver Simple Parenteral Chemotherapy at First Attendance, code SB12Z[76]
Oral administration	£0.00	N/A	N/A	£0.00	£0.00	Assumption

Source: Based on Table 46 of the CS[1]
CS = company submission; GP = general practitioner; IV = intravenous; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; SC = subcutaneous

Monitoring

Costs for monitoring during treatment have been obtained from the NHS Reference Costs[76] and are shown in Table 5.14. Resource use estimates were mainly taken from Corbett et al. 2017,[26] were deemed in line with the guidelines from the British Society for Rheumatology (BSR) for the use of biologics, and were stratified by method of administration (Table 5.14).[97]

Table 5.14: Resource use and costs for administration and monitoring of treatment in the trial and continued treatment periods

Resource	Time period	SC	Oral	IV	Price	Reference	Cost year
Rheumatologist visit	Trial period	2	2	2	£142.74	NHS Reference Cost 2015-2016, code DAPS05[76]	2016
	Continued treatment period	0	1	0			
Full blood count	Trial period	2	2	2	£3.00	NHS Reference Cost 2015-2016, code DAPS05[76]	2016
	Continued treatment period	2	0	2			
Liver function test	Trial period	2	2	2	£1.00	NHS Reference Cost 2015-2016, code DAPS04[76]	2016
	Continued treatment period	2	0	2			
Urea and electrolytes	Trial period	2	2	2	£1.00	NHS Reference Cost 2015-2016, code DAPS04[76]	2016
	Continued treatment period	2	0	2			
ESR	Trial period	2	2	2	£3.00	NHS Reference Cost 2015-2016, code DAPS05[76]	2016
	Continued treatment period	2	0	2			
Chest X-Ray	Trial period	1	1	1	£30.00	NHS Reference Cost 2015-2016, code DAPF [76]	2016
	Continued treatment period	0	0	0			
TB Heaf test	Trial period	1	1	1	£8.91	Rodgers et al. 2011[92]	2016
	Continued treatment period	0	0	0			
ANA test	Trial period	1	1	1	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 [76]	2016
	Continued treatment period	0	0	0			
ds DNA test	Trial period	1	1	1	£3.00	NHS Reference Cost 2015-2016, , code DAPS05 [76]	2016
	Continued treatment period	0	0	0			

Source: Based on Tables 47 and 48 of the CS[1]
ANA = Antinuclear antibody; CS = company submission; DNA = deoxyribonucleic acid; ds = double-stranded; ESR = Erythrocyte sedimentation rate; IV = intravenous; NHS = National Health Service; SC = subcutaneous; TB = Tuberculosis

Disease-related costs and resource use

Disease-related costs are included in the model through estimating costs related to HAQ-DI (see equation 2) and costs related to PASI (see Table 5.15). The CS states that this method is assumed to capture the cost of BSC.[1]

The linear regression to inform HAQ-DI related costs was taken from Kobelt et al. 2002,[50] a study with sample size of 916 patients for the UK cohort. This study was based on rheumatoid arthritis patients. The company updated the costs to 2017 GBP. The company stated that Kobelt et al. 2002 estimated that costs for cDMARDs would account for 15% of the direct cost. To avoid double-counting with drug acquisition costs applied elsewhere in the current model, the company modelled patients on biologic treatment to incur 85% of the HAQ-DI related costs. For BSC, the full HAQ-DI related costs were assumed (i.e. without the 15% reduction). An alternative costing approach by Poole et al. 2010[72] was used in a scenario analysis.

Equation 2 – Health state costs associated with HAQ-DI

$$Annual\ direct\ costs = £565.64\ x\ HAQ + £1{,}867.56$$

Costs related to the treatment of controlled psoriasis were informed by the York model (Rodgers et al. (2011)[92]) and are presented in Table 5.15. Controlled psoriasis is defined as achieving a PASI 75 response. The company assumed that patients with mild-to-moderate and moderate-to-severe concomitant psoriasis incur the same costs, due to lack of data that would allow differential costing. For patients without concomitant psoriasis, it is assumed that no additional psoriasis-related costs occur.

Costs for treating patients with mild-to-moderate concomitant psoriasis who are not treated with or have not responded to active therapy (i.e. uncontrolled psoriasis) are based on UK unit costs for phototherapy and other treatment costs, including drug costs and physician visits estimated from a UK RCT on 232 psoriasis patients randomised to receive calcipotriol or dithranol published in 1999.[98] For patients with uncontrolled moderate-to-severe concomitant psoriasis, costs are based on a Dutch RCT comparing psoriasis treatment with dithranol with ultraviolet B (UVB) phototherapy[99] and adjusted to UK price levels.

Table 5.15: Annual costs for controlled and uncontrolled psoriasis

Description	No psoriasis	Mild to moderate	Moderate to severe
Costs for uncontrolled psoriasis	£0	£892	£2,552
Costs for controlled psoriasis (PASI 75 response)	£0	£72	£72

Source: Based on Table 49 of the CS[1]
CS = company submission; PASI = Psoriasis Area and Severity Index

An overview of all health states and associated costs is shown in Table 5.16. The company did not take into account cost and resource use associated with adverse events.

Table 5.16: List of health states and associated costs in the economic model

Health states	Item	Value	Reference
PsARC response and non-response	**Treatment costs**		
	Ixekizumab	£1,125 per dose	MIMS, January 2017[77]
	Adalimumab	£352.14 per dose	MIMS, January 2017[77]
	Apremilast	£9.82 per dose	MIMS, January 2017[77]

Health states	Item	Value	Reference
	Certolizumab pegol	£357.50 per dose	MIMS, January 2017[77]
	Etanercept (biosimilar)	£164 per dose	MIMS, January 2017[77]
	Golimumab	£762.97 per dose	MIMS, January 2017[77]
	Infliximab (biosimilar)	£1,847.54 per dose	MIMS, January 2017[77]
	Secukinumab 150 mg	£609.39 per dose	MIMS, January 2017[77]
	Secukinumab 300 mg	£1,218.78 per dose	MIMS, January 2017[77]
	Ustekinumab	£2,147.00 per dose	MIMS, January 2017[77]
	BSC	£0	Captured in HCRU due to skin and joint symptoms
	Administration costs		
	Nurse training for SC administration	£43.00 per hour of nurse time	PSSRU, Unit Costs of Health and Social Care 2015, Nurse (GP practice), wage cost per hour[78]
	IV infusion	£236.19 per administration	NHS Reference Cost 2015-2016, Deliver Simple Parenteral Chemotherapy at First Attendance, code SB12Z[76]
	Monitoring costs		
	Rheumatologist visit costs	£142.74 per visit	NHS Reference Cost 2015-2016[76]
	FBC	£3.00 per test	NHS Reference Cost 2015-2016[76]
	LFT	£1.00 per test	NHS Reference Cost 2015-2016[76]
	U&E	£1.00 per test	NHS Reference Cost 2015-2016[76]
	ESR	£3.00	NHS Reference Cost 2015-2016[76]
	Chest X-Ray	£30.00	NHS Reference Cost 2015-2016[76]
	TB Heaf test	£8.91	NHS Reference Cost 2015-2016[76]
	ANA test	£3.00	NHS Reference Cost 2015-2016[76]
	ds DNA test	£3.00	NHS Reference Cost 2015-2016[76]
HCRU due to skin and joint symptoms			
Joint symptoms	HAQ-DI	£565.64 per unit change + £1,867.56	Kobelt et al. 2002[100]
No psoriasis		£0	Annualised cost from Corbett et al. 2016[26]
Mild-to-moderate psoriasis	PASI≥75	£72.00	Annualised cost from Corbett et al. 2016[26]
	PASI<75	£892	Annualised cost from Corbett et al. 2016[26]
Moderate-to-severe psoriasis	PASI≥75	£72.00	Annualised cost from Corbett et al. 2016[26]

Health states	Item	Value	Reference
	PASI<75	£2,552	Annualised cost from Corbett et al. 2016[26]

Source: Based on Table 50 of the CS[1]
ANA = Antinuclear antibody; BSC = best supportive care; CS = company submission; DNA = deoxyribonucleic acid; ds = double-stranded; ESR = Erythrocyte sedimentation rate; FBC = full blood count; GP = General practitioner; HAQ-DI = Health Assessment Questionnaire-Disability Index; HCRU = Health Care Resource Utilisation; IV = intravenous; LFT = liver function test; mg = milligram; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; PSSRU = Personal Social Services Research Unit; SC = subcutaneous; TB = Tuberculosis; U&E = urea and electrolytes test

ERG comment: The ERG's concerns relate to a) whether HAQ-DI associated resource use and costs used in the model were appropriate, b) whether PASI-related costs used in the model were appropriate, c) whether there may be double-counting of resource use and costs when psoriasis and arthritis-related costs are added after being estimated separately, d) whether the cost of BSC is appropriately reflected and, e) the exclusion of costs related to adverse events.

a) The ERG had two major concerns regarding the estimation of HAQ-DI related costs:
Firstly, the ERG was concerned that neither the Kobelt et al. 2002[100] nor the Poole et al. 2010[72] studies were considered appropriate for estimating healthcare resource utilisation associated with the HAQ-DI score. This was because Kobelt et al. is a study in a different patient population (rheumatoid arthritis patients), the study is dated and might not be representative of resource use and costs of patients today while the Poole et al. study was associated with limitations in the calculation of the estimates such as that it did not cover the full range of the HAQ-DI score. When used to predict the costs for the full range of the HAQ-DI score, there could be errors especially for more severe disease. The company's justification provided in response to clarification question B20.a) was that Kobelt et al. and Poole et al. were also used in the revised York model.[25] The company furthermore claimed[25] that neither the SPIRIT trials nor the studies included in D'Angiolella et al. 2018,[101] a review of cost effectiveness studies in PsA, would have been appropriate to inform UK healthcare resource use estimates in the cost effectiveness model because none of these studies reflected UK clinical treatment practice appropriately. The ERG notes that the use of Kobelt et al. 2002 is a limitation and source of uncertainty but acknowledges that there may not have been more appropriate data and therefore also uses the Kobelt et al. 2002 algorithm in its base-case and Poole et al. 2010 in a scenario.
Secondly, the ERG questions the appropriateness of subtracting 15% of the HAQ-DI related costs when patients are treated with active treatment. These 15% were estimated in a study from 1996 (McIntosh, 1996)[102] and likely do not reflect the proportion of active treatment costs within the overall HAQ-DI related costs. However, to the knowledge of the ERG, there are no better estimates available.

b) The resource use and costs related to psoriasis were based on the York 2016 model. The ERG was concerned that the data used to inform uncontrolled mild-to-moderate psoriasis were potentially dated as they were sourced from Poyner et al. 1999.[98] Furthermore, the costs for uncontrolled moderate-to-severe costs were sourced from a Dutch RCT and may therefore not be generalisable to the UK setting.[99] The costs associated with no psoriasis were assumed to be £0 but no evidence was cited to inform this. Lastly, although the costs for controlled mild-to-moderate and moderate-to-severe psoriasis were sourced from the York model,[92] it was not clear where these costs came from. Therefore, the ERG notes that there is substantial uncertainty about the costs of non-active treatment costs of treating psoriasis in patients with psoriatic arthritis.

c) The uncertainty in both HAQ-DI and PASI related costs translates further into uncertainty whether there may be double-counting of costs when arthritis and psoriasis-related costs are added after being estimated independently. While it may be reassuring that the York model made the same assumptions, the ERG considers this another area of uncertainty.
d) The ERG noted a lack of clarity regarding the composition of BSC. It is therefore also unclear whether, as stated by the company, the addition of HAQ-DI and PASI-related costs fully captures the true cost of BSC.
e) The impact of AEs on resource use and costs was not incorporated in the company's analysis. Due to the differing AE profiles of the different treatments (see section 5.2.7) which could have an impact on resource use and costs, this is considered a major limitation.

5.2.10 Cost effectiveness results

The company's deterministic fully incremental base-case results using the PAS price of ixekizumab are presented for the biologic-naïve subpopulation for all psoriasis severity subgroups in Table 5.17and for the biologic-experienced subpopulation for all psoriasis severity subgroups in Table 5.18. It should be noted that these results do not take the PAS prices for secukinumab and apremilast into account.

The company pointed out that when the PAS price of ixekizumab is used (but not using the PAS price for secukinumab and apremilast), ixekizumab is associated with [redacted] in the b/tsDMARD-naïve subgroup with no psoriasis and mild-to-moderate psoriasis and is associated with [redacted] than ustekinumab in the b/tsDMARD-experienced subgroups.1 The ixekizumab q4w sequence was associated with an ICER [redacted] versus BSC in the no psoriasis and mild-to-moderate psoriasis subgroups in both the b/tsDMARD-naïve and b/tsDMARD-experienced populations and the ixekizumab q2w sequence had an ICER [redacted] versus BSC in the moderate-to-severe psoriasis subgroups. In the b/tsDMARD-experienced subgroup, ixekizumab q2w [redacted] ustekinumab.

The company further highlighted that the QALY difference between the b/tsDMARDs with the most and least QALYs in each subgroup is less than one QALY over a lifetime time horizon. In contrast, the range in costs between the least and most expensive treatments, due to the confidential price discounts for apremilast and secukinumab, is likely to be wider than predicted by the model. While these results may not reflect the true cost to the NHS of apremilast and secukinumab, they are more representative of the cost effectiveness of the ixekizumab sequences relative to the other b/tsDMARDs that have been recommended by NICE without a confidential price discount.

Table 5.17: Company's base-case results for b/tsDMARD-naïve subpopulation; PAS price

Treatment sequence	Second-line	Third-line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis								
BSC			£54,046	8.09	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£93,347	9.49	[redacted]	1.39	Extendedly dominated	[redacted]
Ixekizumab q4w	Ustekinumab	BSC	[redacted]	9.69	[redacted]	1.60	[redacted]	Referent
Certolizumab pegol	Ustekinumab	BSC	£99,866	9.67	[redacted]	1.57	Dominated	[redacted]
Secukinumab 150 mg	Ustekinumab	BSC	£100,241	9.78	[redacted]	1.68	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£101,322	9.71	[redacted]	1.61	Dominated	[redacted]
Biosimilar etanercept	Ustekinumab	BSC	£103,692	10.02	[redacted]	1.92	£25,810	[redacted]
Golimumab	Ustekinumab	BSC	£108,195	9.90	[redacted]	1.80	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£127,297	10.12	[redacted]	2.02	£236,122	[redacted]
Mild-to-moderate psoriasis								
BSC			£70,006	7.74	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£105,446	9.16	[redacted]	1.41	Extendedly dominated	[redacted]
Ixekizumab q4w	Ustekinumab	BSC	[redacted]	9.38	[redacted]	1.64	[redacted]	Referent
Certolizumab pegol	Ustekinumab	BSC	£111,375	9.34	[redacted]	1.60	Dominated	[redacted]
Secukinumab 150 mg	Ustekinumab	BSC	£111,743	9.47	[redacted]	1.72	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£112,849	9.39	[redacted]	1.64	Dominated	[redacted]

Treatment sequence	Second-line	Third-line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
Biosimilar etanercept	Ustekinumab	BSC	£114,657	9.69	[redacted]	1.95	£22,948	[redacted]
Golimumab	Ustekinumab	BSC	£118,987	9.59	[redacted]	1.85	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£138,072	9.82	[redacted]	2.08	£175,823	[redacted]
Moderate-to-severe psoriasis								
BSC			£99,884	6.21	Referent	Referent	Referent	[redacted]
Apremilast	Ustekinumab	BSC	£127,576	7.70	[redacted]	1.49	Extendedly dominated	[redacted]
Certolizumab pegol	Ustekinumab	BSC	£132,373	7.90	[redacted]	1.69	Extendedly dominated	[redacted]
Adalimumab	Ustekinumab	BSC	£133,882	7.97	[redacted]	1.77	Extendedly dominated	[redacted]
Ixekizumab q2w	Ustekinumab	BSC	[redacted]	8.11	[redacted]	1.91	[redacted]	Referent
Biosimilar etanercept	Ustekinumab	BSC	£134,567	8.24	[redacted]	2.03	£17,055	[redacted]
Golimumab	Ustekinumab	BSC	£138,550	8.23	[redacted]	2.02	Dominated	[redacted]
Secukinumab 300 mg	Ustekinumab	BSC	£155,532	7.97	[redacted]	1.77	Dominated	[redacted]
Biosimilar infliximab	Ustekinumab	BSC	£157,603	8.51	[redacted]	2.31	£84,228	[redacted]

Source: Based on Table 54 of the CS[1]

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; IXE = ixekizumab; mg = milligram; PAS = patient access scheme; q4w = once every four weeks; QALY = quality-adjusted life year

Table 5.18: Company's base-case results for b/tsDMARD-experienced subpopulation; PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY (£) fully incremental	ICER/QALY (£): IXE sequence vs comparator
No psoriasis						
BSC	£55,942	7.38	Referent	Referent	Referent	[redacted]
Ixekizumab q4w	[redacted]	8.21	[redacted]	0.83	[redacted]	Referent
Ustekinumab	£82,143	8.24	[redacted]	0.86	[redacted]	[redacted]
Mild-to-moderate psoriasis						
BSC	£70,271	7.06	Referent	Referent	Referent	[redacted]
Ixekizumab q4w	[redacted]	7.93	[redacted]	0.87	[redacted]	Referent
Ustekinumab	£94,133	7.97	[redacted]	0.91	[redacted]	[redacted]
Moderate-to-severe psoriasis						
BSC	£99,618	2.26	Referent	Referent	Referent	[redacted]
Ixekizumab q2w	[redacted]	3.24	[redacted]	0.98	[redacted]	Referent
Ustekinumab	£118,915	3.21	[redacted]	0.95	[redacted]	[redacted]

Source: Based on Table 55 of the CS[1]

b/tsDMARD = biologic/targeted synthetic disease-modifying anti-rheumatic drug; BSC = best supportive care; ICER = incremental cost effectiveness ratio; IXE = ixekizumab; mg = milligram; PAS = patient access scheme; q4w = once every four weeks; QALY = quality-adjusted life year

ERG comment: The ERG wishes to highlight that a) there is a difference in absolute costs and QALYs accrued by comparators in this model compared with the York model, and b) that the b/tsDMARD-experienced analyses do not contain all appropriate comparators.

a) The ERG noticed that compared with the updated York model, total costs of comparators were generally lower in the current model for b/tsDMARD-naive and higher for b/tsDMARD-experienced patients. Total QALYs of comparators were generally higher in the current model for b/tsDMARD-naive and lower for b/tsDMARD-experienced patients. More detail on this can be found in section 5.2.12.
b) The ERG considers that the results presented for the b/tsDMARD-experienced subgroups are incomplete because relevant comparators as identified in the scope are missing (secukinumab and certolizumab pegol), see section 5.2.4 for more details.

5.2.11 Sensitivity analyses

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSA) in order to quantify the uncertainty surrounding the base-case results. The PSA contained 2,000 model simulations and PSA results were only shown using the list price for ixekizumab. The PSA showed similar incremental costs and QALYs compared with the deterministic results. Results can be found in Table 57 of the CS[1] and are not reproduced here because they do not take the PAS price into account. At list price, ixekizumab was 0% cost effective at a threshold of £30,000 per QALY gained in all six subgroups.

The company conducted a one-way DSA to study the impact of varying individual parameter values on ICERs of ixekizumab versus secukinumab in the b/tsDMARD-naive and ustekinumab in the b/tsDMARD-experienced population. The three parameters that affected the ICERs most were the PsARC response rates for secukinumab and ixekizumab and the annual discontinuation rate for the b/tsDMARD-naive population, no and mild-to-moderate psoriasis severity. For the moderate-to-severe psoriasis severity level, the three most impactful parameters were the PsARC response for ixekizumab and the treatment costs of ixekizumab and secukinumab, followed by fourth the PsARC response rates for secukinumab and fifth the annual discontinuation rate. In the b/tsDMARD-experienced population, the three most influential parameters were the annual discontinuation rate followed by PsARC response rates for ustekinumab and ixekizumab.

The following scenario analyses were performed by the company (using list prices for all, including ixekizumab):

- Single-treatment comparators in the b/tsDMARD naive population
- Single-treatment comparators in the b/tsDMARD naive population with placebo-adjusted response rates
- Ixekizumab response assessment at 16 weeks instead of at 12 weeks
- Inclusion of secukinumab and certolizumab pegol in b/tsDMARD-experienced patient population
- Alternative excess mortality
- Alternative HAQ-DI related costs (Poole et al. 2010[72])
- HAQ-DI rebound to natural history in BSC
- HAQ-DI rebound to 50% of initial gain
- York model utility coefficients
- 5-level EQ-5D utilities
- PSARC in combination with PASI 75/90/100 as alternative response assessments

These scenarios do have an impact on absolute costs and QALYs but do not change the cost effectiveness conclusions based on list prices, as the ixekizumab sequence was either extendedly dominated or dominated in all scenario analyses which were based on the list price of ixekizumab. Assumptions that had the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, the York utility model coefficients, the Poole et al. 2010 algorithm for costs associated with HAQ-DI,[72] and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab being accounted for).

ERG comment: The ERG considers the deterministic sensitivity analyses to be sufficient. The PSA does not include all relevant parameters for all scenarios, e.g. the Convergence Diagnostic and Output Analysis (CODA) for the extended network for the b/tsDMARD experienced population is not available in the model file. PSA results were not provided for the analyses with ixekizumab PAS price.

5.2.12 Model validation and face validity check

Face validity
Face validity of the conceptual model was assessed in an advisory board with clinical and health economic experts.

Internal validity
The model was developed by an external consultancy company and internal validation was undertaken by another external consultancy company. The programming of the model was checked to identify errors or omissions. A cell-by-cell technical validation was carried out and the VBA code was checked.

Cross validity
The company stated that cross validation by replicating comparisons from previous submissions was difficult because PAS prices for secukinumab and apremilast are confidential.

External validity
The company stated that external validity was difficult to assess, because long term observational studies have not been carried out for ixekizumab.

Predictive validity
A head-to-head study comparing ixekizumab and adalimumab is currently underway and could later be used to assess the predictive validity of the cost effectiveness model.

ERG comment: The ERG has concerns related to the lack of detailed cross validity. The company did provide a cross validation exercise in response to clarification question B21.[25] TA445[13] and TA433[15] were the most relevant studies for cross-validity, as these were also based on the York model and were the most recent TAs. Compared with TA445 (the revised York model):

- Total costs of comparators were generally lower in the current model for b/tsDMARD-naive- and higher for b/tsDMARD-experienced patients.
- Total QALYs of comparators were generally higher in the current model for b/tsDMARD-naive and lower for b/tsDMARD-experienced patients.
- Discrepant results compared with the current model could be explained by
  a. differences in PsARC response probabilities (generally lower in current model),

b. different changes in HAQ-DI for PsARC responders and non-responders (generally larger reduction in current model for PsARC responders),
c. differences in PASI response probabilities as well as PASI baseline scores.

In conclusion, it is unclear why the discrepancies between the current assessment and TA445 exist.

The comparison with TA433 was hampered by the fact that this model did not split the model population into psoriasis and b/tsDMARD-naïve and -experienced subgroups.[15] It was therefore difficult to compare costs and QALYs with the current model. Compared with TA433, total costs of apremilast (the main comparator in TA433) were generally lower in the current model for no- and mild-to-moderate psoriasis subgroups but higher in the moderate-to-severe psoriasis subgroup. Also compared with TA433, total QALYs of apremilast were higher in the current model for no- and mild-to-moderate psoriasis subgroups but lower in the moderate-to-severe psoriasis subgroup.

Details of the cross-validity check provided by the company are shown in Table 5.19 below.

Table 5.19: Cross-validity check

		Current assessment		TA 445		TA433	
Subgroup	**Intervention**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**
Biologic-naïve, no psoriasis	Certolizumab pegol	£99,866	9.67	£122,832	9.074	-	-
	Secukinumab	£100,241	9.78	£120,303	9.067	-	-
	Apremilast	£93,347	9.49	-	-	£116,199*	8.01*
	BSC	£54,046	8.09	£51,436	6.188	-	-
Biologic-naïve, mild-to-moderate psoriasis	Certolizumab pegol	£111,375	9.34	£135,946	8.667	-	-
	Secukinumab	£111,743	9.47	£132,500	8.685	-	-
	Apremilast	£105,446	9.16	-	-	£116,199*	8.01*
	BSC	£70,00	7.74	£67,000	5.676	-	-
Biologic-naïve moderate-to-severe psoriasis	Certolizumab pegol	£132,373	7.90	£159,951	8.377	-	-
	Secukinumab	£155,532	7.97	£179,692	8.524	-	-
	Apremilast	£127,576	7.70	-	-	£116,199*	8.01*
	BSC	£99,884	6.21	£95,965	5.312	-	-
Biologic-experienced, no psoriasis	Ustekinumab	£82,143	7.38	£76,712	7.132	-	-
	BSC	£55,2	8.24	£51,436	6.188	-	-
Biologic-experienced, mild-to-moderate psoriasis	Ustekinumab	£94,133	7.97	£91,246	6.666	-	-
	BSC	£70,271	7.06	£67,000	5.676	-	-
Biologic-experienced,	Ustekinumab	£118,915	3.21	£118,127	6.334	-	-

		Current assessment		TA 445		TA433	
Subgroup	**Intervention**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**	**Total costs**	**Total QALY**
moderate-to-severe psoriasis	BSC	£99,618	2.26	£95,965	5.312	-	-

Source: Response to request for clarification[25]
Footnote: * Population in TA433 was not split into subgroups. Therefore costs and QALYs for the total population in TA433 are shown.
BSC = best supportive care; QALY = quality-adjusted life year; TA = technology appraisal

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.20 summarises the main issues highlighted by the ERG in section 5.2, indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses/incorporated in the ERG base-case.

Table 5.20: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Model structure (section 5.2.2)			
Use of relative effectiveness measure (PsARC response)	+/-	None	Not addressed
Assumption of instantaneous PASI and HAQ-DI improvements	+	None	Not addressed
No modelling of AEs	+	None	Not addressed
Population, interventions and comparators, perspective and time horizon (sections 5.2.3-5.2.5)			
Questionable representativeness of patient population	+/-	None	Not addressed
Baseline PASI scores different from in previous TA	+/-	SA	Not addressed
Selection of treatment sequences unclear	+/-	None	Addressed in SA
Exclusion of comparators in the scope	+	BC (FV)	Partly addressed in SA
Treatment effectiveness and extrapolation (section 5.2.6)			
Calculation of PASI change	+/-	BC (MJ)	Not addressed
Assumption of linear HAQ-DI progression	+	None	Not addressed
Use of a high SMR	+	BC (MJ)	Explored in SA
Assumption of equal treatment discontinuation for all treatments	+	None	Not addressed
Use of NMA results not in line with trial data	+/-	BC (FE)	Not addressed
Health-related quality of life (section 5.2.8)			
Non-adjustment for general population utility values	+/-	BC (MJ)	Addressed in SA
Impacts of AEs on HRQoL not reflected	+	None	Not addressed
Resources and costs (section 5.2.9)			
Modelled HAQ-DI related costs potentially inappropriate	+/-	SA	Addressed in SA
Psoriasis-related costs likely inappropriate	+/-	None	Not addressed

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses	Addressed in company analysis?
Impact of AEs on costs not reflected	+	None	Not addressed
Cost effectiveness analyses (sections 5.2.10 and 5.2.11)			
Comparator costs and QALYs deviate from previous TA445	+/-	None	Not addressed
Validation (section 5.2.12)			
Complete cross validation with previous TAs not performed	NA	None	Partly addressed

Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
AE = adverse event; BC = base-case; ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; HAQ-DI = Health Assessment Questionnaire-Disability Index; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; MJ = matters of judgement; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria; SA = scenario analysis; SMR = standardized mortality ratio; TA = technology appraisal

Based on all considerations in section 5.2 (summarised in Table 5.20), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[103])

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Additionally, exploratory sensitivity analyses were performed by the ERG to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

The ERG's base-case:

Fixing errors

1. NMA results for the reduction in HAQ-DI scores for ixekizumab q4w that are inconsistent with trial data.
   The ERG used the trial data instead of the NMA results.

Fixing violations

2. Use of the limited NMA results for the b/tsDMARD-experienced population, which does not consider PASI50.
   The ERG used the extended NMA for the b/tsDMARD experienced population, which considers PASI50.
3. Exclusion of secukinumab and certolizumab pegol as comparators in b/tsDMARD-experienced patients.
   The ERG included these by using the extended NMA, as per scope.
4. Utilities were not adjusted to general population utility values.
   The ERG adjusted utilities.

Matters of judgment

5. The use of a potentially dated and high SMR.
   The ERG used a SMR derived from more recent data.
6. The use of calculations for PASI change in the model that are inconsistent with the CS report.
   The ERG used the calculations detailed in the CS report (Table 42).

5.3.1 ERG base-case results

The ERG base-case was performed probabilistically for b/tsDMARD-naïve patients and deterministically for b/tsDMARD-experienced patients because there were no probabilistic estimates provided for secukinumab and certolizumab pegol when using the extended NMA (due to CODA not provided for this network). All ERG base-case analyses are conditional on the PAS price of ixekizumab. Additionally, the ERG used secukinumab 300 mg for all psoriasis severity levels in the b/tsDMARD-experienced population because no results were provided for secukinumab 150 mg in the extended NMA. For all analyses including biosimilar etanercept as a comparator, a correlation coefficient of 0.26, instead of 0.4, was used to derive the distribution of PASI 75 responders amongst patients who achieve a PsARC response.

Ixekizumab was [redacted] in all b/tsDMARD-naïve subgroups while it resulted in ICERs of respectively [redacted], [redacted], and [redacted] per QALY gained versus BSC in the no psoriasis, mild-to-moderate psoriasis and moderate-to-severe psoriasis subgroups of the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses).

5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of the following alternative assumptions on the cost effectiveness estimates. These were all performed using the ERG base-case. Results are presented in Table 6.2 in section 6. The ERG used secukinumab 300 mg for all psoriasis severity levels in the b/tsDMARD-experienced population because no results were provided for secukinumab 150 mg in the extended NMA.

Exploratory analyses using the ERG base-case:

1. The use of the company's preferred network for the b/tsDMARD-experienced population, excluding secukinumab and certolizumab pegol from the analysis.
2. Use of Poole et al for HAQ-DI related costs instead of Kobelt et al.
3. Use of the York model baseline PASI scores.
4. Alternative second line treatment in b/tsDMARD-naive patients.
5. Use of PASI 75 and PsARC instead of only PsARC.

5.3.3 Subgroup analyses performed based on the ERG base-case

No subgroup analyses were performed.

5.4 Conclusions of the cost effectiveness section

The ERG considers that the company's approach to use the revised York model as a basis for developing their model was appropriate.

The economic model described in the CS is considered by the ERG to meet the NICE reference case, with the notable exceptions of a) the exclusion of comparators identified in the scope, and b) a network meta-analysis that did not consider all the relevant outcomes as identified in the scope.

a) The absence of secukinumab and certolizumab pegol from the b/tsDMARD-experienced patient population analysis was justified by the unavailability of data in that population, however, it should be noted that studies on these two treatments were conducted in mixed (b/tsDMARD-naive and -experienced) populations.
b) The omission of adverse events from the economic model was considered a major limitation by the ERG. The ERG considers that treatment-specific adverse events could have an impact on treatment discontinuation, HRQoL and cost and resource use, and that not reflecting this in the model could lead to biased outcomes. The direction of this bias is difficult to determine.

The company's deterministic base-case ICERs of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained in the b/tsDMARD-experienced population when compared with BSC but [redacted] when compared with ustekinumab in that population. The cost effectiveness results were fairly robust to scenario and one-way sensitivity analyses conducted by the company, but the most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs

associated with ixekizumab and secukinumab. Scenario analyses indicated that assumptions with the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, the York utility model coefficients, the Poole et al. 2010 algorithm for costs associated with HAQ-DI,[72] and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab.

The ERG incorporated various adjustments to the company's base-case. The ERG base-case shows that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained in the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses).

The ERG identified major and minor issues and uncertainties that affected the cost effectiveness analysis. Major issues and uncertainties are listed in the following. One major limitation was the use of a limited network for the b/tsDMARD-experienced patient population, which omitted PASI 50 as an outcome, resulting in potential bias in favour of treatments with a higher PsARC response (given PASI 50 response was presumably set to 0% in this case). This also resulted in the exclusion of certolizumab pegol and secukinumab as comparators in this population, which deviated from the scope, again likely favouring ixekizumab in this population. This was partly addressed in the ERG base-case, although the data were not made available by the company to perform this analysis probabilistically. Furthermore, treatment sequences used in the model for the b/tsDMARD-naive patient population are excluding relevant treatments, as, in addition to ustekinumab, certolizumab pegol and secukinumab could also be used in second line. An alternative second-line treatment was explored in scenario analysis.

The ERG is concerned about the representativeness of the patient population in the SPIRIT trial programme and its impact on the relevance and validity of the NMA results in the UK context. The allocation of patients to health states in the model was based on a relative measure of response (based on reductions in symptoms), which leads to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. BSC was not accurately described in the CS and the ERG was unable to assess whether BSC was representative of the UK context, and whether the effectiveness and the costs associated with BSC in the cost effectiveness model were valid.

The assumption of equal treatment discontinuation rates for all b/tsDMARD treatments was viewed as a major and influential limitation. Of further concern were the excess mortality, which was considered high, and the fact that the HAQ-DI reduction estimate for ixekizumab q4w responders and non-responders based on the NMA did not reflect the trial data. The omission of adverse events from this submission is of particular concern, given that these differ per treatment and their inclusion would lead to potential differences in HRQoL, costs, and treatment discontinuation rates. Furthermore, the ERG considers there to be large uncertainty about the resource use and cost estimates associated with HAQ-DI and PASI, with several limitations identified in both estimates.

In exploratory analysis the ERG found that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population, except in the scenario in which both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In that scenario, ixekizumab resulted in an ICER of [redacted] per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab resulted in ICERs below [redacted] per QALY gained versus BSC in all psoriasis severity levels in all scenarios, except when both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In this scenario, ixekizumab [redacted]. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses), except in Scenario 1 in moderate-to severe psoriasis when ustekinumab [redacted].

In conclusion, despite the ERG criticism and amendments to the company's cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab had ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 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 both the probabilistic company and ERG base-case analyses. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3. Moreover, the exploratory sensitivity analyses, conditional on the ERG base-case, are presented in Table 6.2. Appendix 2 and the economic model sent by the ERG contain the technical details on the analyses performed by the ERG.

Table 6.1: Probabilistic ERG base-case; PAS price

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
Company base-case (probabilistic, performed by the ERG)						
bDMARD-naïve; no psoriasis						
BSC	£54,046	8.09	-	-	-	[redacted]
APR-UST-BSC	£93,347	9.49	[redacted]	1.39	[redacted]	[redacted]
IXE q4w-UST-BSC	[redacted]	9.69	[redacted]	1.60	[redacted]	Referent
CZP-UST-BSC	£99,866	9.67	[redacted]	1.57	[redacted]	[redacted]
SEC150-UST-BSC	£100,241	9.78	[redacted]	1.68	[redacted]	[redacted]
ADA-UST-BSC	£101,322	9.71	[redacted]	1.61	[redacted]	[redacted]
ETA-UST-BSC	£103,692	10.02	[redacted]	1.92	[redacted]	[redacted]
GOL-UST-BSC	£108,195	9.90	[redacted]	-0.12	[redacted]	[redacted]
INF-UST-BSC	£127,297	10.12	[redacted]	0.10	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,006	7.74	-	-	-	[redacted]
APR-UST-BSC	£105,446	9.16	[redacted]	1.41	[redacted]	[redacted]
IXE q4w-UST-BSC	[redacted]	9.38	[redacted]	1.64	[redacted]	Referent
CZP-UST-BSC	£111,375	9.34	[redacted]	1.60	[redacted]	[redacted]
SEC150-UST-BSC	£111,743	9.47	[redacted]	1.72	[redacted]	[redacted]
ADA-UST-BSC	£112,849	9.39	[redacted]	1.64	[redacted]	[redacted]
ETA-UST-BSC	£114,657	9.69	[redacted]	1.95	[redacted]	[redacted]
GOL-UST-BSC	£118,987	9.59	[redacted]	-0.10	[redacted]	[redacted]
INF-UST-BSC	£138,072	9.82	[redacted]	0.13	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,884	6.21	-	-	-	[redacted]
APR-UST-BSC	£127,576	7.70	[redacted]	1.49	[redacted]	[redacted]
CZP-UST-BSC	£132,373	7.90	[redacted]	1.69	[redacted]	[redacted]
ADA-UST-BSC	£133,882	7.97	[redacted]	1.77	[redacted]	[redacted]
IXE q2w-UST-BSC	[redacted]	8.11	[redacted]	1.91	[redacted]	Referent
ETA-UST-BSC	£134,567	8.24	[redacted]	2.03	[redacted]	[redacted]
GOL-UST-BSC	£138,550	8.23	[redacted]	-0.01	[redacted]	[redacted]
SEC300-UST-BSC	£155,532	7.97	[redacted]	-0.27	[redacted]	[redacted]
INF-UST-BSC	£157,603	8.51	[redacted]	0.27	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£55,942	7.38	-	-	-	[redacted]
IXE q4w-BSC	[redacted]	8.21	[redacted]	0.83	[redacted]	Referent
UST-BSC	£82,143	8.24	[redacted]	0.03	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,271	7.06	-	-	-	[redacted]
IXE q4w-BSC	[redacted]	7.93	[redacted]	0.87	[redacted]	Referent
UST-BSC	£94,133	7.97	[redacted]	0.03	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,618	2.26	-	-	-	[redacted]
IXE q2w-BSC	[redacted]	3.24	[redacted]	0.98	[redacted]	Referent
UST-BSC	£118,915	3.21	[redacted]	-0.03	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
ERG base-case						
bDMARD-naïve; no psoriasis (probabilistic)						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£99,754	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£106,247	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£106,591	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£107,703	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£109,998	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£114,501	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£133,706	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis (probabilistic)						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.61	[redacted]	1.62	[redacted]	[redacted]
IXE q4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent
CZP-UST-BSC	£118,101	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.89	[redacted]	1.91	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£121,313	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£125,644	10.05	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£144,833	10.17	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis (probabilistic)						
BSC	£104,874	6.38	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
APR-UST-BSC	£134,903	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£139,690	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£141,198	8.59	[redacted]	2.22	[redacted]	[redacted]
IXE q2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA-UST-BSC	£141,826	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£145,815	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis (deterministic)						
BSC	£58,838	7.61	-	-	-	[redacted]
IXE q4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP -BSC	£83,355	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£88,828	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£106,747	8.54	[redacted]	-0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis (deterministic)						
BSC	£73,880	7.26	-	-	-	[redacted]
IXE q4w-BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP-BSC	£95,702	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£101,087	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£119,384	8.31	[redacted]	-0.15	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis (deterministic)						
BSC	£104,602	2.23	-	-	-	[redacted]
CZP-BSC	£121,172	3.98	£16,570	1.75	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
IXE q2w-BSC	[redacted]	4.11	[redacted]	0.13	[redacted]	Referent
UST-BSC	£126,390	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300-BSC	£145,424	3.91	[redacted]	-0.22	[redacted]	[redacted]

ADA = adalimumab; APR = apremilast; bDMARD = biologic disease-modifying anti-rheumatic drug; BSC = best supportive care; CZP = certolizumab pegol; ERG = Evidence Review Group; ETA = etanercept; GOL = golimumab; ICER = Incremental cost effectiveness ratio; INF = infliximab; IXE = ixekizumab; PAS = patient access scheme; q2w = once every two weeks; q4w = once every four weeks; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

Table 6.2: Deterministic scenario analyses conditional on ERG base-case, PAS price

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
ERG base-case (deterministic)						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£99,754	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£106,247	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£106,591	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£107,703	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£109,998	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£114,501	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£133,706	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.61	[redacted]	1.62	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent
CZP-UST-BSC	£118,101	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.89	[redacted]	1.91	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£121,313	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£125,644	10.05	[redacted]	-0.04	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
INF-UST-BSC	£144,833	10.17	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]
APR-UST-BSC	£134,903	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£139,690	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£141,198	8.59	[redacted]	2.22	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA -UST-BSC	£141,826	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£145,815	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP-BSC	£83,355	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£88,828	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£106,747	8.54	[redacted]	-0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	£0	[redacted]
IXEq4w-BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP-BSC	£95,702	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£101,087	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£119,384	8.31	[redacted]	-0.15	[redacted]	[redacted]

Treatment sequence	**Total costs (£)**	**Total QALYs**	**Incremental Costs**	**Incremental QALY**	**Full incremental ICER (£/QALY)**	**ICER IXE versus comparator**
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	£0	[redacted]
CZP-BSC	£121,172	3.98	[redacted]	1.75	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	4.11	[redacted]	0.13	[redacted]	Referent
UST-BSC	£126,390	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300-BSC	£145,424	3.91	[redacted]	-0.22	[redacted]	[redacted]
Scenario 1: The use of the company's preferred network for the bDMARD-experienced population, excluding secukinumab and certolizumab pegol from the analysis.						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£96,450	9.77	[redacted]	1.42	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.92	[redacted]	1.57	[redacted]	Referent
CZP-UST-BSC	£103,043	9.96	[redacted]	1.61	[redacted]	[redacted]
SEC 150-UST-BSC	£103,393	10.03	[redacted]	1.68	[redacted]	[redacted]
ADA-UST-BSC	£104,495	10.00	[redacted]	1.65	[redacted]	[redacted]
ETA 150-UST-BSC	£106,901	10.22	[redacted]	1.87	[redacted]	[redacted]
GOL-UST-BSC	£111,437	10.20	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£130,648	10.30	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£109,258	9.48	[redacted]	1.49	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.63	[redacted]	1.65	[redacted]	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£115,255	9.67	[redacted]	1.69	[redacted]	[redacted]
SEC150-UST-BSC	£115,598	9.76	[redacted]	1.78	[redacted]	[redacted]
ADA-UST-BSC	£116,725	9.71	[redacted]	1.73	[redacted]	[redacted]
ETA-UST-BSC	£118,563	9.96	[redacted]	1.98	[redacted]	[redacted]
GOL-UST-BSC	£122,924	9.93	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£142,118	10.04	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]
APR-UST-BSC	£132,710	8.14	[redacted]	1.76	[redacted]	[redacted]
CZP-UST-BSC	£137,563	8.38	[redacted]	2.00	[redacted]	[redacted]
ADA-UST-BSC	£139,069	8.42	[redacted]	2.04	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.50	[redacted]	2.12	[redacted]	Referent
ETA-UST-BSC	£139,770	8.79	[redacted]	2.41	[redacted]	[redacted]
GOL-UST-BSC	£143,781	8.68	[redacted]	-0.10	[redacted]	[redacted]
SEC300-UST-BSC	£160,813	8.36	[redacted]	-0.42	[redacted]	[redacted]
INF-UST-BSC	£162,942	8.90	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
IXEq4w-BSC	[redacted]	8.40	[redacted]	0.79	[redacted]	Referent
UST-BSC	£85,151	8.49	[redacted]	0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
IXEq4w -BSC	[redacted]	8.18	[redacted]	0.92	[redacted]	Referent
UST-BSC	£97,830	8.28	[redacted]	0.10	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	-	[redacted]
IXEq2w -BSC	[redacted]	3.80	[redacted]	1.57	[redacted]	Referent
UST-BSC	£123,956	3.77	[redacted]	-0.03	[redacted]	[redacted]
Scenario 2: Use of Poole et al.[72] for HAQ-DI related costs instead of Kobelt et al.[100]						
bDMARD-naïve; no psoriasis						
BSC	£36,728	8.35	-	-	-	[redacted]
APR-UST-BSC	£72,980	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£79,793	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£80,172	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£81,297	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£83,130	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£87,305	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£106,666	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£36,728	7.99	-	-	-	[redacted]
APR-UST-BSC	£72,980	9.61	[redacted]	1.62	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£79,793	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£80,172	9.89	[redacted]	1.91	[redacted]	[redacted]
ADA-UST-BSC	£81,297	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£83,130	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£87,305	10.05	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£106,666	10.17	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£37,361	6.38	-	-	£0	[redacted]
APR-UST-BSC	£73,474	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£80,270	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£81,772	8.59	[redacted]	2.22	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA-UST-BSC	£83,580	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£87,757	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£103,068	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£107,108	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£44,052	7.61	-	-	£0	[redacted]
IXEq4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP-BSC	£63,939	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£69,163	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£87,760	8.54	[redacted]	-0.10	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£37,680	7.26	-	-	£0	[redacted]
IXEq4w -BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP -BSC	£58,297	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£63,602	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£82,091	8.31	[redacted]	-0.15	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£36,414	2.23	-	-	-	[redacted]
CZP -BSC	£57,191	3.98	[redacted]	1.75	[redacted]	[redacted]
IXEq2w -BSC	[redacted]	4.11	[redacted]	1.88	[redacted]	Referent
UST-BSC	£62,512	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300 -BSC	£80,978	3.91	[redacted]	-0.22	[redacted]	[redacted]
Scenario 3: Use of the York model baseline PASI scores.						
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.67	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.36	[redacted]	1.69	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.52	[redacted]	1.85	[redacted]	Referent
CZP-UST-BSC	£118,101	9.56	[redacted]	1.89	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.66	[redacted]	1.99	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.60	[redacted]	1.93	[redacted]	[redacted]
ETA-UST-BSC	£121,313	9.87	[redacted]	2.20	[redacted]	[redacted]
GOL-UST-BSC	£125,644	9.82	[redacted]	-0.05	[redacted]	[redacted]
INF-UST-BSC	£144,833	9.95	[redacted]	0.08	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	7.12	-	-	-	[redacted]
APR-UST-BSC	£134,903	8.91	[redacted]	1.79	[redacted]	[redacted]
CZP-UST-BSC	£139,690	9.12	[redacted]	2.00	[redacted]	[redacted]
ADA-UST-BSC	£141,198	9.16	[redacted]	2.04	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	9.23	[redacted]	2.11	[redacted]	Referent
ETA-UST-BSC	£141,826	9.48	[redacted]	2.36	[redacted]	[redacted]
GOL-UST-BSC	£145,815	9.39	[redacted]	-0.09	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	9.12	[redacted]	-0.36	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.57	[redacted]	0.09	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	6.32	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	7.53	[redacted]	1.21	[redacted]	Referent
CZP-BSC	£95,702	7.52	[redacted]	0.00	[redacted]	[redacted]
UST-BSC	£101,087	7.65	[redacted]	0.12	[redacted]	[redacted]
SEC300-BSC	£119,384	7.51	[redacted]	-0.14	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	5.09	-	-	-	[redacted]
CZP-BSC	£121,172	6.48	[redacted]	1.39	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	6.60	[redacted]	1.51	[redacted]	Referent
UST-BSC	£126,390	6.61	[redacted]	0.01	[redacted]	[redacted]
SEC300-BSC	£145,424	6.44	[redacted]	-0.17	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
Scenario 4: Alternative second line treatment in bDMARD-naive patients.						
Second-line certolizumab pegol						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-CZP-BSC	£94,747	9.80	[redacted]	1.45	[redacted]	[redacted]
IXEq4w-CZP-BSC	[redacted]	9.95	[redacted]	1.60	[redacted]	Referent
SEC150-CZP-BSC	£101,737	10.07	[redacted]	1.71	[redacted]	[redacted]
ADA-CZP-BSC	£102,840	10.03	[redacted]	1.68	[redacted]	[redacted]
ETA-CZP-BSC	£105,293	10.25	[redacted]	1.90	[redacted]	[redacted]
GOL-CZP-BSC	£109,844	10.23	[redacted]	-0.02	[redacted]	[redacted]
INF-CZP-BSC	£129,054	10.33	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-CZP-BSC	£107,261	9.51	[redacted]	1.53	[redacted]	[redacted]
IXEq4w-CZP-BSC	[redacted]	9.67	[redacted]	1.68	[redacted]	Referent
SEC150-CZP-BSC	£113,658	9.80	[redacted]	1.81	[redacted]	[redacted]
ADA-CZP-BSC	£114,785	9.75	[redacted]	1.76	[redacted]	[redacted]
ETA-CZP-BSC	£116,679	10.00	[redacted]	2.02	[redacted]	[redacted]
GOL-CZP-BSC	£121,058	9.96	[redacted]	-0.04	[redacted]	[redacted]
INF-CZP-BSC	£140,252	10.08	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
APR-CZP-BSC	£130,123	8.22	[redacted]	1.84	[redacted]	[redacted]
ADA-CZP-BSC	£136,556	8.49	[redacted]	2.12	[redacted]	[redacted]
IXEq2w-CZP-BSC	[redacted]	8.58	[redacted]	2.20	[redacted]	Referent
ETA-CZP-BSC	£137,333	8.86	[redacted]	2.49	[redacted]	[redacted]
GOL-CZP-BSC	£141,368	8.76	[redacted]	-0.10	[redacted]	[redacted]
SEC300-CZP-BSC	£158,263	8.44	[redacted]	-0.42	[redacted]	[redacted]
INF-CZP-BSC	£160,531	8.97	[redacted]	0.11	[redacted]	[redacted]
Second-line secukinumab						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-		[redacted]
APR-SEC-BSC	£115,979	9.77	[redacted]	1.42	[redacted]	[redacted]
IXEq4w-SEC-BSC	[redacted]	9.93	[redacted]	1.58	[redacted]	Referent
CZP-SEC-BSC	£121,980	9.96	[redacted]	1.61	[redacted]	[redacted]
ADA-SEC-BSC	£123,452	10.00	[redacted]	1.65	[redacted]	[redacted]
ETA-SEC-BSC	£125,210	10.23	[redacted]	1.88	[redacted]	[redacted]
GOL-SEC-BSC	£129,547	10.21	[redacted]	-0.02	[redacted]	[redacted]
INF-SEC-BSC	£148,725	10.30	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	£0	[redacted]
APR-SEC-BSC	£128,749	9.49	[redacted]	1.51	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
IXEq4w-SEC-BSC	[redacted]	9.65	[redacted]	1.66	[redacted]	Referent
CZP-SEC-BSC	£134,155	9.69	[redacted]	1.71	[redacted]	[redacted]
ADA-SEC-BSC	£135,646	9.73	[redacted]	1.74	[redacted]	[redacted]
ETA-SEC-BSC	£136,836	9.98	[redacted]	2.00	[redacted]	[redacted]
GOL-SEC-BSC	£140,998	9.95	[redacted]	-0.04	[redacted]	[redacted]
INF-SEC-BSC	£160,160	10.06	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	£0	[redacted]
APR-SEC-BSC	£152,123	8.20	[redacted]	1.83	[redacted]	[redacted]
CZP-SEC-BSC	£156,388	8.44	[redacted]	2.06	[redacted]	[redacted]
ADA-SEC-BSC	£157,914	8.48	[redacted]	2.10	[redacted]	[redacted]
ETA-SEC-BSC	£157,970	8.85	[redacted]	2.47	[redacted]	[redacted]
IXEq2w-SEC-BSC	[redacted]	8.56	[redacted]	-0.29	[redacted]	Referent
GOL-SEC-BSC	£161,783	8.74	[redacted]	-0.10	[redacted]	[redacted]
INF-SEC-BSC	£180,913	8.96	[redacted]	0.11	[redacted]	[redacted]
Scenario 5: Use of PASI 75 & PsARC instead of only PsARC						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£88,297	9.41	[redacted]	1.06	[redacted]	[redacted]
ETA-UST-BSC	£89,270	9.45	[redacted]	1.10	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£89,445	9.47	[redacted]	1.12	[redacted]	[redacted]
ADA-UST-BSC	£93,971	9.59	[redacted]	1.24	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.79	[redacted]	1.44	[redacted]	Referent
SEC-UST-BSC	£98,711	9.82	[redacted]	1.46	[redacted]	[redacted]
GOL-UST-BSC	£100,301	9.79	[redacted]	-0.03	[redacted]	[redacted]
INF-UST-BSC	£124,354	10.13	[redacted]	0.32	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£102,249	9.10	[redacted]	1.12	[redacted]	[redacted]
ETA-UST-BSC	£103,121	9.14	[redacted]	1.16	[redacted]	[redacted]
CZP-UST-BSC	£103,147	9.16	[redacted]	1.18	[redacted]	[redacted]
ADA-UST-BSC	£107,381	9.29	[redacted]	1.30	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.50	[redacted]	1.51	[redacted]	Referent
SEC-UST-BSC	£111,545	9.53	[redacted]	1.55	[redacted]	[redacted]
GOL-UST-BSC	£113,031	9.50	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£136,306	9.87	[redacted]	0.34	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	-	[redacted]
APR-UST-BSC	£128,012	7.71	[redacted]	1.33	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£128,430	7.79	[redacted]	1.41	[redacted]	[redacted]
ETA-UST-BSC	£128,704	7.77	[redacted]	1.40	[redacted]	[redacted]
ADA-UST-BSC	£132,082	7.93	[redacted]	1.55	[redacted]	[redacted]
GOL-UST-BSC	£136,374	8.19	[redacted]	1.81	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.34	[redacted]	1.96	[redacted]	Referent
SEC300-UST-BSC	£155,462	8.19	[redacted]	-0.15	[redacted]	[redacted]
INF-UST-BSC	£158,093	8.70	[redacted]	0.36	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
SEC300-BSC	£63,744	7.70	[redacted]	0.08	[redacted]	[redacted]
IXEq4w-BSC	[redacted]	8.13	[redacted]	0.52	[redacted]	Referent
CZP-BSC	£73,787	8.18	[redacted]	0.57	[redacted]	[redacted]
UST-BSC	£84,054	8.45	[redacted]	0.27	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	£0	[redacted]
SEC300-BSC	£78,735	7.35	[redacted]	0.09	[redacted]	[redacted]
IXEq4w-BSC	[redacted]	7.87	[redacted]	0.61	[redacted]	Referent
CZP-BSC	£87,175	7.94	[redacted]	0.68	[redacted]	[redacted]
UST-BSC	£96,859	8.24	[redacted]	0.30	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-BSC	£114,685	3.32	[redacted]	1.09	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	3.34	[redacted]	0.02	[redacted]	Referent
UST-BSC	£123,230	3.78	[redacted]	0.46	[redacted]	[redacted]
SEC300-BSC	£139,794	3.63	[redacted]	-0.15	[redacted]	[redacted]

Note: Small discrepancies between full incremental and pairwise ICERs are caused by rounding. Full incremental ICERs are correct.
ADA = adalimumab; APR = apremilast; bDMARD = biologic disease-modifying anti-rheumatic drug; BSC = best supportive care; CZP = certolizumab pegol; ERG = Evidence Review Group; ETA = etanercept; GOL = golimumab; ICER = Incremental cost effectiveness ratio; INF = infliximab; IXE = ixekizumab; PAS = patient access scheme; q2w = once every two weeks; q4w = once every four weeks; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

7. END OF LIFE

Not relevant for this submission.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

The company presented direct evidence from two RCTs, SPIRIT-P1 and SPIRIT-P2 that compared ixekizumab to placebo in adults with PsA. SPIRIT-P1 was conducted in biological DMARD-naïve patients whilst SPIRIT-P2 was conducted in those with experience of biological DMARDs. SPIRIT-P1 included 417 patients and SPIRIT-P2 363 patients and both were well conducted, multinational trials. Across the two trials approximately [redacted] of patients were from the UK.

In both SPIRIT trials, significantly more patients achieved an ACR 20 response at week 24 with ixekizumab compared to placebo (SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 62.1%, placebo 30.2%; SPIRIT-P2: IXE 80 q4w 53.3%, IXE 80 q2w 48.0%, placebo 19.5%; p<0.001 for all comparisons to placebo). In both SPIRIT trials, the percentage of patients who achieved a PsARC response at week 12 as well as week 24 were statistically significantly greater for both ixekizumab groups compared to placebo in all cases (Week 12 – SPIRIT-P1: IXE 80 q4w 55.1%, IXE 80 q2w 61.2%, placebo 34.0%; SPIRIT-P2: IXE 80 q4w 50.0%, IXE 80 q2w 52.0%, placebo 23.7%. Week 24 – SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 66.0%, placebo 32.1%; SPIRIT-P2: IXE 80 q4w 55.7%, IXE 80 q2w 47.2%, placebo 20.3%). In terms of quality of life, at week 12 patients in the two ixekizumab groups achieved significantly greater mean change from baseline in HAQ-DI total scores in both SPIRIT trials. As not all participants in the SPIRIT trials would have been eligible for biological therapy under current NICE criteria, the company conducted a subgroup analysis using an integrated set of patients from SPIRIT-P1 and P2 who met the NICE criteria. The total number of patients available for analysis was [redacted]. [redacted] patients who received ixekizumab 80 mg Q4W or Q2W achieved an ACR 20 response at week 24 compared to placebo ([redacted] and [redacted] vs. [redacted] respectively). In the 24-week double-blind treatment phase patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials. Adverse events across the two SPIRIT trials were mainly of mild or moderate severity and the proportion of patients who discontinued medication due to AEs was low across all treatment groups. There were no deaths across the two trials in the double-blind periods. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials.

In the absence of trials directly comparing the active treatments specified in the NICE scope, the company conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, PASI 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, ixekizumab was [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted], with [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders and [redacted] were the most effect treatments.

There was less evidence for bMARD-experienced patients (fewer than five trials in most analyses) and ixekizumab [redacted] ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate [redacted]

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab but the differences were [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

Economic evaluation

The company's deterministic base-case ICERs of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained in the b/tsDMARD-experienced population when compared with BSC but [redacted] when compared with ustekinumab in that population at all severity levels. The ERG has incorporated various adjustments to the company base-case (probabilistic results for the b/tsDMARD-naïve population and deterministic results for the b/tsDMARD-experienced population). In the ERG base-case, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses). Additionally, the ERG explored different scenarios based on the ERG base-case analysis. In those analyses, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population, except in the scenario in which both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In that scenario, ixekizumab had an ICER of [redacted] per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab had ICERs below [redacted] per QALY gained versus BSC in all psoriasis severity levels in all scenarios, except when both PASI 75 and PsARC responses were used simultaneously to determine treatment response. In this scenario, ixekizumab [redacted].

In conclusion, despite the ERG criticism and amendments to company cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab provided ICERs [redacted] per QALY gained versus BSC in the b/tsDMARD-experienced population. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

8.2 Strengths and limitations of the assessment

Following clarification, the company submission searches were well presented and reproducible. Searches were carried out on a range of databases and supplementary resources. However, the ERG was concerned about the overall quality of the searches conducted, as there were numerous inconsistencies, inaccuracies, errors and redundancy throughout. The extensive use of restrict to focus, date limit (2000-2017), omission of the NHS EED database and application of language limits were all considered overly restrictive. It is possible that relevant evidence may have been missed as a consequence.

Two randomised controlled trials comparing ixekizumab to placebo are presented in the CS, one in patients with experience of bDMARDs and one in patients naïve to bDMARDs. Both multinational

trials included a small number of UK patients (approximately [redacted] across the two trials). Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. A separate analysis of the NICE ITT population [redacted] in relation to placebo is provided in the CS based on [redacted] patients across the two trials. The committee will need to decide, based on the factors highlighted by the ERG in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice. Another weakness in the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope, i.e. the main results in the CS came from a NMA.

The cost effectiveness model is well built and transparent. The treatment effectiveness estimates from a network of studies are a strength, as is the attempt to consider treatment sequences. The company performed many relevant sensitivity and scenario analyses to reflect uncertainty about the cost effectiveness results. The model was relatively robust to these changes, with some notable exceptions as detailed in the previous sections.

Health states in the model are based on a relative measure of response (based on reductions in symptoms), which leads to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. Further limitations are the exclusion of comparators identified in the scope and the omission of adverse events from the NMA and economic model. For b/tsDMARD-experienced patient population, only a limited network was used, which omitted PASI 50 as an outcome. The ERG considers a weakness the assumption of equal treatment discontinuation rates for all b/tsDMARD treatments. The representativeness of the patient population in the SPIRIT trial programme, excess mortality in this population, resource use and cost estimates associated with HAQ-DI and PASI pose areas of uncertainty.

8.3 Suggested research priorities

Research is lacking directly comparing the active comparators in the scope to determine the best treatment available for patients with PsA. The ERG notes that there is an ongoing trial (SPIRIT-H2H) due to complete in April 2019 which compares ixekizumab to adalimumab in bDMARD naïve patients. It should also be noted that using direct evidence rather than NMA results would give more reliable estimates for both, clinical as well as cost effectiveness.

9. REFERENCES

[1] Eli Lilly and Company Limited. *Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194]. Document B: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*: Eli Lilly and Company Limited, 2018 [accessed 8.2.18]. 205p.

[2] Koolaee R, Takeshita J, Ogdie A. Epidemiology and natural history of psoriatic arthritis: an update - what dermatologists need to know. *Curr Derm Rep* 2013;2:66-76.

[3] Lories RJ, de Vlam K. Tumour necrosis factor inhibitors in the treatment of psoriatic arthritis: a view on effectiveness, clinical practice and toxicity. *Expert Opin Biol Ther* 2014;14(12):1825-36.

[4] Husni ME. Comorbidities in Psoriatic Arthritis. *Rheum Dis Clin North Am* 2015;41(4):677-98.

[5] Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. *P T* 2010;35(12):680-9.

[6] Ali Y, Tom BD, Schentag CT, Farewell VT, Gladman DD. Improved survival in psoriatic arthritis with calendar time. *Arthritis Rheum* 2007;56(8):2708-14.

[7] McAteer H. *Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]: Professional organisation submission from Psoriasis Association*, 2018 [accessed 21.3.18]. 6p.

[8] Ogdie A, Langan S, Love T, Haynes K, Shin D, Seminara N, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology (Oxford)* 2013;52(3):568-75.

[9] Tintle SJ, Gottlieb AB. Psoriatic arthritis for the dermatologist. *Dermatol Clin* 2015;33(1):127-48.

[10] Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3(1):55-78.

[11] Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54(8):2665-73.

[12] Psoriasis Association. *Diagnosis of psoriatic arthritis [Internet]*. Northampton: Psoriasis Association, April 2016 [accessed 15.3.18]. 2p. Available from: https://www.psoriasis-association.org.uk/media/InformationSheets/PsA_Diagnosis.pdf

[13] National Institute for Health and Care Excellence. *Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs. Technology appraisal guidance 445 [Internet]*. London: NICE, 2017 [accessed 20.2.18]. 36p. Available from: https://www.nice.org.uk/guidance/ta445

[14] National Institute for Health and Care Excellence. *Golimumab for the treatment of psoriatic arthritis. Technology appraisal guidance 220 [Internet]*. London: NICE, 2011 [accessed 21.3.18]. 40p. Available from: https://www.nice.org.uk/guidance/ta220

[15] National Institute for Health and Care Excellence. *Apremilast for treating active psoriatic arthritis. Technology appraisal guidance 433 [Internet]*. London: NICE, 2017 [accessed 21.3.18]. 31p. Available from: https://www.nice.org.uk/guidance/ta433

[16] National Institute for Health and Care Excellence. *Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. Technology appraisal guidance 199 [Internet]*. London: NICE, 2010 [accessed 22.3.18]. 43p. Available from: https://www.nice.org.uk/guidance/ta199

[17] van de Kerkhof PC, Reich K, Kavanaugh A, Bachelez H, Barker J, Girolomoni G, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. *J Eur Acad Dermatol Venereol* 2015;29(10):2002-10.

[18] Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic Arthritis and Burden of Disease: Patient Perspectives from the Population-Based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) Survey. *Rheumatol Ther* 2016;3(1):91-102.

[19] Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor alpha inhibitor therapy: results from the Danish Nationwide DANBIO Registry. *Arthritis Rheum* 2013;65(5):1213-23.

[20] Mease P. A short history of biological therapy for psoriatic arthritis. *Clin Exp Rheumatol* 2015;33(Suppl 93):S104-S108.

[21] National Institute for Health and Care Excellence. *Ustekinumab for treating active psoriatic arthritis. Technology appraisal guidance 340 [Internet]*. London: NICE, 2015 [accessed 21.3.18]. 58p. Available from: https://www.nice.org.uk/guidance/ta340

[22] Korendowych E, Packham J. *Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]: Professional organisation submission from British Society for Rheumatology*, 2018 [accessed 21.3.18]. 12p.

[23] Chandler D. *Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]: Professional organisation submission from Psoriasis and Psoriatic Arthritis Alliance (PAPAA)*, 2018 [accessed 21.3.18]. 7p.

[24] National Institute for Health and Care Excellence. *Ixekizumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance 442 [Internet]*. London: NICE, 2017 [accessed 23.3.18]. 27p. Available from: https://www.nice.org.uk/guidance/ta442

[25] Eli Lilly and Company Limited. *Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]: response to request for clarification from the ERG*: Eli Lilly and Company Limited, 2018 [accessed 15.3.18]. 95p.

[26] Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M, et al. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation. *Health Technol Assess* 2017;21(56):1-326.

[27] Rose-Parfitt E. *Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]: Professional organisation submission from Rheumatology Pharmacists UK (RPUK) on behalf of the United Kingdom Clinical Pharmacy Association (UKCPA)*, 2018 [accessed 21.3.18]. 12p.

[28] Eli Lilly and Company Limited. *Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194]: Appendices*: Eli Lilly and Company Limited, Feb 2018 [accessed 8.2.18]. 283p.

[29] Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions [Internet]*. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011 [accessed 23.3.11]. Available from: http://handbook.cochrane.org/

[30] van der Heijde D, Dankert T, Nieman F, Rau R, Boers M. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. *Rheumatology (Oxford)* 1999;38(10):941-7.

[31] Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2017;76(1):79-87.

[32] Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester G-R, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet* 2017;389(10086):2317-2327.

[33] Eli Lilly and Company. *1. RHBE Clinical Study Report: a multicenter, randomized, double-blind, placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-experienced patients with active psoriatic arthritis. LY2439821 (Ixekizumab) - Psoriatic Arthritis [PDF provided with the company's submission]*: Eli Lilly and Company, 28 Jul 2017 [accessed 8.2.18]. 7321p.

[34] Eli Lilly and Company Ltd. *ANNEX I: Summary of product characteristics (Taltz) [PDF supplied with the company's submission]*: Eli Lilly and Company Ltd.,, n.d. [accessed 7.2.18]. 74p.

[35] Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials [Internet]. Sheffield: ScHARR, University of Sheffield, 2011 (updated Sept 2016) [accessed 9.4.18]. Available from: http://www.nicedsu.org.uk

[36] Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52(10):3279-89.

[37] Thom H, Jugl S, McInnes I, Nash P, Ritchlin C, Kanters S, et al. *Psoriatic Arthritis Response Criteria scores: results of a placebo-adjusted network meta-analysis with secukinumab [Internet]*, 2016 [accessed 12.2.18]. 1p. Available from: https://www.ispor.org/research_pdfs/52/pdffiles/PMS10.pdf

[38] Genovese M, Mease PJ, Thomson G, Kivitz A, Perdok R, Weinberg M, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007;34(5):1040-50.

[39] Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009;60(4):976-86.

[40] Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2005;52(4):1227-36.

[41] Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005;64(8):1150-7.

[42] Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000;356(9227):385-390.

[43] Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50(7):2264-72.

[44] Mease P, FitzGerald O, et al. Efficacy and safety of tofacitinib, an oral janus kinase inhibitor, or adalimumab in patients with active psoriatic arthritis and an inadequate response to conventional synthetic DMARDs: a randomized, placebo-controlled, phase 3 trial. *Arthritis Rheumatol* 2016;68(Suppl 10).

[45] Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014;73(6):1020-6.

[46] Cutolo M, Myerson G, Fleischmann R, Lioté F, Díaz-González F, Van den Bosch F, et al. A phase iii, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol* 2016;43(9):1724-34.

[47] Edwards C, Blanco F, Crowley J, Birbara C, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis* 2016;75(6):1065-73.

[48] Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014;73(1):48-55.

[49] Eli Lilly and Company. *1. RHAP Clinical Study Report Amendment: a multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis. LY2439821 (Ixekizumab) - Psoriatic Arthritis. I1F-MC-RHAP Clinical Study Report Amendment Body: Protocol I1F-MC-RHAP (Phase 3) [PDF provided with the company's submission]*: Eli Lilly and Company, 3 Oct 2016 [accessed 8.2.18]. 8829p.

[50] Eli Lilly and Company. *1. RHAP Clinical Study Report: a multicenter, randomized, double-blind, active and placebo-controlled 24-week study followed by long-term evaluation of efficacy and safety of ixekizumab (LY2439821) in biologic disease-modifying antirheumatic drug-naive patients with active psoriatic arthritis. LY2439821 (Ixekizumab) - Psoriatic Arthritis. Protocol I1F-MC-RHAP [PDF provided with the company's submission]*: Eli Lilly and Company, 3 Aug 2016 [accessed 8.2.18]. 5360p.

[51] Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014;73(6):990-9.

[52] Bilal J, Riaz IB, Kamal MU, Elyan M, Sudano D, Khan MA. A systematic review and meta-analysis of efficacy and safety of novel interleukin inhibitors in the management of psoriatic arthritis. *J Clin Rheumatol* 2018;24(1):6-13.

[53] Cawson MR, Mitchell SA, Knight C, Wildey H, Spurden D, Bird A, et al. Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic arthritis. *BMC Musculoskelet Disord* 2014;15(1):26.

[54] Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M, et al. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation. *Health Technol Assess* 2017;21(56):1-326.

[55] Gharaibeh M, Xu Y, Lee J, Chitnis M, Collier D. Efficacy of biologics and new anti-inflammatory agents used in the treatment of active psoriatic arthritis: systematic literature review and network meta-analysis of the evidence. *Arthritis Rheum* 2017.

[56] Kawalec P, Holko P, Mocko P, Pilc A. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. *Rheumatol Int* 2018;38(2):189-201.

[57] Song GG, Lee YH. Relative efficacy and safety of apremilast, secukinumab, and ustekinumab for the treatment of psoriatic arthritis. *Z Rheumatol* 2017;Epub ahead of print:1-8.

[58] Strand V, Husni ME, Singh R, Betts K, Song Y, Griffith J, et al. Network meta-analysis of targeted immunomodulators in the treatment of biologic-naive psoriatic arthritis. *Arthritis Rheum* 2017.

[59] Wu D, Yue J, Tam LS. Efficacy and safety of biologics targeting interleukin- 6, -12/23 and -17 pathways for peripheral psoriatic arthritis: a network meta-analysis. *Rheumatology* 2018;57(3):563-571.

[60] Atteno M, Peluso R, Costa L, Padula S, Iervolino S, Caso F, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol* 2010;29(4):399-403.

[61] Glanville J, Kaunelis D, Mensinkai S, Picheca L. *Pruning Emtree: does focusing Embase subject headings impact search strategy precision and sensitivity? [Internet]*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2015 [accessed 14.7.16]. 79p. Available from: https://www.cadth.ca/pruning-emtree-embase

[62] Duffy S, Ross J, Misso K, de Kock S, Noake C, Stirk L. *Is it possible to focus EMTREE without loss of sensitivity when searching Embase for systematic reviews? Analysis of Cochrane Reviews and HTA reports (Oral G1) [Internet]. Paper presented at 15th EAHIL Conference; 6-11 Jun 2016; Seville, Spain*, 2016 [accessed 14.7.16] Available from: http://www.bvsspa.es/eahil2016/wp-content/uploads/2016/05/G1.pdf

[63] Lefebvre C, Manheimer E, Glanville J. 6.4.9 Language, date and document format restrictions (Chapter 6: Searching for studies) [Internet]. In: Higgins JPT, Green S, editors. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011 [accessed 25.5.17]. Available from: http://handbook.cochrane.org/

[64] Eli Lilly and Company Limited. *Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]: response to request for clarification from the ERG. Addendum (A10)*: Eli Lilly and Company Limited, 2018 [accessed 21.3.18]. 6p.

[65] Christophers E, Barker JN, Griffiths CE, Dauden E, Milligan G, Molta C, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Eur Acad Dermatol Venereol* 2010;24(5):548-54.

[66] Gniadecki R, Robertson D, Molta CT, Freundlich B, Pedersen R, Li W, et al. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *J Eur Acad Dermatol Venereol* 2012;26(11):1436-43.

[67] Wade AG, Crawford GM, Pumford N, Koscielny V, Maycock S, McConnachie A. Baseline characteristics and patient reported outcome data of patients prescribed etanercept: web-based and telephone evaluation. *BMC Med Res Methodol* 2011;11:91.

[68] Tillett W, Shaddick G, Jobling A, Askari A, Cooper A, Creamer P, et al. Effect of anti-TNF and conventional synthetic disease-modifying anti-rheumatic drug treatment on work disability and clinical outcome in a multicentre observational cohort study of psoriatic arthritis. *Rheumatology (Oxford)* 2017;56(4):603-612.

[69] Tillett W, Askari A, Cooper A, Creamer P, Clunie G. Long term outcomes in psoriatic arthritis 2; a prospective multicentre observational study of work disability in psoriatic arthritis: First report of the clinical and socioeconomic associations of work disability in psoriatic arthritis. *Arthritis Rheum* 2013;65:S134.

[70] Sokoll K, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol* 2001;28(2):1842-6.

[71] Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. *Arthritis Care Res (Hoboken)* 2010;62(3):345-53.

[72] Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. *Rheumatology (Oxford)* 2010;49(10):1949-56.

[73] Mughal F, Cawston H, Cure S, Morris J, Tencer T, Zhang F. Cost-effectiveness of apremilast in psoriatic arthritis in Scotland. *Value Health* 2015;18(7):A644.

[74] Han C, Genovese M, Deodhar A, Hsu B, Hsia E. Sustained improvement in health-related quality of life, work productivity, employability and reduced healthcare resource utilization of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis treated with golimumab: 5-year results from three phase III studies. *Rheumatology* 2014;54:i74.

[75] Mughal F, Gagnon J. Budget impact of apremilast for active psoriatic arthritis in the UK. *Value Health* 2016;19(7):A532.

[76] Department of Health. *NHS reference costs 2014 to 2015 [Internet]*. London: Department of Health, 2015 [accessed 22.3.18] Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477919/2014-15_Reference_costs_publication.pdf

[77] Monthly Index of Medical Specialities (MIMS) [Internet]. Haymarket Media Group Ltd., n.d. [accessed 22.3.18]. Available from: https://www.mims.co.uk/

[78] Curtis L, Burns A. *Unit Costs of Health and Social Care*. Canterbury: Personal Social Services Research Unit (PSSRU), University of Kent, 2015 [accessed 22.3.18] Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2015/

[79] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal [Internet]*. London: NICE, 2014 [accessed 8.2.18]. 98p. Available from: nice.org.uk/process/pmg19

[80] National Institute for Health and Care Excellence. *Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]: Clarification letter*. London: NICE, 28.2.18 [accessed 28.2.18]. 9p.

[81] National Institute for Health and Care Excellence. *Spondyloarthritis in over 16s: diagnosis and management. NICE guideline 65 [Internet]*. London: NICE, 2017 [accessed 21.3.18]. 32p. Available from: https://www.nice.org.uk/guidance/ng65

[82] AbbVie Limited. Summary of product characteristics (SPC): Humira 40 mg/0.8 ml vial for paediatric use [Internet]. 27 Mar 2018 [accessed 12.4.18]. Available from: https://www.medicines.org.uk/emc/medicine/21201

[83] Celgene Ltd. Summary of product characteristics (SPC): Otezla 30mg tablets [Internet]. 9 Jan 2018 [accessed 12.4.18]. Available from: https://www.medicines.org.uk/emc/medicine/29792

[84] UCB Pharma Limited. Summary of product characteristics (SPC): Cimzia 200 mg solution for injection in pre-filled pen [Internet]. 17 Jan 2018 [accessed 12.4.18]. Available from: https://www.medicines.org.uk/emc/product/7387

[85] Pfizer Limited. Summary of product characteristics (SPC): Enbrel 25 mg powder and solvent for solution for injection [Internet}. 5 Apr 2018 [accessed 12.4.18]. Available from: https://www.medicines.org.uk/emc/medicine/3343

[86] Merck Sharp & Dohme Limited. Summary of product characteristics (SPC): Simponi 50 mg solution for injection in pre-filled pen [Internet]. 21 Feb 2017 [accessed 12.4.18]. Available from: https://www.medicines.org.uk/emc/product/8122

[87] Merck Sharp & Dohme Limited. Summary of product characteristics (SPC): Remicade 100mg powder for concentrate for solution for infusion [Internet]. 15 Mar 2018 [accessed 12.4.18]. Available from: https://www.medicines.org.uk/emc/medicine/3236/

[88] Novartis Pharmaceuticals UK Ltd. Summary of product characteristics (SPC): Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen [Internet]. 1 Sep 2017 [accessed 12.4.18]. Available from: https://www.medicines.org.uk/emc/medicine/29848

[89] National Institute for Health and Care Excellence. *Single Technology Appraisal Appendix B. Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs: Final scope.* London: NICE, Nov 2017 [accessed 8.2.18]. 5p.

[90] Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S64-85.

[91] National Institute for Health and Care Excellence. *Musculoskeletal conditions overview. NICE Pathway [Internet]*. London: NICE, 2013 [accessed 22.3.18] Available from: https://pathways.nice.org.uk/pathways/musculoskeletal-conditions

[92] Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(10):i-xxi, 1-329.

[93] Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health Qual Life Outcomes* 2003;1:20.

[94] Eli Lilly and Company Limited. *Updated model for Single technology appraisal (STA) submission: Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs [ID1194] (ID1194 ixekizumab model - scenarios 27032018AW) [Excel spreadsheet provided by the company]*: Eli Lilly and Company Limited, 2018 [accessed 3.4.18]

[95] van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708-15.

[96] Lachin JM. Fallacies of last observation carried forward analyses. *Clin Trials* 2016;13(2):161-8.

[97] Coates LC, Tillett W, Chandler D, Helliwell PS, Korendowych E, Kyle S, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology (Oxford)* 2013;52(10):1754-7.

[98] Poyner T, Wall A, Adnitt P, Menday A. Economic impact of psoriasis treatment on the patient and on the National Health Service. *J Dermatolog Treat* 2009;10(1):25-29.

[99] Hartman M, Prins M, Swinkels O, Severens J, de Boo T, van der Wilt G, et al. Cost-effectiveness analysis of a psoriasis care instruction programme with dithranol compared with UVB phototherapy and inpatient dithranol treatment. *Br J Dermatol* 2002;147:538-544.

[100] Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. *Arthritis Rheum* 2002;46(9):2310-9.

[101] D'Angiolella LS, Cortesi PA, Lafranconi A, Micale M, Mangano S, Cesana G, et al. Cost and cost effectiveness of treatments for psoriatic arthritis: a systematic literature review. *PharmacoEcon* 2018.

[102] McIntosh E. The cost of rheumatoid arthritis. *Br J Rheumatol* 1996;35(8):781-90.

[103] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

Appendix 1: ERG search strategies

Detailed critique of clinical effectiveness searches:

- The database searches were clearly structured (population and study design), using a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation.
- During the clarification process, the ERG asked why the clinical effectiveness searches were restricted to English language.[80] The company responded that '*Most key clinical publications are typically published in the English languages and all publications identified as relevant in previous appraisals in PsA were in the English language'.*[64] The ERG did not accept this explanation as adequate reassurance that language bias had not been introduced during the search process. Current best practice states that *'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'*.[63]
- In the Medline, Embase and CENTRAL search for the initial review, line #2 was an orphan line and omitted from the final results. Interleukin was incorrect spelled, and IL was incorrectly included in the term "Interluekin IL-17a".
- In the Medline and CENTRAL searches for the initial review, Emtree subject indexing terms were used incorrectly instead of MeSH terms. Throughout both strategies, the Emtree terms retrieved 0 hits in the population and intervention/comparator facets.
- The Updated Medline search is incorrectly reported as having a date limit of *'August 2018 to May 2017'*.
- The PICO criteria presented in Table 9 (page 18)[28], list *'systematic literature reviews'* as an inclusion criteria for study design. Searches were restricted to randomised controlled trials. A systematic review study design filter was not used and specific systematic review databases, such as CDSR or DARE, were not searched. Therefore, attempts to identify SLRs were sub-optimal.
- No attempts were made to tailor the search to find non-randomised or adverse events literature.

Detailed critique of cost effectiveness searches:

- The NHS Economic Evaluation Database (NHS EED) was not searched and would have been a useful addition to the company's searches. In the clarification response B3, the company stated that "*The Centre for Reviews and Dissemination was searched for relevant cost effectiveness data. The CRD search included the NHS EED, DARE and HTA databases*".[25] The ERG's test search of DARE, NHS EED and HTA databases via the Cochrane Library demonstrated that the searches presented in the company submission were only carried out on the HTA database. NHS EED and DARE were not searched. The company searches reported in Tables 37 and 41 of the clarification response document searches restricted only to the HTA database. It is important to note that the ERG's test search below demonstrated that there were 17 references unique to NHS EED that were not retrieved from the HTA database. These references were potentially relevant economic studies.

ERG search of DARE, NHS EED and HTA via the Cochrane Library (Wiley)

Searched 9.4.18

#1 psoriatic arthritis in Other Reviews, Technology Assessments and Economic Evaluations 85

#2 psoriatic arthritis in Technology Assessments 36

#3 psoriatic arthritis in Economic Evaluations 17

#4 #3 not #2 17 [unique references in NHS EED, not contained in HTA database]

Company searches presented in the clarification response[25]

Table 37 Search string for CEM studies in CRD-HTA

Search	Query - models	Items found*
1	(psoriatic arthritis) IN HTA	33

Table 41 Search string for model input studies in CRD-HTA

Search	Query	Items found*
1	(psoriatic arthritis) IN HTA	33

- The PubMed strategy presented in Table 34 of the clarification response[25] contained a spelling error in the MeSH terms for "Markov Chain" in line #13. "Markov Chaines" [MESH] is not a valid MESH term and retrieved 0 hits. The ERG conducted a test search to explore the potential impact for this spelling error. The correct MeSH term (line #6) retrieves 12250 PubMed records (line #8) not picked up by the free text equivalent (line #7). This consequential typographical error would impair recall of references reporting use of this analytical method.

ERG test search for Markov Chains in PubMed (Internet)

Searched 9.4.18

Search	Add to builder	Query	Items found	Time
#8	Add	Search **(#6 NOT #7)**	12250	10:23:15
#7	Add	Search **"markov chains"[Title/Abstract]**	629	10:21:48
#6	Add	Search **"Markov Chains"[Mesh:NoExp]**	12570	10:21:20

- Medline and Embase searches for both CEM and model inputs presented in Tables 26, 30, 35, 36, 39 and 40 of the clarification response, all show extensive use of Restrict to Focus in the MeSH and Emtree subject indexing.[25] The ERG noted the for both CEM and model inputs Medline and Embase searches used extensive focused MeSH and Emtree indexing terms which may have adversely affect recall of the search strategies. When restriction to focus (RTF) is applied to subject indexing terms, only Major subject indexing headings are retrieved. The ERG considered the extensive use of RTF overly restrictive and potentially impairing recall of possibly relevant references and did not consider the extensive implementation of RFT in the Embase and Medline searches adequately sensitive for this systematic review. Extensive RTF was applied to the indexing within the cost facet for the CEM Embase and Medline searches, where only Major subject indexing headings were retrieved. The model inputs searches in Embase showed that extensive RTF was applied to the Quality of life/HRQOL, cost, and UK/Europe components. The Medline model inputs searches showed that extensive RTF was applied to the Quality of life/HRQOL, and cost components. Recent investigations have been conducted into the impact of using RTF in Emtree on overall search sensitivity and recall.[61, 62] Current recommendations for best practice advocate caution when considering introduction of RTF in the population facet of an Embase search. Furthermore, prudence is also recommended when considering Emtree RTF in more than two concepts,[61, 62] as the ERG noted in the CS CEM and model input searches. The ERG considered the extensive use of RTF overly restrictive and potentially impairing recall of possibly relevant references and did not consider the extensive implementation of RTF in the Embase and Medline searches adequately sensitive for this systematic review.

- When the ERG requested further details and hits per line for CEM Embase search strategy, the company responded that the actual Embase update strategy was not available *"due to technical issues"* and provided a copy of the search protocol instead *"as an approximation"*.[64] The ERG was concerned at the lack of accuracy in the documentation and reporting of the CEM search methods, and did not consider the protocol search an accurate report or adequate proxy for the CEM updated Embase search.
- The PubMed update search for model inputs contained incorrect use of Ovid truncation and indexing through the Quality of Life/HRQoL and cost facets. Ovid commands do not work in PubMed, therefore the following search lines reported in Table 38 would have failed to perform adequately: lines #4, #16 and #18. These errors would have impacted on how well that model inputs search performed overall and may have resulted in potentially relevant studies being missed.
- The Ovid Medline search for model inputs (Table 40) contained syntax errors in line #4.[64] This affected successful inclusion of "index of well-being" in the search strategy. As the word "of" is a stop word, line #4 was not searched as the company intend. Stop words are frequently occurring words (such as and, the, of) that are ignored by Ovid to improve search processing time. In order to force Ovid to search for a phrase containing a stop word, the phrase must be contained within quotation marks, e.g. "index of well being". Effectively the company searched for "index" appearing anywhere in the .tw. fields, and "well being" variants appearing anywhere in the .tw. fields. In the ERG test search below, the CS search logic is reproduced in line #1. Correct application of quotation marks could have increase specificity to search for the phrase properly, as demonstrated in lines #2-4. The company's approach will have resulted in a high number of incorrect results being retrieved by this term.

ERG test search for "index of well being" in Medline (Ovid)

# ▲	Searches	Results
1	(index of and (wellbeing or well being or well-being)).tw.	4127
2	"index of well-being".tw.	80
3	"index of well being".tw.	80
4	"index of wellbeing".tw.	4

ERG Rapid appraisal search to identify systematic reviews, protocols, meta-analyses and health technology assessments

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 3/March 2018: all years
Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue April/2015: all years
Health Technology Assessment Database (HTA) (Wiley): Issue 4/Oct 2016 : all years
Searched 20.3.18

#1 MeSH descriptor: [Arthritis, Psoriatic] explode all trees 258
#2 (Psoria* near/4 (Arthrit* or Arthropath* or polyarthrit* or poly-arthrit* or rheumat*)):ti,ab,kw 1097
#3 ("Arthritis mutilans" or Spondyloarthrit* or Spondylo-arthrit*):ti,ab,kw 428
#4 "alibert bazin disease":ti,ab,kw 0
#5 #1 or #2 or #3 or #4 in Cochrane Reviews (Reviews and Protocols) 14
#6 #1 or #2 or #3 or #4 in Other Reviews 20
#7 #1 or #2 or #3 or #4 in Technology Assessments 39

CDSR search retrieved 14 records.
DARE search retrieved 20 records.
HTA search retrieved 39 records.

KSR Evidence: 2015-2018/03/20
Searched 20.3.18
https://ksrevidence.com/
Searched across any field

Any field		**Results**
psoriatic		64
Psoria	AND Arthrit	63
Psoria	AND Arthropath	5
Psoria	AND polyarthrit	0
Psoria	AND rheumat	53
Arthritis mutilans OR Spondyloarthritis		37
alibert bazin disease		0
Total retrieved		**222**
After deduplication		**106**

Duplicate records were removed in Endnote.

Embase (Ovid): 2017-2018/03/19
Searched 20.3.18
1 exp meta-analysis/ (140210)
2 "systematic review"/ (161171)
3 "meta analysis (topic)"/ (36687)
4 "systematic review"/ (161171)
5 "systematic review (topic)"/ (21856)
6 biomedical technology assessment/ (12722)
7 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kw. (10040)
8 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw. (161694)
9 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw. (28004)
10 (data synthes* or data extraction* or data abstraction*).ti,ab,kw. (25292)
11 (handsearch* or hand search*).ti,ab,kw. (9635)
12 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw. (27231)
13 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kw. (11857)
14 (meta regression* or metaregression*).ti,ab,kw. (7480)
15 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. (358792)
16 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. (214243)
17 (cochrane or (health adj2 technology assessment) or evidence report).jw. (26059)
18 (comparative adj3 (efficacy or effectiveness)).ti,ab,kw. (15642)
19 (outcomes research or relative effectiveness).ti,ab,kw. (11360)
20 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw. (3146)
21 or/1-20 (523243)
22 animal/ (1838304)

23 animal experiment/ (2172333)
24 (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. (6659144)
25 or/22-24 (6659146)
26 exp human/ (19344078)
27 human experiment/ (399545)
28 or/26-27 (19345606)
29 25 not (25 and 28) (5188401)
30 21 not 29 (510953)
31 psoriatic arthritis/ (17324)
32 (Psoria$ adj4 (Arthrit$ or Arthropath$ or polyarthrit$ or poly-arthrit$ or rheumat$)).ti,ab,ot,hw. (20893)
33 (Arthritis mutilans or Spondyloarthrit$ or Spondylo-arthrit$).ti,ab,ot,hw. (6110)
34 "alibert bazin disease".ti,ab,ot,hw. (1)
35 or/31-34 (25587)
36 35 and 30 (1513)
37 limit 36 to yr="2017 -Current" (273)

SR filter adapted from:
Canadian Agency for Drugs and Technologies in Health. Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO [Internet]. Ottawa: CADTH, (April 2016) [accessed 9.11.17]. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters

Appendix 2: ERG updates, overview of modified cells and VBA code

1. NMA results for Ixekizumab q4w that are not in line with trial data.

Modified cells:

- 'Input Data Default'!L172:M172
- 'Input Data Default'!L198:M198
- 'Input Data Default'!L224:M224
- 'Input Data Default'!L250:M250
- 'Input Data Default'!L276:M276
- 'Input Data Default'!L302:M302

2. Use of limited network for the b/tsDMARD-experienced population, which does not consider PASI50.

The network 3B has been used for treatment administered to b/tsDMARD-experienced patients. Hence:

- POP 6: (Line 1) Bio-naive UK 1A // (Line 2) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-naive patients
- POP 15: (All lines) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-experienced patients

Modified VBA in 'ResetGlobalInputs ()'-sub:

Ln27, Col 10:

```
If Worksheets("ERG").Range("ERG_2") = 1 Then

    .Range("UITreatmentHistory") = 6 'Patient subpopulation / NMA network

    ElseIf Worksheets("ERG").Range("ERG_2") = 2 Then

    .Range("UITreatmentHistory") = 15 'Patient subpopulation / NMA network

    Else: .Range("UITreatmentHistory") = 1 'Patient subpopulation / NMA network

    End If
```

3. Exclusion of secukinumab and certolizumab pegol as comparators in b/tsDMARD-experienced patients.

The network 3B has been used for treatment administered to b/tsDMARD-experienced patients. Hence:

- POP 6: (Line 1) Bio-naive UK 1A // (Line 2) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-naive patients
- POP 15: (All lines) Bio-exp 3B (incl secu, cert) has been used for all analyses concerning b/tsDMARD-experienced patients

Modified VBA in 'ResetGlobalInputs ()'-sub:

Ln27, Col 10:

```
If Worksheets("ERG").Range("ERG_2") = 1 Then
```

```
.Range("UITreatmentHistory") = 6 'Patient subpopulation / NMA network
ElseIf Worksheets("ERG").Range("ERG_2") = 2 Then
.Range("UITreatmentHistory") = 15 'Patient subpopulation / NMA network
Else: .Range("UITreatmentHistory") = 1 'Patient subpopulation / NMA network
End If
```

4. Utilities were not adjusted to general population utility values.

Modified VBA in 'ResetUtilityCalc()'-sub:

Ln 46, Col 9:

```
If Worksheets("ERG").Range("ERG_4") = 1 Then
.Range("UIUtilityCap") = "Yes"
ElseIf Worksheets("ERG").Range("ERG_4") = 0 Then
.Range("UIUtilityCap") = "No"
End If
```

5. The use of a potentially dated and high SMR.

Modified VBA code in 'InputReadMain()'-sub:

Ln 288, Col 5:

```
If Worksheets("ERG").Range("ERG_5") = 1 Then
   inputMortalityRatesPsA = 1.05


   Else
   inputMortalityRatesPsA = Worksheets("Mortality").Range("IDataMortalityPsAHR")
   inputMortalityRatePsAMaleWang =
Worksheets("Mortality").Range("IDataMortalityPsAMaleHR")
   inputMortalityRatePsAFemaleWang =
Worksheets("Mortality").Range("IDataMortalityPsAFemaleHR")


   End If
```

6. The use of calculations for PASI change in the model that are inconsistent with the CS report.

Modified VBA-code PASIRedRespFunction:

Ln 507, Col 17:

```
If tPsARC <> 0 Then

        If Worksheets("ERG").Range("ERG_6") = 1 Then

        PASIRedRespFunction = inputBaselinePASI - inputBaselinePASI * 0.25

        Else: PASIRedRespFunction = inputBaselinePASI - inputBaselinePASI * (0.25 * pPsARCPASI75 + 0.5 * (pPsARCNonPASI75 - pPsARCNonPASI50) + 1 * pPsARCNonPASI50) / tPsARC

        End If

    End If
```

Additional remarks concerning the ERG analyses:

- In order to be able to include biosimilar etanercept in all analyses (i.e. b/tsDMARD-naive patients, mild-to-moderate and moderate-to-severe psoriasis), the correlation coefficient of 0.255977942567321 between PsARC and PASI (Cell L19 of the Main-worksheet)
- There were no NMA estimates for Secukinumab 150mg when using the extended NMA, therefore Secukinumab 300mg has been used in all analyses involving this network.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs

ERRATUM

This document contains errata in respect to the ERG report. The ERG noted an error in the company's implementation of the PSA. The ERG has now fixed this error and provides the corrected probabilistic results in tables as well as in the text of the report. The ERG also added critique points to the report to reflect this error. Furthermore, the ERG noted that the CiC marking was missing from one set of results and has updated the CiC marking of all ERG results.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
18	Added more detail to description of ERG ICERs
118	Added critique point on PSA to ERG comment
123	Added a bullet point about the PSA to Fixing errors
124	Corrected probabilistic ICERs
128-132	Replaced Table 6.1 with corrected probabilistic analyses and CiC marking
133-146	Replaced Table 6.2 with corrected CiC marking
149	Added more detail to description of ERG ICERs

typographical errors, incorrect truncation and syntax mistakes in several of the cost effectiveness PubMed searches. Searches of the health technology assessment database (HTA) and the Health Economic Evaluations Database (HEED) contained unnecessary costs or HRQoL/Utilities search filters which were overly restrictive. Searching the NHS Economic Evaluation database would have been beneficial. Due to these issues, it is possible that potentially relevant studies may have been missed, however the impact of this is difficult to assess without undertaking these reviews independently.

Health states in the cost effectiveness model are based on a relative measure of response (reductions in symptoms), which may lead to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. Further limitations are the exclusion of comparators identified in the scope and the omission of adverse events from the economic model. For the b/tsDMARD-experienced patient population, only a limited network was used, which omitted PASI 50 as an outcome. Moreover, the ERG considers the assumption of equal treatment discontinuation rates for all b/tsDMARD treatments as a weakness. The representativeness of the patient population in the SPIRIT trial programme, excess mortality in this population, resource use and cost estimates associated with HAQ-DI and PASI pose areas of uncertainty.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The company's deterministic base-case ICERs of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. In the b/tsDMARD-experienced population, ixekizumab (with PAS) had ICERs [redacted] per QALY gained when compared with BSC. It [redacted] when compared with ustekinumab in no and mild-to moderate psoriasis and [redacted] in moderate-to severe psoriasis. The ERG incorporated various adjustments to the company base-case (probabilistic results for the b/tsDMARD-naïve population and deterministic results for the b/tsDMARD-experienced population). In the ERG base-case, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained versus BSC (no and mild-to-moderate psoriasis subgroups) and certolizumab pegol (moderate-to-severe psoriasis subgroup) in the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses for the no and mild-to-moderate psoriasis subgroups). Additionally, the ERG explored different scenarios based on the ERG base-case analysis. In those analyses, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population except in the scenario in which both PASI 75 and PsARC were used to determine treatment response. In that scenario, ixekizumab had an ICER of [redacted] per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab had ICERs [redacted] per QALY gained versus BSC in all psoriasis severity levels in all scenarios, except when both PASI 75 and PsARC were used to determine treatment response. In this scenario, ixekizumab [redacted].
In conclusion, despite the ERG criticism and amendments to the company cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab provided ICERs [redacted] per QALY gained versus BSC or certolizumab pegol in the b/tsDMARD-experienced population. In this population, when compared to ustekinumab, ixekizumab [redacted] in all psoriasis severity levels. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

These scenarios do have an impact on absolute costs and QALYs but do not change the cost effectiveness conclusions based on list prices, as the ixekizumab sequence was either extendedly dominated or dominated in all scenario analyses which were based on the list price of ixekizumab. Assumptions that had the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, the York utility model coefficients, the Poole et al. 2010 algorithm for costs associated with HAQ-DI,[72] and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab being accounted for).

ERG comment: The ERG considers the deterministic sensitivity analyses to be sufficient. The PSA implementation was flawed and corrected by the ERG, and the PSA does not include all relevant parameters for all scenarios, e.g. the Convergence Diagnostic and Output Analysis (CODA) for the extended network for the b/tsDMARD experienced population is not available in the model file. PSA results reported were incorrect, and were not provided for the analyses with ixekizumab PAS price.

5.2.12 Model validation and face validity check

Face validity
Face validity of the conceptual model was assessed in an advisory board with clinical and health economic experts.

Internal validity
The model was developed by an external consultancy company and internal validation was undertaken by another external consultancy company. The programming of the model was checked to identify errors or omissions. A cell-by-cell technical validation was carried out and the VBA code was checked.

Cross validity
The company stated that cross validation by replicating comparisons from previous submissions was difficult because PAS prices for secukinumab and apremilast are confidential.

External validity
The company stated that external validity was difficult to assess, because long term observational studies have not been carried out for ixekizumab.

Predictive validity
A head-to-head study comparing ixekizumab and adalimumab is currently underway and could later be used to assess the predictive validity of the cost effectiveness model.

ERG comment: The ERG has concerns related to the lack of detailed cross validity. The company did provide a cross validation exercise in response to clarification question B21.[25] TA445[13] and TA433[15] were the most relevant studies for cross-validity, as these were also based on the York model and were the most recent TAs. Compared with TA445 (the revised York model):

- Total costs of comparators were generally lower in the current model for b/tsDMARD-naive- and higher for b/tsDMARD-experienced patients.
- Total QALYs of comparators were generally higher in the current model for b/tsDMARD-naive and lower for b/tsDMARD-experienced patients.

Based on all considerations in section 5.2 (summarised in Table 5.20), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[103])

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Additionally, exploratory sensitivity analyses were performed by the ERG to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

The ERG's base-case:

Fixing errors

1. Flawed implementation of the PSA, resulting in deterministic results being reported.

   The ERG corrected the code used for the PSA.
2. NMA results for the reduction in HAQ-DI scores for ixekizumab q4w that are inconsistent with trial data.

   The ERG used the trial data instead of the NMA results.

Fixing violations

3. Use of the limited NMA results for the b/tsDMARD-experienced population, which does not consider PASI50.

   The ERG used the extended NMA for the b/tsDMARD experienced population, which considers PASI50.
4. Exclusion of secukinumab and certolizumab pegol as comparators in b/tsDMARD-experienced patients.

   The ERG included these by using the extended NMA, as per scope.
5. Utilities were not adjusted to general population utility values.
   The ERG adjusted utilities.

Matters of judgment

6. The use of a potentially dated and high SMR.
   The ERG used a SMR derived from more recent data.
7. The use of calculations for PASI change in the model that are inconsistent with the CS report.
   The ERG used the calculations detailed in the CS report (Table 42).

5.3.1 ERG base-case results

The ERG base-case was performed probabilistically for b/tsDMARD-naïve patients and deterministically for b/tsDMARD-experienced patients because there were no probabilistic estimates provided for secukinumab and certolizumab pegol when using the extended NMA (due to CODA not provided for this network). All ERG base-case analyses are conditional on the PAS price of ixekizumab. Additionally, the ERG used secukinumab 300 mg for all psoriasis severity levels in the b/tsDMARD-experienced population because no results were provided for secukinumab 150 mg in the extended NMA. For all analyses including biosimilar etanercept as a comparator, a correlation coefficient of 0.26, instead of 0.4, was used to derive the distribution of PASI 75 responders amongst patients who achieve a PsARC response.

Ixekizumab was [redacted] in all b/tsDMARD-naïve subgroups while, in the b/tsDMARD-experienced population, it resulted in ICERs of [redacted] and [redacted] per QALY gained versus BSC in the no psoriasis and mild-to-moderate psoriasis subgroups respectively, and [redacted] per QALY gained versus certolizumab pegol in the moderate-to-severe psoriasis subgroup. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses for the no psoriasis and mild-to-moderate psoriasis subgroups).

5.3.2 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of the following alternative assumptions on the cost effectiveness estimates. These were all performed using the ERG base-case. Results are presented in Table 6.2 in section 6. The ERG used secukinumab 300 mg for all psoriasis severity levels in the b/tsDMARD-experienced population because no results were provided for secukinumab 150 mg in the extended NMA.

Exploratory analyses using the ERG base-case:

1. The use of the company's preferred network for the b/tsDMARD-experienced population, excluding secukinumab and certolizumab pegol from the analysis.
2. Use of Poole et al for HAQ-DI related costs instead of Kobelt et al.
3. Use of the York model baseline PASI scores.
4. Alternative second line treatment in b/tsDMARD-naive patients.
5. Use of PASI 75 and PsARC instead of only PsARC.

5.3.3 Subgroup analyses performed based on the ERG base-case

No subgroup analyses were performed.

5.4 Conclusions of the cost effectiveness section

The ERG considers that the company's approach to use the revised York model as a basis for developing their model was appropriate.

The economic model described in the CS is considered by the ERG to meet the NICE reference case, with the notable exceptions of a) the exclusion of comparators identified in the scope, and b) a network meta-analysis that did not consider all the relevant outcomes as identified in the scope.

a) The absence of secukinumab and certolizumab pegol from the b/tsDMARD-experienced patient population analysis was justified by the unavailability of data in that population, however, it should be noted that studies on these two treatments were conducted in mixed (b/tsDMARD-naive and -experienced) populations.
b) The omission of adverse events from the economic model was considered a major limitation by the ERG. The ERG considers that treatment-specific adverse events could have an impact on treatment discontinuation, HRQoL and cost and resource use, and that not reflecting this in the model could lead to biased outcomes. The direction of this bias is difficult to determine.

The company's deterministic base-case ICERs of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained in the b/tsDMARD-experienced population when compared with BSC but was [redacted] when compared with ustekinumab in that population. The cost effectiveness results were fairly robust to scenario and one-

Table Error! No text of specified style in document.**.1: Probabilistic ERG base-case; PAS price**

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
Company base-case (probabilistic, performed by the ERG)						
bDMARD-naïve; no psoriasis						
BSC	£54,514	8.09	-	-	-	[redacted]
APR - UST - BSC	£94,340	9.50	[redacted]	1.41	[redacted]	[redacted]
IXE Q4W - UST - BSC	[redacted]	9.72	[redacted]	1.62	[redacted]	Referent
CZP - UST - BSC	£101,135	9.44	[redacted]	1.34	[redacted]	[redacted]
SEC 150 - UST - BSC	£101,314	9.80	[redacted]	1.70	[redacted]	[redacted]
ADA - UST - BSC	£102,621	9.73	[redacted]	1.64	[redacted]	[redacted]
ETA - UST - BSC	£104,074	10.00	[redacted]	1.91	[redacted]	[redacted]
GOL - UST - BSC	£109,091	9.91	[redacted]	-0.10	[redacted]	[redacted]
INF - UST - BSC	£129,033	10.15	[redacted]	0.14	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£70,174	7.75	-	-	-	[redacted]
APR - UST - BSC	£106,250	9.18	[redacted]	1.43	[redacted]	[redacted]
IXE Q4W - UST - BSC	[redacted]	9.41	[redacted]	1.66	[redacted]	Referent
SEC 150 - UST - BSC	£112,555	9.49	[redacted]	1.74	[redacted]	[redacted]
CZP - UST - BSC	£113,045	9.13	[redacted]	1.38	[redacted]	[redacted]
ADA - UST - BSC	£113,950	9.42	[redacted]	1.66	[redacted]	[redacted]
ETN - UST - BSC	£115,270	9.71	[redacted]	1.95	[redacted]	[redacted]
GOL - UST - BSC	£119,971	9.62	[redacted]	-0.09	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
INF - UST - BSC	£139,567	9.86	[redacted]	0.15	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£99,797	6.20	-	-	-	[redacted]
APR - UST - BSC	£128,058	7.71	[redacted]	1.51	[redacted]	[redacted]
CZP - UST - BSC	£133,696	7.68	[redacted]	1.48	[redacted]	[redacted]
ADA - UST - BSC	£134,631	7.99	[redacted]	1.79	[redacted]	[redacted]
IXE Q2W - UST - BSC	[redacted]	8.14	[redacted]	1.94	[redacted]	Referent
ETA - UST - BSC	£134,951	8.27	[redacted]	2.07	[redacted]	[redacted]
GOL - UST - BSC	£139,232	8.25	[redacted]	-0.03	[redacted]	[redacted]
SEC 300 - UST - BSC	£156,842	8.00	[redacted]	-0.27	[redacted]	[redacted]
INF - UST - BSC	£158,762	8.54	[redacted]	0.27	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£55,815	7.38	-	-	-	[redacted]
IXE Q4W - BSC	[redacted]	8.24	[redacted]	0.86	[redacted]	Referent
UST - BSC	£83,137	8.27	[redacted]	0.03	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£70,137	7.07	-	-	-	[redacted]
IXE Q4W - BSC	[redacted]	7.97	[redacted]	0.90	[redacted]	Referent
UST - BSC	£95,039	8.00	[redacted]	0.03	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£99,959	2.31	-	-	-	[redacted]
IXE Q2W - BSC	[redacted]	3.31	[redacted]	1.00	[redacted]	Referent
UST - BSC	£119,976	3.27	[redacted]	-0.03	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
ERG base-case						
bDMARD-naïve; no psoriasis (probabilistic)						
BSC	£ 57,674	8.37	-	-	-	[redacted]
APR - UST - BSC	£ 98,358	9.81	[redacted]	1.44	[redacted]	[redacted]
IXE Q4W - UST - BSC	[redacted]	9.98	[redacted]	1.61	[redacted]	Referent
SEC 150 - UST - BSC	£ 105,259	10.07	[redacted]	1.70	[redacted]	[redacted]
CZP - UST - BSC	£ 105,272	9.75	[redacted]	1.37	[redacted]	[redacted]
ADA - UST - BSC	£ 106,764	10.03	[redacted]	1.66	[redacted]	[redacted]
ETA - UST - BSC	£ 108,248	10.25	[redacted]	1.88	[redacted]	[redacted]
GOL - UST - BSC	£ 113,357	10.23	[redacted]	-0.02	[redacted]	[redacted]
INF - UST - BSC	£ 133,602	10.39	[redacted]	0.14	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis (probabilistic)						
BSC	£ 74,457	8.01	-	-	-	[redacted]
APR - UST - BSC	£ 110,847	9.51	[redacted]	1.50	[redacted]	[redacted]
IXE Q4W - UST - BSC	[redacted]	9.70	[redacted]	1.69	[redacted]	Referent
SEC 150 - UST - BSC	£ 117,141	9.79	[redacted]	1.78	[redacted]	[redacted]
CZP - UST - BSC	£ 117,606	9.47	[redacted]	1.46	[redacted]	[redacted]
ADA - UST - BSC	£ 118,552	9.75	[redacted]	1.74	[redacted]	[redacted]
ETA - UST - BSC	£ 119,897	9.99	[redacted]	1.98	[redacted]	[redacted]
GOL - UST - BSC	£ 124,677	9.96	[redacted]	-0.03	[redacted]	[redacted]
INF - UST - BSC	£ 144,619	10.11	[redacted]	0.12	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
bDMARD-naïve; moderate-to-severe psoriasis (probabilistic)						
BSC	£ 105,156	6.42	-	-	-	[redacted]
APR - UST - BSC	£ 133,529	8.21	[redacted]	1.79	[redacted]	[redacted]
CZP - UST - BSC	£ 139,134	8.21	[redacted]	1.78	[redacted]	[redacted]
ADA - UST - BSC	£ 140,118	8.49	[redacted]	2.07	[redacted]	[redacted]
IXE q2w - UST - BSC	[redacted]	8.56	[redacted]	2.14	[redacted]	Referent
ETA - UST - BSC	£ 140,454	8.82	[redacted]	2.39	[redacted]	[redacted]
GOL-UST-BSC	£ 144,780	8.76	[redacted]	-0.06	[redacted]	[redacted]
SEC300-UST-BSC	£ 162,661	8.44	[redacted]	-0.38	[redacted]	[redacted]
INF - UST - BSC	£ 164,601	8.95	[redacted]	0.13	[redacted]	[redacted]
bDMARD-experienced; no psoriasis (deterministic)						
BSC	£58,838	7.61	-	-	-	[redacted]
IXE q4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP -BSC	£83,355	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£88,828	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£106,747	8.54	[redacted]	-0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis (deterministic)						
BSC	£73,880	7.26	-	-	-	[redacted]
IXE q4w-BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP-BSC	£95,702	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£101,087	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£119,384	8.31	[redacted]	-0.15	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis (deterministic)						

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	ICER versus baseline (£/QALY)	ICER IXE versus comparator
BSC	£104,602	2.23	-	-	-	[redacted]
CZP-BSC	£121,172	3.98	[redacted]	1.75	[redacted]	[redacted]
IXE q2w-BSC	[redacted]	4.11	[redacted]	0.13	[redacted]	Referent
UST-BSC	£126,390	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300-BSC	£145,424	3.91	[redacted]	-0.22	[redacted]	[redacted]

ADA = adalimumab; APR = apremilast; bDMARD = biologic disease-modifying anti-rheumatic drug; BSC = best supportive care; CZP = certolizumab pegol; ERG = Evidence Review Group; ETA = etanercept; GOL = golimumab; ICER = Incremental cost effectiveness ratio; INF = infliximab; IXE = ixekizumab; PAS = patient access scheme; q2w = once every two weeks; q4w = once every four weeks; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

Table Error! No text of specified style in document.**.2: Deterministic scenario analyses conditional on ERG base-case, PAS price**

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
ERG base-case (deterministic)						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£99,754	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£106,247	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£106,591	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£107,703	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£109,998	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£114,501	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£133,706	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.61	[redacted]	1.62	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent
CZP-UST-BSC	£118,101	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.89	[redacted]	1.91	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£121,313	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£125,644	10.05	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£144,833	10.17	[redacted]	0.08	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	-	[redacted]
APR-UST-BSC	£134,903	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£139,690	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£141,198	8.59	[redacted]	2.22	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA -UST-BSC	£141,826	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£145,815	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP-BSC	£83,355	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£88,828	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£106,747	8.54	[redacted]	-0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	-	[redacted]
IXEq4w-BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent
CZP-BSC	£95,702	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£101,087	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£119,384	8.31	[redacted]	-0.15	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-BSC	£121,172	3.98	[redacted]	1.75	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	4.11	[redacted]	0.13	[redacted]	Referent
UST-BSC	£126,390	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300-BSC	£145,424	3.91	[redacted]	-0.22	[redacted]	[redacted]
Scenario 1: The use of the company's preferred network for the bDMARD-experienced population, excluding secukinumab and certolizumab pegol from the analysis.						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£96,450	9.77	[redacted]	1.42	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.92	[redacted]	1.57	[redacted]	Referent
CZP-UST-BSC	£103,043	9.96	[redacted]	1.61	[redacted]	[redacted]
SEC 150-UST-BSC	£103,393	10.03	[redacted]	1.68	[redacted]	[redacted]
ADA-UST-BSC	£104,495	10.00	[redacted]	1.65	[redacted]	[redacted]
ETA 150-UST-BSC	£106,901	10.22	[redacted]	1.87	[redacted]	[redacted]
GOL-UST-BSC	£111,437	10.20	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£130,648	10.30	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£109,258	9.48	[redacted]	1.49	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.63	[redacted]	1.65	[redacted]	Referent
CZP-UST-BSC	£115,255	9.67	[redacted]	1.69	[redacted]	[redacted]
SEC150-UST-BSC	£115,598	9.76	[redacted]	1.78	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
ADA-UST-BSC	£116,725	9.71	[redacted]	1.73	[redacted]	[redacted]
ETA-UST-BSC	£118,563	9.96	[redacted]	1.98	[redacted]	[redacted]
GOL-UST-BSC	£122,924	9.93	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£142,118	10.04	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	-	[redacted]
APR-UST-BSC	£132,710	8.14	[redacted]	1.76	[redacted]	[redacted]
CZP-UST-BSC	£137,563	8.38	[redacted]	2.00	[redacted]	[redacted]
ADA-UST-BSC	£139,069	8.42	[redacted]	2.04	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.50	[redacted]	2.12	[redacted]	Referent
ETA-UST-BSC	£139,770	8.79	[redacted]	2.41	[redacted]	[redacted]
GOL-UST-BSC	£143,781	8.68	[redacted]	-0.10	[redacted]	[redacted]
SEC300-UST-BSC	£160,813	8.36	[redacted]	-0.42	[redacted]	[redacted]
INF-UST-BSC	£162,942	8.90	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
IXEq4w-BSC	[redacted]	8.40	[redacted]	0.79	[redacted]	Referent
UST-BSC	£85,151	8.49	[redacted]	0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	8.18	[redacted]	0.92	[redacted]	Referent
UST-BSC	£97,830	8.28	[redacted]	0.10	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	-	[redacted]
IXEq2w -BSC	[redacted]	3.80	[redacted]	1.57	[redacted]	Referent
UST-BSC	£123,956	3.77	[redacted]	-0.03	[redacted]	[redacted]
Scenario 2: Use of Poole et al.[72] for HAQ-DI related costs instead of Kobelt et al.[100]						
bDMARD-naïve; no psoriasis						
BSC	£36,728	8.35	-	-	-	[redacted]
APR-UST-BSC	£72,980	9.89	[redacted]	1.54	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	10.04	[redacted]	1.69	[redacted]	Referent
CZP-UST-BSC	£79,793	10.08	[redacted]	1.73	[redacted]	[redacted]
SEC150-UST-BSC	£80,172	10.15	[redacted]	1.80	[redacted]	[redacted]
ADA-UST-BSC	£81,297	10.12	[redacted]	1.77	[redacted]	[redacted]
ETA-UST-BSC	£83,130	10.34	[redacted]	1.99	[redacted]	[redacted]
GOL-UST-BSC	£87,305	10.31	[redacted]	-0.02	[redacted]	[redacted]
INF-UST-BSC	£106,666	10.41	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£36,728	7.99	-	-	-	[redacted]
APR-UST-BSC	£72,980	9.61	[redacted]	1.62	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.76	[redacted]	1.78	[redacted]	Referent
CZP-UST-BSC	£79,793	9.80	[redacted]	1.82	[redacted]	[redacted]
SEC150-UST-BSC	£80,172	9.89	[redacted]	1.91	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
ADA-UST-BSC	£81,297	9.84	[redacted]	1.85	[redacted]	[redacted]
ETA-UST-BSC	£83,130	10.09	[redacted]	2.10	[redacted]	[redacted]
GOL-UST-BSC	£87,305	10.05	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£106,666	10.17	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£37,361	6.38	-	-	-	[redacted]
APR-UST-BSC	£73,474	8.33	[redacted]	1.95	[redacted]	[redacted]
CZP-UST-BSC	£80,270	8.56	[redacted]	2.18	[redacted]	[redacted]
ADA-UST-BSC	£81,772	8.59	[redacted]	2.22	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.68	[redacted]	2.30	[redacted]	Referent
ETA-UST-BSC	£83,580	8.96	[redacted]	2.58	[redacted]	[redacted]
GOL-UST-BSC	£87,757	8.85	[redacted]	-0.11	[redacted]	[redacted]
SEC300-UST-BSC	£103,068	8.55	[redacted]	-0.41	[redacted]	[redacted]
INF-UST-BSC	£107,108	9.07	[redacted]	0.11	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£44,052	7.61	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	8.54	[redacted]	0.93	[redacted]	Referent
CZP-BSC	£63,939	8.53	[redacted]	-0.02	[redacted]	[redacted]
UST-BSC	£69,163	8.64	[redacted]	0.09	[redacted]	[redacted]
SEC300-BSC	£87,760	8.54	[redacted]	-0.10	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£37,680	7.26	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	8.36	[redacted]	1.09	[redacted]	Referent

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP -BSC	£58,297	8.35	[redacted]	-0.01	[redacted]	[redacted]
UST-BSC	£63,602	8.46	[redacted]	0.11	[redacted]	[redacted]
SEC300-BSC	£82,091	8.31	[redacted]	-0.15	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£36,414	2.23	-	-	-	[redacted]
CZP -BSC	£57,191	3.98	[redacted]	1.75	[redacted]	[redacted]
IXEq2w -BSC	[redacted]	4.11	[redacted]	1.88	[redacted]	Referent
UST-BSC	£62,512	4.13	[redacted]	0.02	[redacted]	[redacted]
SEC300 -BSC	£80,978	3.91	[redacted]	-0.22	[redacted]	[redacted]
Scenario 3: Use of the York model baseline PASI scores.						
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.67	-	-	-	[redacted]
APR-UST-BSC	£112,192	9.36	[redacted]	1.69	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.52	[redacted]	1.85	[redacted]	Referent
CZP-UST-BSC	£118,101	9.56	[redacted]	1.89	[redacted]	[redacted]
SEC150-UST-BSC	£118,438	9.66	[redacted]	1.99	[redacted]	[redacted]
ADA-UST-BSC	£119,574	9.60	[redacted]	1.93	[redacted]	[redacted]
ETA-UST-BSC	£121,313	9.87	[redacted]	2.20	[redacted]	[redacted]
GOL-UST-BSC	£125,644	9.82	[redacted]	-0.05	[redacted]	[redacted]
INF-UST-BSC	£144,833	9.95	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	7.12	-	-	-	[redacted]
APR-UST-BSC	£134,903	8.91	[redacted]	1.79	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£139,690	9.12	[redacted]	2.00	[redacted]	[redacted]
ADA-UST-BSC	£141,198	9.16	[redacted]	2.04	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	9.23	[redacted]	2.11	[redacted]	Referent
ETA-UST-BSC	£141,826	9.48	[redacted]	2.36	[redacted]	[redacted]
GOL-UST-BSC	£145,815	9.39	[redacted]	-0.09	[redacted]	[redacted]
SEC300-UST-BSC	£162,971	9.12	[redacted]	-0.36	[redacted]	[redacted]
INF-UST-BSC	£164,972	9.57	[redacted]	0.09	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	6.32	-	-	-	[redacted]
IXEq4w -BSC	[redacted]	7.53	[redacted]	1.21	[redacted]	Referent
CZP-BSC	£95,702	7.52	[redacted]	0.00	[redacted]	[redacted]
UST-BSC	£101,087	7.65	[redacted]	0.12	[redacted]	[redacted]
SEC300-BSC	£119,384	7.51	[redacted]	-0.14	[redacted]	[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	5.09	-	-	-	[redacted]
CZP-BSC	£121,172	6.48	[redacted]	1.39	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	6.60	[redacted]	1.51	[redacted]	Referent
UST-BSC	£126,390	6.61	[redacted]	0.01	[redacted]	[redacted]
SEC300-BSC	£145,424	6.44	[redacted]	-0.17	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
Scenario 4: Alternative second line treatment in bDMARD-naive patients.						
Second-line certolizumab pegol						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-CZP-BSC	£94,747	9.80	[redacted]	1.45	[redacted]	[redacted]
IXEq4w-CZP-BSC	[redacted]	9.95	[redacted]	1.60	[redacted]	Referent
SEC150-CZP-BSC	£101,737	10.07	[redacted]	1.71	[redacted]	[redacted]
ADA-CZP-BSC	£102,840	10.03	[redacted]	1.68	[redacted]	[redacted]
ETA-CZP-BSC	£105,293	10.25	[redacted]	1.90	[redacted]	[redacted]
GOL-CZP-BSC	£109,844	10.23	[redacted]	-0.02	[redacted]	[redacted]
INF-CZP-BSC	£129,054	10.33	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-CZP-BSC	£107,261	9.51	[redacted]	1.53	[redacted]	[redacted]
IXEq4w-CZP-BSC	[redacted]	9.67	[redacted]	1.68	[redacted]	Referent
SEC150-CZP-BSC	£113,658	9.80	[redacted]	1.81	[redacted]	[redacted]
ADA-CZP-BSC	£114,785	9.75	[redacted]	1.76	[redacted]	[redacted]
ETA-CZP-BSC	£116,679	10.00	[redacted]	2.02	[redacted]	[redacted]
GOL-CZP-BSC	£121,058	9.96	[redacted]	-0.04	[redacted]	[redacted]
INF-CZP-BSC	£140,252	10.08	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
APR-CZP-BSC	£130,123	8.22	[redacted]	1.84	[redacted]	[redacted]
ADA-CZP-BSC	£136,556	8.49	[redacted]	2.12	[redacted]	[redacted]
IXEq2w-CZP-BSC	[redacted]	8.58	[redacted]	2.20	[redacted]	Referent
ETA-CZP-BSC	£137,333	8.86	[redacted]	2.49	[redacted]	[redacted]
GOL-CZP-BSC	£141,368	8.76	[redacted]	-0.10	[redacted]	[redacted]
SEC300-CZP-BSC	£158,263	8.44	[redacted]	-0.42	[redacted]	[redacted]
INF-CZP-BSC	£160,531	8.97	[redacted]	0.11	[redacted]	[redacted]
Second-line secukinumab						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-SEC-BSC	£115,979	9.77	[redacted]	1.42	[redacted]	[redacted]
IXEq4w-SEC-BSC	[redacted]	9.93	[redacted]	1.58	[redacted]	Referent
CZP-SEC-BSC	£121,980	9.96	[redacted]	1.61	[redacted]	[redacted]
ADA-SEC-BSC	£123,452	10.00	[redacted]	1.65	[redacted]	[redacted]
ETA-SEC-BSC	£125,210	10.23	[redacted]	1.88	[redacted]	[redacted]
GOL-SEC-BSC	£129,547	10.21	[redacted]	-0.02	[redacted]	[redacted]
INF-SEC-BSC	£148,725	10.30	[redacted]	0.07	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-SEC-BSC	£128,749	9.49	[redacted]	1.51	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
IXEq4w-SEC-BSC	[redacted]	9.65	[redacted]	1.66	[redacted]	Referent
CZP-SEC-BSC	£134,155	9.69	[redacted]	1.71	[redacted]	[redacted]
ADA-SEC-BSC	£135,646	9.73	[redacted]	1.74	[redacted]	[redacted]
ETA-SEC-BSC	£136,836	9.98	[redacted]	2.00	[redacted]	[redacted]
GOL-SEC-BSC	£140,998	9.95	[redacted]	-0.04	[redacted]	[redacted]
INF-SEC-BSC	£160,160	10.06	[redacted]	0.08	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	-	[redacted]
APR-SEC-BSC	£152,123	8.20	[redacted]	1.83	[redacted]	[redacted]
CZP-SEC-BSC	£156,388	8.44	[redacted]	2.06	[redacted]	[redacted]
ADA-SEC-BSC	£157,914	8.48	[redacted]	2.10	[redacted]	[redacted]
ETA-SEC-BSC	£157,970	8.85	[redacted]	2.47	[redacted]	[redacted]
IXEq2w-SEC-BSC	[redacted]	8.56	[redacted]	-0.29	[redacted]	Referent
GOL-SEC-BSC	£161,783	8.74	[redacted]	-0.10	[redacted]	[redacted]
INF-SEC-BSC	£180,913	8.96	[redacted]	0.11	[redacted]	[redacted]
Scenario 5: Use of PASI 75 & PsARC instead of only PsARC						
bDMARD-naïve; no psoriasis						
BSC	£56,906	8.35	-	-	-	[redacted]
APR-UST-BSC	£88,297	9.41	[redacted]	1.06	[redacted]	[redacted]
ETA-UST-BSC	£89,270	9.45	[redacted]	1.10	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£89,445	9.47	[redacted]	1.12	[redacted]	[redacted]
ADA-UST-BSC	£93,971	9.59	[redacted]	1.24	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.79	[redacted]	1.44	[redacted]	Referent
SEC-UST-BSC	£98,711	9.82	[redacted]	1.46	[redacted]	[redacted]
GOL-UST-BSC	£100,301	9.79	[redacted]	-0.03	[redacted]	[redacted]
INF-UST-BSC	£124,354	10.13	[redacted]	0.32	[redacted]	[redacted]
bDMARD-naïve; mild-to-moderate psoriasis						
BSC	£73,609	7.99	-	-	-	[redacted]
APR-UST-BSC	£102,249	9.10	[redacted]	1.12	[redacted]	[redacted]
ETA-UST-BSC	£103,121	9.14	[redacted]	1.16	[redacted]	[redacted]
CZP-UST-BSC	£103,147	9.16	[redacted]	1.18	[redacted]	[redacted]
ADA-UST-BSC	£107,381	9.29	[redacted]	1.30	[redacted]	[redacted]
IXEq4w-UST-BSC	[redacted]	9.50	[redacted]	1.51	[redacted]	Referent
SEC-UST-BSC	£111,545	9.53	[redacted]	1.55	[redacted]	[redacted]
GOL-UST-BSC	£113,031	9.50	[redacted]	-0.04	[redacted]	[redacted]
INF-UST-BSC	£136,306	9.87	[redacted]	0.34	[redacted]	[redacted]
bDMARD-naïve; moderate-to-severe psoriasis						
BSC	£104,874	6.38	-	-	-	[redacted]
APR-UST-BSC	£128,012	7.71	[redacted]	1.33	[redacted]	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-UST-BSC	£128,430	7.79	[redacted]	1.41	[redacted]	[redacted]
ETA-UST-BSC	£128,704	7.77	[redacted]	1.40	[redacted]	[redacted]
ADA-UST-BSC	£132,082	7.93	[redacted]	1.55	[redacted]	[redacted]
GOL-UST-BSC	£136,374	8.19	[redacted]	1.81	[redacted]	[redacted]
IXEq2w-UST-BSC	[redacted]	8.34	[redacted]	1.96	[redacted]	Referent
SEC300-UST-BSC	£155,462	8.19	[redacted]	-0.15	[redacted]	[redacted]
INF-UST-BSC	£158,093	8.70	[redacted]	0.36	[redacted]	[redacted]
bDMARD-experienced; no psoriasis						
BSC	£58,838	7.61	-	-	-	[redacted]
SEC300-BSC	£63,744	7.70	[redacted]	0.08	[redacted]	[redacted]
IXEq4w-BSC	[redacted]	8.13	[redacted]	0.52	[redacted]	Referent
CZP-BSC	£73,787	8.18	[redacted]	0.57	[redacted]	[redacted]
UST-BSC	£84,054	8.45	[redacted]	0.27	[redacted]	[redacted]
bDMARD-experienced; mild-to-moderate psoriasis						
BSC	£73,880	7.26	-	-	-	[redacted]
SEC300-BSC	£78,735	7.35	[redacted]	0.09	[redacted]	[redacted]
IXEq4w-BSC	[redacted]	7.87	[redacted]	0.61	[redacted]	Referent
CZP-BSC	£87,175	7.94	[redacted]	0.68	[redacted]	[redacted]
UST-BSC	£96,859	8.24	[redacted]	0.30		[redacted]
bDMARD-experienced; moderate-to-severe psoriasis						
BSC	£104,602	2.23	-	-	-	[redacted]

Treatment sequence	Total costs (£)	Total QALYs	Incremental Costs	Incremental QALY	Full incremental ICER (£/QALY)	ICER IXE versus comparator
CZP-BSC	£114,685	3.32	[redacted]	1.09	[redacted]	[redacted]
IXEq2w-BSC	[redacted]	3.34	[redacted]	0.02	[redacted]	Referent
UST-BSC	£123,230	3.78	[redacted]	0.46	[redacted]	[redacted]
SEC300-BSC	£139,794	3.63	[redacted]	-0.15	[redacted]	[redacted]

Note: Small discrepancies between full incremental and pairwise ICERs are caused by rounding. Full incremental ICERs are correct.

ADA = adalimumab; APR = apremilast; bDMARD = biologic disease-modifying anti-rheumatic drug; BSC = best supportive care; CZP = certolizumab pegol; ERG = Evidence Review Group; ETA = etanercept; GOL = golimumab; ICER = Incremental cost effectiveness ratio; INF = infliximab; IXE = ixekizumab; PAS = patient access scheme; q2w = once every two weeks; q4w = once every four weeks; QALY = quality-adjusted life year; SEC = secukinumab; UST = ustekinumab

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] compared to ustekinumab but the differences were [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

Economic evaluation

The company's deterministic base-case ICERs of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. In the b/tsDMARD-experienced population, ixekizumab (with PAS) had ICERs [redacted] per QALY gained when compared with BSC. It was [redacted] when compared with ustekinumab in no and mild-to moderate psoriasis and [redacted]ustekinumab in moderate-to severe psoriasis. The ERG incorporated various adjustments to the company base-case (probabilistic results for the b/tsDMARD-naïve population and deterministic results for the b/tsDMARD-experienced population). In the ERG base-case, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained versus BSC (no and mild-to-moderate psoriasis subgroups) and certolizumab pegol (moderate-to-severe psoriasis subgroup) in the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses for the no and mild-to-moderate psoriasis subgroups). Additionally, the ERG explored different scenarios based on the ERG base-case analysis. In those analyses, ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population except in the scenario in which both PASI 75 and PsARC were used to determine treatment response. In that scenario, ixekizumab had an ICER of [redacted]per QALY gained versus BSC in the moderate-to-severe psoriasis subgroup. In the b/tsDMARD-experienced population, ixekizumab had ICERs below [redacted]per QALY gained versus BSC in all psoriasis severity levels in all scenarios, except when both PASI 75 and PsARC were used to determine treatment response. In this scenario, ixekizumab [redacted].

In conclusion, despite the ERG criticism and amendments to the company cost effectiveness analysis, ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population. Ixekizumab provided ICERs [redacted] per QALY gained versus BSC or certolizumab pegol in the b/tsDMARD-experienced population. In this population, when compared to ustekinumab, ixekizumab [redacted] in all psoriasis severity levels. Using both PASI 75 and PsARC responses simultaneously to determine treatment response was the most influential scenario analysis performed by the ERG.

8.2 Strengths and limitations of the assessment

Following clarification, the company submission searches were well presented and reproducible. Searches were carried out on a range of databases and supplementary resources. However, the ERG was concerned about the overall quality of the searches conducted, as there were numerous inconsistencies, inaccuracies, errors and redundancy throughout. The extensive use of restrict to focus, date limit (2000-2017), omission of the NHS EED database and application of language limits were all considered overly restrictive. It is possible that relevant evidence may have been missed as a consequence.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 26 April 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 – The second paragraph contains two typographical errors: 'etaneracept' and 'secukinab'.	This should be amended to 'etanercept' and 'secukinumab'	Typographical error	Typographical errors have been corrected.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 – In the fourth paragraph, it is stated that 'for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]'. The odds ratios for the comparison between [redacted] (not provided by the manufacturer in the clarification response) [redacted]. [redacted] was the only other treatment to be associated with a [redacted] was associated with a significant improvement relative to [redacted]	This should be amended to clarify that with the exception of [redacted] from other treatments and that with the exception of [redacted] from other treatments	Factual accuracy	Changed sentence to "These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response [redacted] from other treatments and that with the exception of [redacted] from other treatments".

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 – The third paragraph contains a typographical error: 'bMARD'	This should be amended to 'bDMARD'	Typographical error	Typographical error has been corrected.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 – The third paragraph states that there were fewer than five trials in most analyses for bDMARD-experienced patients. At most, there were four trials across all analyses. The current wording could imply that some analyses were informed by five or more trials	This should be corrected to '(at most four trials in an analysis)'	Factual accuracy	The statement "fewer than five trials in most analyses" has been replaced with "at most four trials in an analysis".

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 – In the fourth paragraph, only the conditional probabilities of treatment-emergent adverse events for the ixekizumab rates are presented. Lilly would suggest providing the conditional probabilities for other	Conditional probabilities for treatment emergent adverse events of other active treatments should be provided in this paragraph.	To provide context to the estimated adverse event rates for ixekizumab.	This is not a factual error. NB: The relevant Table 10 (containing results for all active treatments) of the response to request for clarification was reproduced as Table 4.20 of

active treatments in this paragraph for context.			the ERG report. No correction required.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 – In the first paragraph, it should be noted that a scenario analysis was conducted in which the length of the trial period was set to 16 weeks in accordance with the SmPC.	Amend to state that a 16-week stopping rule was considered in a sensitivity analysis.	To provide further detail on the discussion of the stopping rule for ixekizumab	This is not a factual error. The statement makes it clear that the 12-week stopping rule was implemented in the company's base-case. The scenario is described later in the report. No correction required.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 – The last paragraph states that the complex PAS scheme of ustekinumab was modelled in the company submission. The complex PAS scheme of ustekinumab applies to the 90 mg dosing regimen. This was not a comparator in the economic evaluation.	Please amend to indicate that the complex PAS scheme of certolizumab pegol was implemented in the model.	Factual accuracy	This is not a factual error. In this paragraph, it is not stated that ustekinumab is used as a comparator. No correction required.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 – The second paragraph states that 'The most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab' in the one-way sensitivity analyses.	This should be amended to 'the most influential parameters were PsARC rates of first-line treatments…'	The one-way sensitivity analyses presented in the company submission were presented only for the ixekizumab sequence versus the secukinumab sequence in the bDMARD-naïve population and versus the ustekinumab sequence in the bDMARD-experienced population. The comparisons were selected for illustrative purposes only and were not exhaustive.	This section aimed to summarise the company submission. The described information was obtained from the company submission. For clarity, this sentence has been amended to reflect that the company's sensitivity analyses were not exhaustive.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 – The last paragraph discusses Lilly's use of the limited network and the weaknesses associated with this network.	It should be made clearer that the use of the limited network in the bDMARD-experienced population was motivated by the unavailability of bDMARD-experienced data from the certolizumab pegol and secukinumab trials. The majority of patients in these trials were bDMARD-naïve and as prior bDMARD exposure is a likely treatment effect modifier, the comparators were omitted from the base case bDMARD-experienced network. The omission of PASI 50 from the network was a consequence of omitting these comparators.	To clarify the rationale for Lilly's preference for the limited network	This is not a factual error. No correction required.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – In the second paragraph, the ERG state that they are not able to assess whether the effectiveness and costs associated with BSC in the cost-effectiveness model are valid.	It should be stated that the approach to costing BSC in the current analysis follows the approach of the 2016 York model.	To provide the context that this is a limitation of the York model which has been widely accepted in the health economic evaluation of treatments in PsA	This is not a factual error. The use of similar methods to older assessments does not imply that these are fully validated. No correction required.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – It is noted in the third paragraph that the assumption of equal treatment discontinuation rates was viewed as a major and influential limitation. By definition, ixekizumab and the more recently recommended therapies will not have the long-term registry data that might inform discontinuation rates for older drugs.	The comment should be amended to state that ixekizumab does not have the long-term 'real world' data of older comparators.	To correctly represent the limitations of the available evidence	This is not a factual error. No correction required.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – In the second paragraph in Section 1.6.2, the reference to the number and proportion of UK patients in the SPIRIT trials should be treated as academic-in-confidence.	This information should be marked as academic-in-confidence	To maintain confidentiality and ensure that confidential information is redacted	This statement has been highlighted as academic in confidence.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – In the second paragraph in Section 1.6.2, the lack of direct evidence available on ixekizumab in relation to the other comparators in the scope is noted as a weakness of the submission.	It should be noted that this limitation is not specific to ixekizumab and that direct evidence is not available for any other active comparator.	To provide context on the availability of direct data as a weakness that affects the assessment of other treatments in PsA	This is not a factual error. No correction required.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 – In the second paragraph, the use of a relative measure of response to define health states in the model is noted as a weakness of the analysis.	It should be stated that the relative measure of response used to define model health states, i.e. PsARC, is the treatment response criteria specified by NICE to determine treatment continuation.	To provide context for the definition of health states that is considered to be a weakness by the ERG	This is not a factual error. No correction required.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 – In the last paragraph, the ERG states "ixekizumab remained [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population".	It should be noted that some treatments that have previously been considered [redacted] in the ERG's analyses.	To provide context for the predicted results of the model	This is not a factual error. No correction required.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 – There is a typographical error in the second paragraph: 'dactilytis' should be corrected to 'dactylitis'.	This should be amended to 'dactylitis'	Typographical error	The word has been marked "[sic!]" as this was a typographical error in the cited company submission.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 – The stopping rule of 12 weeks is noted for etanercept, adalimumab and infliximab.	The stopping rule of 12 weeks applies to all TNF-alpha inhibitors. Furthermore, it should be noted that the stopping rule for secukinumab, an IL-17 agent, is 16 weeks.	To provide context for the discussion of a stopping rule for ixekizumab	This is not a factual error As indicated in the report, some drugs were used to illustrate the concept of a stopping rule. A reference has been provided for further details.

			No correction required.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29 – In the list of comparators in the scope, it is noted that the bDMARDs are recommended either alone or in combination with methotrexate. Apremilast is listed in a separate bullet point.	It should be noted in the list of comparators included in the scope that apremilast is recommended either alone or in combination with DMARDs	Factual accuracy	This is not a factual error The current text is in line with the final scope issued by NICE as well as Table 3.1 of the report which was based on Table 1 of the CS. No correction required.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31 – There is a typographical error in the second paragraph: 'clnicaltrials.gov'	This should be amended to 'clinicaltrials.gov'	Typographical error	Typographical error has been corrected.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35 – The lack of direct evidence of ixekizumab in relation to the other DMARDs is noted. Please refer to Issue 13.	As per Issue 13	As per Issue 13	This is not a factual error No correction required.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41 – In the second paragraph, the number of years since PsA diagnosis is incorrectly stated for SPIRIT-P1 and SPIRIT-P2.	The numbers should be amended to 6.7 years in SPIRIT-P1 and 10.0 years in SPIRIT-P2.	Factual accuracy	This has been corrected and is now in line with the numbers reported in Table 4.3 of the report.

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41 – In the fifth bullet point of the ERG's comments, the number of rheumatologists and dermatologists in the Adelphi DSP should be treated as academic in confidence.	This information should be highlighted yellow and underlined to indicate this information is academic-in-confidence.	To maintain confidentiality and ensure that confidential information is redacted	This statement has been highlighted as academic in confidence.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 – In the first bullet point of the ERG's comments, the number of patients that have been exposed to ixekizumab in SPIRIT-P1 and SPIRIT-P2 is incorrect.	This number should be amended to 454.	Factual accuracy	"456 patients" has been replaced with "454 patients".

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71 – In Table 4.18, the placebo response values have been erroneously duplicated in the row "ustekinumab 90mg q12w". This is a typographical error that has been copied over from the CS.	The row "ustekinumab 90mg q12w" should be deleted.	Factual accuracy and removal of duplicate row	The row "Ustekinumab 90 mg q12w" has been deleted to address an error in the CS.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 – In Table 4.22, the first three rows in the table have been erroneously duplicated at the end of the table. This typographical error has been copied over from the clarification response document.	The duplicate rows (placebo, adalimumab 40 mg q2w and apremilast 30 mg bid) ought to be deleted from the table.	Removal of duplicate rows	The duplicate rows "Placebo", "Adalimumab 40 mg q2w" and Apremilast 30 mg bid have been removed to address an error in the clarification response document.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74 – In the third bullet point of the 'Critique of the indirect comparison and/or multiple treatment comparison', the change in baseline HAQ-DI for	These values should be corrected to [redacted] for ixekizumab 80 mg q4w and [redacted] for ixekizumab 80 mg q2w	Factual accuracy	Sentence was changed to read "For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and

ixekizumab responders from the NMA are incorrect ([redacted] for ixekizumab 80mg q4w and [redacted] for 80 mg q2w).			[redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data".

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74 – The ERG states that a limitation of the NMA is the use of different time points in the networks.	It should be noted that the time points for each treatment in the networks align with the time points for response assessment as recommended by NICE.	To provide context to the use of different time points that is considered to be a limitation by the ERG	This is not a factual error No correction required.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 – In the first paragraph of Section 4.6, it is stated that no direct evidence was presented for ixekizumab in relation to the active comparators. Please refer to Issue 13.	As per Issue 13	As per Issue 13	This is not a factual error No correction required.

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 – In the second paragraph of Section 4.6, the proportion of UK patients in	As per Issue 12	As per Issue 12	This statement has been highlighted as academic in

SPIRIT-P1 and SPIRIT-P2 should be treated as academic-in-confidence.			confidence.

Issue 30

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 – In the second paragraph of Section 4.6, the number of patients that have been exposed to ixekizumab in SPIRIT-P1 and SPIRIT-P2 is incorrect. Please refer to Issue 23.	As per Issue 23	As per Issue 23	“456 patients” has been replaced with “454 patients”.

Issue 31

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 – The first paragraph contains two typographical errors: ‘etaneracept’ and ‘secukinab’.	This should be amended to ‘etanercept’ and ‘secukinumab’	Typographical error	Typographical errors have been corrected (page 76).

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 – The second paragraph contains a typographical error: ‘bMARD’	This should be amended to ‘bDMARD’	Typographical error	Typographical error has been corrected

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 – The second paragraph states that there were fewer than five trials in most analyses for bDMARD-experienced patients. At most, there were four trials across all analyses. The current wording could imply that some analyses were informed by five or more trials.	This should be corrected to '(at most four trials in an analysis)'	Factual accuracy	The statement "fewer than five trials in most analyses" has been replaced with "at most four trials in an analysis".

Issue 34

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 - In the third paragraph, it is stated that 'for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted]. Please refer to Issue 2	As per Issue 2	As per Issue 2	Changed sentence to "These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of [redacted] other treatments and that with the exception of [redacted] from other treatments".

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79 – In Table 5.1, the inclusion criteria for Outcomes is noted to be "QALY-based outcomes" Lilly omitted in the CS to note that the inclusion criteria for outcomes also included studies that focussed on health utilities, UK-specific health care resource utilisation and costs, and Japanese health care resource utilisation and costs (initial review only)	The inclusion criteria in the table should be updated to incorporate 'Health utilities', 'UK-specific healthcare resource utilisation and costs', and 'Japanese health care resource utilisation and costs (initial review only)'	Factual accuracy	Table 5.1 is based on the CS. No correction required.

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85 - It should be noted in point a) of the ERG's comments that the relative measure of response used to define model health states is the treatment response criteria specified by NICE to determine treatment continuation. Please refer to Issue 14.	As per Issue 14.	As per Issue 14.	This is not a factual error. No correction required.

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 – In point d) of the ERG's comment, it is noted that adverse events have not been incorporated in the cost-effectiveness model.	It should be noted that adverse events have not been incorporated in the York model.	To provide the context that this is a limitation of the York model which has been widely accepted in the health economic evaluation of treatments in PsA	This is not a factual error. No correction required.

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 – In point e) of the ERG's comments, the ERG state that they are not able to assess whether the effectiveness and costs associated with BSC in the cost-effectiveness model are valid. Please refer to Issue 10.	As per Issue 10	As per Issue 10	This is not a factual error. No correction required.

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 – In point f) of the ERG's comments, the ERG state that the cycle length of one month in the cost-effectiveness model may overestimate health benefits in the trial period and potentially distribute resource use over a	It should be noted that the cycle length of the York model is three months.	To clarify that this limitation is a feature of the York model and is not specific to the current model	This is not a factual error. No correction required.

longer period of time relative to clinical practice.			

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 – In the second paragraph of Section 5.2.3, the ERG state that the severity of psoriasis is defined as “a) no psoriasis, b) mild-to-moderate psoriasis (BSA≥3% and PASI≤10), and c) moderate-to-severe psoriasis (BSA>3% and PASI>10)”. Lilly clarified the definition of psoriasis severity informing the baseline PASI and HAQ-DI scores in clarification response B5a).	The definition of response in this paragraph should be changed to “a) no psoriasis, b) mild-to-moderate psoriasis (PASI<12, sPGA≥3 and BSA≥10%), and c) moderate-to-severe psoriasis (PASI≥12 and sPGA≥3 and BSA≥10%)”	Factual accuracy	This is not a factual error. This section aimed to summarise the company submission. The described information was obtained from the company submission. In the following ERG comment, the response given by the company is reproduced. No correction required.

Issue 41

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 89 – In the second paragraph, it is stated that ‘the CS does not describe how the treatment sequences have been selected’. Lilly have provided a justification for the treatment sequences in CS and clarification	The justification provided by Lilly in clarification responses B8a) and B8b) should be noted in the ERG report.	To provide context for the selection of treatment sequences	This is not a factual error. This statement refers to the company submission (not the clarification response). No correction required.

responses B8a) and B8b).			

Issue 42

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93 – In point b) of the ERG's comments, the ERG state that Lilly's exclusion of certolizumab pegol and secukinumab from the base case bDMARD-experienced network 'contradicts its argument of not using the same evidence to estimate the effectiveness of certolizumab pegol and secukinumab in the b/tsDMARD-experienced subgroup because the studies do not provide estimates for b/tsDMARD-naïve and b/tsDMARD-experienced patients separately.'	It should be noted that approximately 30% of patients in the certolizumab pegol and secukinumab trials were bDMARD-experienced. As the majority of patients in these trials were bDMARD-naïve, Lilly do not believe it to be a contradiction to include these trials in the bDMARD-naïve network.	To add context to this point that is considered a contradiction by the ERG.	This is not a factual error. No correction required.

Issue 43

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 – in point g) of the ERG's comments, the ERG note that they preferred to use the trial data for reduction in HAQ-DI scores for ixekizumab q4w rather than the reduction derived from the NMA. Lilly believe that it would not be	The reduction in HAQ-DI conditional on PsARC response derived from the NMA should be used for ixekizumab q4w.	Consistency in using the NMA to inform HAQ-DI reduction in the model	This is not a factual error. No correction required.

appropriate to use the naïve data for ixekizumab q4w in the model and data derived from the NMA for all other treatments.			

Issue 44

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101 – in Section 5.2.7, the ERG comment that not incorporating adverse events is a substantial weakness of the model.	It should be noted that adverse events have not been incorporated in the York model.	To provide the context that this is a limitation of the York model which has been widely accepted in the health economic evaluation of treatments in PsA	This is not a factual error. No correction required.

Issue 45

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107 – In Table 5.13, there are typographical errors in the total trial period cost and total annual cost of SC self-injection and IV infusion that have been carried over from the CS.	The total trial period costs should be £43.00 for SC self-injection and £708.57 for IV infusion. The total annual cost for IV infusion should be £1,535.24.	Factual accuracy.	This Table is referenced as based on the CS. No correction required.

Issue 46

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 123 – In the last paragraph, the ERG states that ixekizumab was not cost-effective compared	It should be noted that the referent for the ICER calculation is ixekizumab.	To clearly represent the results of the analyses presented by the company in the bDMARD-	This is not a factual error. No correction required.

to ustekinumab in the company's deterministic base case. It should be noted that in the pairwise comparison of the two therapies, the referent for the ICER calculation is ixekizumab.		experienced population	

Issue 47

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 123 – In the last paragraph, it is noted that 'the most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab'. Please refer to Issue 8.	As per Issue 8	As per Issue 8	This section aimed to summarise the company submission. The described information was obtained from the company submission. For clarity, this sentence has been amended to reflect that the company's sensitivity analyses were not exhaustive (page 125).

Issue 48

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 133, 134, 135, 137, 138, 140, 141, 142, 144 – an ICER of £0 is noted for the referent treatment BSC in the analyses presented on these pages.	This should be amended to 'Referent'.	Correct terminology for the referent treatment	No incidences of £0 for BSC as indicated by the company were found in the corrected ERG report. No correction required.

Issue 49

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 147 – The second paragraph contains two typographical errors: ‘etaneracept’ and ‘secukinab’.	This should be amended to ‘etanercept’ and ‘secukinumab’	Typographical error	Typographical errors have been corrected.

Issue 50

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 147 – The third paragraph contains a typographical error: ‘bMARD’	This should be amended to ‘bDMARD’	Typographical error	Typographical error has been corrected (page 148).

Issue 51

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 149 – In the first paragraph, the reference to the number and proportion of UK patients in the SPIRIT trials should be treated as academic-in-confidence.	This should be marked as academic-in-confidence	To maintain confidentiality and ensure that confidential information is redacted	This statement has been highlighted as academic in confidence (page 150).

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Ixekizumab for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs

ERRATUM

This document contains errata in the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page	Change
13	• Typographical errors corrected (etanercept, secukinumab, bDMARD) • The statement "fewer than five trials in most analyses" was replaced with "at most four trials in an analysis" • Changed sentence "These showed that for bDMARD-naïve patients [redacted] was the most effective treatment across all categories of ACR response but it was [redacted] to "These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of ixekizumab q2w was [redacted] from other treatments and that with the exception of [redacted], ixekizumab q4w was [redacted] from other treatments".
16	• Amended sentence "The most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab." to read "The most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab.".
17	• The statement on the number and proportion of UK patients in the SPIRIT trials has been marked as academic in confidence
21	• "[sic!]" has been added to mark a typographical error in text quoted from the CS
31	• Typographical error corrected (clinicaltrials.gov)
41	• Mean disease duration (time since PsA diagnosis) for the SPIRIT trials corrected • Missing ")" has been added in the fifth bullet point • The number of rheumatologists and dermatologists in the Adelphi DSP has been marked as academic in confidence
59	• "456 patients" has been replaced with "454 patients"
71	• In Table 4.18, the row "Ustekinumab 90 mg q12w" has been deleted
73	• In Table 4.22, the duplicate rows "Placebo", "Adalimumab 40 mg q2w" and Apremilast 30 mg bid have been deleted
74	• The sentence "For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data." Was changed to read "For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data".
75	• The statement on the proportion of UK patients in the SPIRIT trials has been marked as academic in confidence • "456 patients" has been replaced with "454 patients"
76	• Typographical errors corrected (etanercept, secukinumab, bDMARD)

Page	Change
	• The statement "fewer than five trials in most analyses" was replaced with "at most four trials in an analysis" • Changed sentence "These showed that for bDMARD-naïve patients_[redacted] was the most effective treatment across all categories of ACR response but it was [redacted]" to "These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of ixekizumab q2w was [redacted] from other treatments and that with the exception of [redacted] from other treatments".
125	• Amended sentence "The cost effectiveness results were fairly robust to scenario and one-way sensitivity analyses conducted by the company, but the most influential parameters were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab." to read "The cost effectiveness results were fairly robust to scenario and one-way sensitivity analyses conducted by the company, but the most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab.".
148	• Typographical error corrected (etanercept, secukinumab, bDMARD)
150	• The statement on the number and proportion of UK patients in the SPIRIT trials has been marked as academic in confidence

groups than in the placebo group in both SPIRIT trials. Adverse events (AEs) across the two SPIRIT trials were mainly of mild or moderate severity and the proportion of patients who discontinued medication due to AEs was low across all treatment groups. There were no deaths across the two trials in the double-blind periods. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials.

In the absence of trials directly comparing the active treatments specified in the NICE scope, the company conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, Psoriasis Area and Severity Index (PASI) 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, PASI response and PsARC response, [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted], [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders and [redacted] were the most effective treatments.

There was less evidence for bDMARD-experienced patients (at most four trials in an analysis) and ixekizumab was [redacted] to ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate but it [redacted] to ixekizumab.

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of ixekizumab q2w was [redacted] from other treatments and that with the exception of [redacted] from other treatments. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab but the differences were [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company conducted a systematic review of the evidence for ixekizumab and its potential comparators in adults with PsA as per the NICE scope. The submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. A range of databases were searched, and additional searches of conference proceedings, trials registers and websites were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. However, the ERG has major concerns regarding the searches, as detailed in section 1.6.2.

The company presented two multicentre, randomised controlled trials of ixekizumab (SPIRIT-P1 and P2). Randomised trials represent the highest level of primary studies in medical research. This evidence base includes patients with experience of bDMARDs and those without and outcomes relevant to the NICE scope. Both trials are well-conducted. Both compare ixekizumab to placebo. The double-blind period of the SPIRIT trials is 24 weeks so long-term effectiveness results cannot be fully determined. The extension periods do, however, provide information on long-term safety. At week 16 in the trials, patients were permitted rescue therapy in case of inadequate response so results up to

the NHS Reference Costs. Furthermore, the company estimated the costs associated with HAQ-DI and PASI scores separately. HAQ-DI related costs were estimated using a linear regression informed by a study with sample size of 916 rheumatoid arthritis patients in the UK, dated 2002. PASI-related costs were sourced from the York model and justification was not provided for each cost item.

The company's deterministic base-case incremental cost effectiveness ratios (ICERs) of ixekizumab (with PAS) compared with other comparators showed that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per quality-adjusted life year QALY gained in the b/tsDMARD-experienced population when compared with BSC. It was [redacted] when compared with ustekinumab in that population in the no and mild-to-moderate psoriasis groups [redacted] in the moderate-to-severe group. The cost effectiveness results were fairly robust to scenario- and one-way sensitivity analyses conducted by the company. The most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab. Scenario analyses indicated that assumptions with the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, alternative (i.e. the York model) utility model coefficients, an alternative (i.e. the Poole et al. 2010) algorithm for costs associated with HAQ-DI and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab being accounted for).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The cost effectiveness searches in the company submission and clarification response were reported in enough detail for the ERG to appraise them. Separate searches were conducted to identify cost effectiveness models and model input studies.

Reviewing the overall evidence, the ERG considers that the company's approach to use the revised York model as a basis for developing their model was appropriate. However, a limitation with this and the York model was that the allocation of patients to health states in the model was based on a relative measure of response (based on reductions in symptoms). This may lead to health states being composed of heterogeneous patient populations for which it is arguably difficult to assign costs and HRQoL estimates.

The economic model described in the CS is considered by the ERG to meet the NICE reference case, with the notable exceptions of a) the exclusion of comparators identified in the scope and b) a NMA (in the CS base-case) that did not consider all the relevant outcomes as identified in the scope, such as adverse events. Addressing a), the company justified the absence of secukinumab and certolizumab pegol from the b/tsDMARD-experienced patient population analysis by the unavailability of data in that population. However, it should be noted that studies on these two treatments were conducted in mixed populations, i.e. b/tsDMARD-naive and –experienced patients. Regarding b), the omission of adverse events from the NMA and economic model was considered a major limitation by the ERG, given that these differ per treatment and their inclusion would lead to potential differences in HRQoL, costs, and treatment discontinuation rates. Furthermore, the use of a limited network for the b/tsDMARD-experienced patient population, which omitted PASI 50 as an outcome, was considered by the ERG to result in potential bias in favour of treatments with a higher PsARC response (given PASI 50 response was presumably set to 0% in this case). This also resulted

in the exclusion of certolizumab pegol and secukinumab as comparators in this population, i.e. deviating from the scope, which again likely favoured ixekizumab in this population. Furthermore, treatment sequences used in the model for the b/tsDMARD-naive patient population exclude relevant treatments as, in addition to ustekinumab, certolizumab pegol and secukinumab could also be used in second line.

The ERG is concerned about the representativeness of the patient population in the SPIRIT trial programme and its impact on the relevance and validity of the NMA results for the UK context. BSC was not accurately described in the model and the ERG was unable to assess whether BSC was representative of the UK context and whether the effectiveness as well as the costs associated with BSC in the cost effectiveness model were valid.

The assumption of equal treatment discontinuation rates for all b/tsDMARD treatments was viewed as a major and influential limitation. Of further concern were the excess mortality which was considered potentially too high and the fact that the HAQ-DI reduction estimate for ixekizumab q4w responders and non-responders based on the NMA was inconsistent with the trial data. Furthermore, the ERG considers there to be large uncertainty about the resource use and cost estimates associated with HAQ-DI and PASI, with several limitations identified in both estimates.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. The company's clarification response provided sufficient details for the ERG to appraise the searches. Additional searches were carried out for conference abstracts and clinical trials. The clinical evidence is based on two multinational RCTs covering a group of patients naïve to bDMARDs and those with prior experience of bDMARDs.

The cost effectiveness model is well built and transparent. The treatment effectiveness estimates from a network of studies are a strength as is the attempt to consider treatment sequences. The company performed many relevant sensitivity- and scenario analyses to reflect uncertainty about the cost effectiveness results. The model was relatively robust to these changes, with some notable exceptions as detailed in section 1.5 of this report.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned about the overall quality of the searches for studies on clinical effectiveness as it identified numerous inconsistencies, omissions, inaccuracies and errors. This and the application of an English language restriction mean that it is possible that relevant evidence was missed.

The main trials in the submission included a small number of UK patients (approximately [redacted] across the two trials). Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. The committee will need to decide, based on the factors highlighted by the ERG in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice. Another weakness of the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope.

Cost effectiveness searches of Medline and Embase contained extensive focussed MeSH and Emtree indexing which may have adversely impacted on search strategy recall. The ERG noted several typographical errors, incorrect truncation and syntax mistakes in several of the cost effectiveness

The CS states that *'switching to another anti-TNF is a well-established practice in the NHS'*.[1] The company also states that treatment may be less successful with these agents at second line, i.e. *'less than 50% of the patients who achieved an ACR 20, 50 and 70 response after treatment with a TNF-alpha inhibitor in first-line, achieved such a response after receiving treatment with a second-line TNF-alpha inhibitor.*[19]'The average persistence on anti-TNF-alpha therapies in relation to the chronic nature of PsA is highlighted. '*Average survival/persistence of patients with PsA on anti-TNFα therapy is in the range of 2 to 4 years for the first agent and shorter for subsequent anti-TNFα therapies'* based on a literature review.[20]

The company state the unmet need for ixekizumab as providing a new mechanism of action to obtain and sustain efficacy at a similar level to that of the anti-TNF-alpha therapies in both patients naïve to biologic DMARDs as well as those experienced with acceptable safety and minimal disturbance to lifestyle. The CS further state that '*treatments should be able to treat the core joint symptoms of PsA as well as the skin symptoms (psoriasis and nail psoriasis) and the extra-articular PsA symptoms (such as enthesitis and dactilytis [sic!])'*.[1]

The CS states that *'ixekizumab is the first monoclonal antibody to block both active forms of IL-17A (IL-17A is expressed in both homodimer and heterodimer forms) with high binding affinity.[REF CS 64] It is the second anti IL-17 (and third biologic therapy) to offer an alternative mechanism of action to TNF-α inhibitors'*.[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify randomised controlled trial (RCT) evidence of ixekizumab and potential relevant comparator treatments for psoriatic arthritis.

4.1.1 Searches

Initial searches were reported for Medline, Medline In-process & Other Non-Indexed Citations, Medline Daily Update, PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). These were undertaken in August 2016 (1990-2016). Update searches were reported for May 2017 (2016-2017). The database host was not reported for the initial searches, Ovid was reported as the host for the update searches. The date the searches were conducted was provided.

Medline and Embase searches included unreferenced randomised controlled trials study design filters. The EBM Reviews CENTRAL search did not include an RCT filter. Medline, Embase and CENTRAL searches were all restricted to English language publications only. Searches of the following trials registers were reported in the appendices of the company submission (section 1.2.1) for 01/01/2016-09/05/2017: clinicaltrials.gov and World Health Organisation (WHO) ICTRP (International Clinical Trials Registry Platform).

Additional searches of the following conferences abstracts were reported: European League Against Rheumatism (EULAR, 2017 only), American College of Rheumatology/Association for Rheumatology Health Professionals (ACR/ARHP, 2016 only) and Asia Pacific Rheumatology Congress (APLAR, not included in the update). However, no details of the conference proceedings search terms, date of searches or results were provided.

The company submission noted that the initial review and update searches were conducted by different third-party vendors.[1] In Appendix D, the company acknowledgment significant mistakes in the Embase, Medline and CENTRAL searches (1990-2016).[28] The mistakes were corrected in the update searches (2016-2017). Unfortunately, the corrected searches were not repeated to cover the date span of the initial searches. The company reported checking whether the flawed initial review searches had missed studies.[28] The cross-checking process involved checking whether relevant included studies from previous systematic reviews (SRs) and network meta-analyses (NMAs) were picked up. The company was satisfied that *'it was deemed to be likely that the initial review captured all relevant studies over the period 1990-2016'*.[1, 28] The process for identifying candidate SRs and NMAs to check the initial review against was not reported in the CS nor appendices. In the clarification response,[25] the company reported selecting SRs and NMAs from the updated RCT search as well as from TA445;[13] independent searches specifically for SRs were not conducted by the company.

ERG comment:

- The main clinical effectiveness searches (1990-2016) contained consequential errors and flaws which will have impacted on retrieval of RCTs. Although the mistakes were corrected in the update searches (2016-2017), corrected searches were not re-run. Relevant studies could have been missed due to these mistakes.
- The company's approach to checking whether studies were missed or not was sub-optimal. Only RCT searches were conducted for the clinical effectiveness review. The company reported in the submission[28] and the clarification response[25] that earlier SRs and NMAs were used to cross-check for missed studies and as a method of validation for the review. As no SR searches were

The mean age of patients in SPIRIT-P1 was 49.5 and 51.9 years in SPIRIT-P2. Just under half were male (SPIRIT-P1: 46.0% and SPIRIT-P2: 46.6%). Most patients across the two trials were white (SPIRIT-P1: 94% and SPIRIT-P2: 91.5%). In total, 3.6% of the patients in SPIRIT-P1 and 5.8% in SPIRIT-P2 were Asian. The SPIRIT-P1 study was conducted with the majority of patients from Europe (73.4%) whereas in SPIRIT-P2 41% were from Europe.

Mean BMI in SPIRIT-P1 was 30.0 (SD 8.5) and 30.9 (SD 7.2) in SPIRIT-P2. The mean disease duration (time since PsA diagnosis) was 6.7 years in SPIRIT-P1 and 10.0 years in SPIRIT-P2. Current psoriasis occurred in 94.5% of patients in SPIRIT-P1 and in 93.4% of patients in SPIRIT-P2. Moderate to severe psoriasis was found in 13.8% of SPIRIT-P1 and 10.5% of SPIRIT-P2 patients. In SPIRIT-P1 58% had current enthesitis and 37.6% had current dactylitis. In SPIRIT-P2 the corresponding figures were 60.9% and 17.1%).[1]

ERG comment:

- Approximately 85% of the participants in SPIRIT-P1 had received a cDMARD which is normally given before a bDMARD in clinical practice so 15% of the patients in SPIRIT-P1 are not relevant to the population in the scope.
- Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. A separate analysis of the NICE ITT population is provided in the CS based on [redacted] patients across the two trials.[1]
- Non-white participants are underrepresented across the two trials.
- Mean BMI in the SPIRIT trials is within the obese classification so patients in the trials may be more overweight than those seen in practice.
- The ERG asked the company to clarify whether patients included in those trials are representative of UK clinical practice. The company replied that they had sourced real world data to assess the representativeness of patients in the SPIRIT trials for UK practice.[25] In the Adelphi Psoriatic Arthritis Disease Specific Programme (DSP), a total of [redacted] patient record forms were completed by [redacted] rheumatologists and [redacted] UK dermatologists. Of these patients, [redacted] were bDMARD-naïve and [redacted] bDMARD experienced (based on the Adelphi Psoriatic Arthritis DSP; as cited in the Clarification response).[25] The company also compared the patients to a recently published UK study from The Health Improvement Network (THIN).[8]
- The company stated that patients in SPIRIT-P1 had higher baseline CRP and a greater number of tender and swollen joints than patients in the Adelphi study therefore '*at least the same level of ACR response rates would be expected to be achieved in UK practice as was demonstrated by SPIRIT-P1*'.[25]This is an assumption made by the company.
- The ERG noted that mean age and proportion of males was similar in the SPIRIT-P1 trial and the UK Adelphi study (biological-naïve) and THIN database studies. However, BMI did appear to be a little higher in SPIRIT-P1. The UK PsA patients in Adelphi DSP had slightly higher rates of prior conventional synthetic DMARD (csDMARD) use ([redacted] of UK PSA bio-naive patients).
- The ERG noted that mean age was similar in the SPIRIT-P2 trial and the UK Adelphi study (bio-experienced). The proportion of males was slightly higher ([redacted] in Adelphi vs. 46.6% in Spirit-P2). Again, BMI did appear to be a little higher in SPIRIT-P2. The company stated that '*The rate of prior csDMARD use is consistent in SPIRIT-P2 with the Adelphi DSP dataset. 77.5% of bio-experienced patients randomized to IXE80MGQ4W received prior csDMARD use compared to [redacted] of bio-experienced patients in the Adelphi DSP dataset.*'[25]
- Patients in SPIRIT-P2 generally had more severe disease at baseline than those bio-experienced patients treated in UK clinical practice as captured by Adelphi DSP. SPIRIT-P2 included a

ERG comment:

- In total, 454 patients have been exposed to ixekizumab across the two SPIRIT trials. This has revealed an increased but manageable set of adverse events when compared to placebo.
- Safety is evaluated in a double-blind manner for just 24 weeks. However, the long-term extension phases of the trials (up to two years available in SPIRIT-P1) add weight to the evidence of an acceptable safety profile in a population of patients with psoriatic arthritis.
- The increased incidence of infection with ixekizumab compared to placebo is noted. The Summary of Product Characteristics (SmPC) for ixekizumab notes that it '*should be used with caution in patients with clinically important chronic infection. If such an infection develops, monitor carefully and discontinue Taltz if the patient is not responding to standard therapy or the infection becomes serious. Taltz should not be resumed until the infection resolves. Taltz must not be given to patients with active tuberculosis (TB). Consider anti-TB therapy prior to initiation of Taltz in patients with latent TB*'.[34] Patients will need to be made aware of the increased risk of infections.
- Including both psoriatic arthritis trials and trials of plaque psoriasis, the SmPC notes that a total of 7,339 patients have been treated with ixekizumab representing 13,645.6 years of exposure. The SmPC notes that serious hypersensitivity reactions, including some cases of anaphylaxis, angioedema, urticaria and, rarely, late (10-14 days following injection) serious hypersensitivity reactions including widespread urticaria, dyspnea and high antibody titres have been reported. Cases of new or exacerbations of Crohn's disease and ulcerative colitis have also been reported. Caution is advised when prescribing ixekizumab to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, and that patients should be monitored closely. Furthermore, ixekizumab should not be used with live vaccines.[34] Regarding the SPIRIT trials, it was noted that injection site reactions were statistically significantly more common in ixekizumab groups in comparison to placebo.[34]
- The only direct safety comparisons, as for effectiveness comparisons, are between placebo and ixekizumab. However, SPIRIT-P1 has a reference adalimumab arm and it can be observed that occurrence of adverse events was similar in the adalimumab group to the ixekizumab groups although fewer of the adalimumab events appeared to be attributable to the drug. Additional safety comparisons between treatments are reported in the NMA results in section 4.3.

4.2.7 Ongoing trials

The CS mentioned two ongoing trials.[1] The first (SPIRIT-P3) has a dosage which is not in line with the licence, i.e. ixekizumab 80 mg q2w was given to all patients irrespective of psoriasis severity. Hence no further description of the trial was given in the CS. The second ongoing trial (SPIRIT-H2H) was described. SPIRIT-H2H was started in August 2017, is currently recruiting patients and is due to complete in April 2019. This randomised, open label trial will compare ixekizumab to adalimumab with 275 bDMARD naïve patients in each arm.[1]

ERG comment:

- Neither of the two ongoing trials at their current stage would have informed the submission. The ERG notes that SPIRIT-H2H will provide a direct comparison with adalimumab which is not available in the current submission.

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

As SPIRIT-P1 and SPIRIT-P2 were in different patient populations separate Bayesian network meta-analyses (NMAs) were performed for each population to compare ixekizumab with relevant

Table 4.1: PASI response for the biologic-experienced population

Treatment	PASI 75 (95% CrI)	PASI 90 (95% CrI)	PASI 100 (95% CrI)
Placebo	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg q12w	[redacted]	[redacted]	[redacted]

Source: Based on Table 26 of the CS[1]
Note: PASI 50 data were not included in the dataset as it was not reported by these studies.
CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

Table 4.2: PASI response for the biologic-experienced population including secukinumab and certolizumab pegol (pooled doses)

Treatment	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol pooled doses	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q2w	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg q4w	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 45 mg q12w	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on Table 32 of the CS appendices[28]
bid = twice daily; CrI = credible interval; CS = company submission; mg = milligram; PASI = Psoriasis Area and Severity Index; PASI 50 = ≥50% improvement from baseline in PASI score; PASI 75 = ≥75% improvement from baseline in PASI score; PASI 90 = ≥90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; q2w = once every two weeks; q4w = once every four weeks; q12w = once every 12 weeks

The fixed effect NMA results for ACR response are shown in Table 4.19 These show that ixekizumab 80 mg q4w had the [redacted] of achieving an ACR 20 response [redacted], an ACR 50 response [redacted] and an ACR 70 response [redacted] which were [redacted] than the response with placebo but not ixekizumab 80 mg q2w or ustekinumab 45 mg.

Treatment	SAEs
Etanercept 25 mg biw/50 mg qiw	[redacted]
Golimumab 50 mg q4w	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Secukinumab 150 mg q4w	[redacted]
Secukinumab 300 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]
Ustekinumab 90 mg q12w	[redacted]
Source: Based on Table 11 of the response to request for clarification[25] bid = twice daily; biw = twice weekly; CS = company submission; kg = kilogram; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly; SAE = serious adverse event	

NMA results for DAE are shown in Table 4.22 and show that the estimated probabilities of discontinuing due to an AE were [redacted] for ixekizumab 80 mg q2w and [redacted] for ixekizumab 80 mg q4w. Certolizumab pegol (pooled doses) had the [redacted] and ustekinumab 45 mg [redacted]

Table 4.3: Conditional probabilities of experiencing a DAE

Treatment	DAEs
Placebo	[redacted]
Adalimumab 40 mg q2w	[redacted]
Apremilast 30 mg bid	[redacted]
Certolizumab pegol pooled doses	[redacted]
Golimumab 50 mg q4w	[redacted]
Infliximab 5 mg/kg q8w	[redacted]
Ixekizumab 80 mg q2w	[redacted]
Ixekizumab 80 mg q4w	[redacted]
Ustekinumab 45 mg q12w	[redacted]
Ustekinumab 90 mg q12w	[redacted]
Source: Based on Table 12 of the response to request for clarification[25] bid = twice daily; biw = twice weekly; CS = company submission; DAE = discontinuation due to adverse event; kg = kilogram; mg = milligram; q2w = once every two weeks; q4w = once every four weeks; q8w = once every eight weeks; q12w = once every 12 weeks; qiw = once weekly	

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

- The NMA used standard Bayesian analysis methods as recommended in the NICE Decision Support Unit (DSU) Technical Support Documents 2.[35] The data and programs used for the PsARC, PASI and change in HAQ-DI were supplied by the company and checked by the ERG.

Due to the small size of most networks and the fact that many edges only contained a single trial, fixed effect models were used in the submission and economic model. Results from random effects models were also supplied in the clarification response and reviewed by the ERG. The ERG considers the NMA analysis methods and the presentation of fixed effect results to be appropriate, given the small size of many of the networks and little difference in fit between fixed and random effects models.

- Additional NMA results were provided in the clarification response for other outcomes including ACR response and adverse events (treatment-emergent, serious and discontinuation due to adverse events). However, the ERG did not have the associated data so these NMA results could not be verified.
- The ERG could verify the results for the PsARC and PASI outcomes. However, for change in HAQ-DI for PsARC responders and non-responders the results from the NMA for ixekizumab q2w and q4w produced by the ERG did not match those provided by the company. Results for other treatments from the same model could be reproduced but not those for ixekizumab. As there was only one study providing input data for ixekizumab in the dataset provided by the company the model estimates should have been similar to the study estimates. For PsARC responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data. For PsARC non-responders, the changes from baseline in HAQ-DI for ixekizumab 80 mg q4w were [redacted] from the NMA and [redacted] in the trial data and for 80 mg q2w they were [redacted] from the NMA and [redacted] in the trial data.
- Potential limitations of the NMA analyses are:
  - The use of different timepoints, including 12, 14, 16, and 24 weeks although sensitivity analyses replacing ixekizumab week 12 data with week 16 data showed little impact on the results.
  - As stated in the CS, the networks may have contained undetectable heterogeneity and inconsistency which could not be evaluated in some of the smaller networks so the treatment effects from the fixed effects models may be too precise.
  - To include other key comparators (apremilast, secukinumab and certolizumab pegol), trial data were included for the full population (rather than only biologic-naïve or biologic-experienced). *"If prior biologic exposure is an effect modifier for these treatments, the NMA results will not be representative of the treatment effect in a pure biologic-naïve/experienced population"* (section 2.9.3 of the CS[1]).
  - As the NMA analyses are based on indirect comparisons they are a weaker source of evidence than direct treatment comparisons obtained within a RCT and need to be treated with caution given the potential for clinical and statistical heterogeneity.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As described in section 4.1.1, the ERG did not consider the company's explanation of cross-checking recall of their flawed RCT searches adequate. The company checked recall of their searches against included studies in SRs, NMAs and health technology assessments (HTAs) also picked up in the RCT searches. Specific searches for SRs, NMAs and HTAs were not carried out nor were searches of SR or HTA databases conducted.

Therefore, the ERG conducted independent rapid appraisal searches to retrieve systematic reviews, meta-analyses and HTAs, searching the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), KSR Evidence, and Embase (Ovid). The ERG screened the rapid appraisal results and checked included

studies against the company submission. Full details of the independent rapid appraisal are presented in Appendix 1.

The ERG identified eight relevant publications, including SLRs, NMA and HTA reports.[52-59] These were checked for relevant primary studies potentially missed in the CS. Screening the results of the rapid appraisal searches, the ERG did not identify any study missed in the CS. However, the ERG identified one randomised study (Atteneo et al. 2010[60]) which has been excluded at the full paper review stage and was labelled as excluded for "Study design".[28] As detailed in section 4.1.1, the ERG believes that the appropriate response to address the substantial errors in the CS searches would have been to repeat the corrected searches to ensure the submission was based on a robust systematic review search. It should be noted that no full search was conducted by the ERG due to the limited time available for the assessment, i.e. not identifying relevant studies in the rapid appraisal should not be seen as evidence of absence of relevant studies missed in the CS.

4.6 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for ixekizumab and its comparators in patients with PsA as per the NICE scope. The company presented direct evidence from two RCTs, SPIRIT-P1 and SPIRIT-P2 that compared ixekizumab to placebo in adults with PsA. No direct evidence was presented for ixekizumab in relation to any of the other comparators in the NICE scope.

SPIRIT-P1 was conducted in biological DMARD naïve patients whilst SPIRIT-P2 was conducted in those with experience of biological DMARDs. SPIRIT-P1 included 417 patients and SPIRIT-P2 363 patients and both were well conducted, multinational trials. Across the two trials approximately [redacted] of patients were from the UK. Both trials demonstrated superiority of ixekizumab in relation to placebo on outcomes of importance to patients such as ACR criteria and PSARC measures during the double-blind phase of the trial up to 24 weeks. The company also provided more limited evidence on the efficacy of ixekizumab in relation to placebo for a population reflective of NICE current guidance on use of bDMARDs.

In total, 454 patients have been exposed to ixekizumab across the two SPIRIT trials. Data on adverse events are presented in the CS for the 24-week double blind period of the two SPIRIT trials and for the extension period (up to week 52). In the double-blind treatment phase patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials. Adverse events across the two SPIRIT trials were mainly of mild or moderate severity. There were no deaths across the two trials in the double-blind periods. The proportion of patients who discontinued medication due to AEs was low across all treatment groups with no statistically significant differences between ixekizumab and placebo groups. The most frequently reported AEs were infections which were comparable across groups. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials. The only direct safety comparisons, as for effectiveness comparisons, are between placebo and ixekizumab. However, SPIRIT-P1 has a reference adalimumab arm and it can be observed that occurrence of adverse events was similar in the adalimumab group to the ixekizumab groups although fewer of the adalimumab events appeared to be attributable to the drug.

Ixekizumab represents an additional option for PsA alongside the existing biologic treatments after two or more non-biological approaches have been tried. The need for additional options has been highlighted by patient and professional organisations. However, in order to be added to the options or indeed to be used preferentially over another agent, the comparable or superior performance of ixekizumab needs to be investigated through comparison with all of the relevant biological agents. In

this submission, in the absence of trials directly comparing active treatments the company has conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, PASI 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders and [redacted] were the most effect treatments.

There was less evidence for bDMARD-experienced patients (at most four trials in an analysis) and ixekizumab was [redacted] ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate but it was [redacted].

Additional NMA results for ACR 20/50/70 response and adverse events (AEs) were provided in the response to request for clarification. These showed that for bDMARD-naïve patients with the exception of [redacted], the ACR response of [redacted] from other treatments and that with the exception of [redacted] from other treatments. For bDMARD-experienced patients, both ixekizumab regimens had [redacted] ACR response compared to ustekinumab but [redacted]. Estimated conditional probabilities of treatment-emergent AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; serious AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w; and discontinuations due to AEs were [redacted] for ixekizumab q2w and [redacted] for ixekizumab q4w.

way sensitivity analyses conducted by the company, but the most influential parameters in the company's sensitivity analyses (which were not exhaustive) were PsARC rates for ixekizumab, secukinumab, ustekinumab, the annual discontinuation rates and treatment costs associated with ixekizumab and secukinumab. Scenario analyses indicated that assumptions with the greatest impact on the ICER for the ixekizumab sequences versus BSC relative to the base-case were HAQ-DI rebound to natural history in the BSC treatment state, the York utility model coefficients, the Poole et al. 2010 algorithm for costs associated with HAQ-DI,[72] and combining PsARC and PASI rates as the treatment continuation rule. Furthermore, the inclusion of certolizumab pegol and secukinumab in the b/tsDMARD-experienced population led to certolizumab pegol being cost effective (at list prices for ixekizumab and secukinumab but with PAS schemes for certolizumab pegol and ustekinumab.

The ERG incorporated various adjustments to the company's base-case. The ERG base-case shows that ixekizumab [redacted] in all psoriasis severity levels in the b/tsDMARD-naive population and had ICERs [redacted] per QALY gained in the b/tsDMARD-experienced population. In all psoriasis severity levels of the b/tsDMARD-experienced population, ixekizumab led to [redacted] compared to ustekinumab (the only other comparator for which an ICER was calculated in the fully incremental analyses).

The ERG identified major and minor issues and uncertainties that affected the cost effectiveness analysis. Major issues and uncertainties are listed in the following. One major limitation was the use of a limited network for the b/tsDMARD-experienced patient population, which omitted PASI 50 as an outcome, resulting in potential bias in favour of treatments with a higher PsARC response (given PASI 50 response was presumably set to 0% in this case). This also resulted in the exclusion of certolizumab pegol and secukinumab as comparators in this population, which deviated from the scope, again likely favouring ixekizumab in this population. This was partly addressed in the ERG base-case, although the data were not made available by the company to perform this analysis probabilistically. Furthermore, treatment sequences used in the model for the b/tsDMARD-naive patient population are excluding relevant treatments, as, in addition to ustekinumab, certolizumab pegol and secukinumab could also be used in second line. An alternative second-line treatment was explored in scenario analysis.

The ERG is concerned about the representativeness of the patient population in the SPIRIT trial programme and its impact on the relevance and validity of the NMA results in the UK context. The allocation of patients to health states in the model was based on a relative measure of response (based on reductions in symptoms), which leads to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. BSC was not accurately described in the CS and the ERG was unable to assess whether BSC was representative of the UK context, and whether the effectiveness and the costs associated with BSC in the cost effectiveness model were valid.

The assumption of equal treatment discontinuation rates for all b/tsDMARD treatments was viewed as a major and influential limitation. Of further concern were the excess mortality, which was considered high, and the fact that the HAQ-DI reduction estimate for ixekizumab q4w responders and non-responders based on the NMA did not reflect the trial data. The omission of adverse events from this submission is of particular concern, given that these differ per treatment and their inclusion would lead to potential differences in HRQoL, costs, and treatment discontinuation rates. Furthermore, the ERG considers there to be large uncertainty about the resource use and cost estimates associated with HAQ-DI and PASI, with several limitations identified in both estimates.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

The company presented direct evidence from two RCTs, SPIRIT-P1 and SPIRIT-P2 that compared ixekizumab to placebo in adults with PsA. SPIRIT-P1 was conducted in biological DMARD-naïve patients whilst SPIRIT-P2 was conducted in those with experience of biological DMARDs. SPIRIT-P1 included 417 patients and SPIRIT-P2 363 patients and both were well conducted, multinational trials. Across the two trials approximately [redacted] of patients were from the UK.

In both SPIRIT trials, significantly more patients achieved an ACR 20 response at week 24 with ixekizumab compared to placebo (SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 62.1%, placebo 30.2%; SPIRIT-P2: IXE 80 q4w 53.3%, IXE 80 q2w 48.0%, placebo 19.5%; $p<0.001$ for all comparisons to placebo). In both SPIRIT trials, the percentage of patients who achieved a PsARC response at week 12 as well as week 24 were statistically significantly greater for both ixekizumab groups compared to placebo in all cases (Week 12 – SPIRIT-P1: IXE 80 q4w 55.1%, IXE 80 q2w 61.2%, placebo 34.0%; SPIRIT-P2: IXE 80 q4w 50.0%, IXE 80 q2w 52.0%, placebo 23.7%. Week 24 – SPIRIT-P1: IXE 80 q4w 57.9%, IXE 80 q2w 66.0%, placebo 32.1%; SPIRIT-P2: IXE 80 q4w 55.7%, IXE 80 q2w 47.2%, placebo 20.3%). In terms of quality of life, at week 12 patients in the two ixekizumab groups achieved significantly greater mean change from baseline in HAQ-DI total scores in both SPIRIT trials. As not all participants in the SPIRIT trials would have been eligible for biological therapy under current NICE criteria, the company conducted a subgroup analysis using an integrated set of patients from SPIRIT-P1 and P2 who met the NICE criteria. The total number of patients available for analysis was [redacted]. [redacted] patients who received ixekizumab 80 mg Q4W or Q2W achieved an ACR 20 response at week 24 compared to placebo [redacted] and [redacted] vs. [redacted] respectively). In the 24-week double-blind treatment phase patients experienced more adverse events in the ixekizumab groups than in the placebo group in both SPIRIT trials. Adverse events across the two SPIRIT trials were mainly of mild or moderate severity and the proportion of patients who discontinued medication due to AEs was low across all treatment groups. There were no deaths across the two trials in the double-blind periods. Injection site reactions were statistically significantly more common with ixekizumab than placebo in both SPIRIT trials.

In the absence of trials directly comparing the active treatments specified in the NICE scope, the company conducted a Bayesian NMA of relevant trials for the outcomes of PsARC response, PASI 50/75/90/100 and change in HAQ-DI. Separate analyses were performed for bDMARD-naïve and bDMARD-experienced patients. The results for bDMARD-naïve patients showed that [redacted] had the best performance for PASI response but it was [redacted]. For PsARC response the most effective treatments were [redacted]. For both outcomes, [redacted] to all other treatments. For change from baseline in HAQ-DI the NMA results showed that in PsARC responders all treatments were significantly better than placebo except for [redacted] having the largest change from baseline. Changes in HAQ-DI score were smaller for PsARC non-responders [redacted] were the most effect treatments.

There was less evidence for bDMARD-experienced patients (fewer than five trials in most analyses) and ixekizumab was [redacted] to ustekinumab for PsARC response. For PASI response, ustekinumab had the [redacted] response rate but it was [redacted] to ixekizumab.

Two randomised controlled trials comparing ixekizumab to placebo are presented in the CS, one in patients with experience of bDMARDs and one in patients naïve to bDMARDs. Both multinational trials included a small number of UK patients (approximately [redacted] across the two trials). Furthermore, NICE recommends that bDMARDs are given after two cDMARDs have been tried. However, in the SPIRIT trials patients have not all received two prior cDMARDs. A separate analysis of the NICE ITT population [redacted] in relation to placebo is provided in the CS based on [redacted] patients across the two trials. The committee will need to decide, based on the factors highlighted by the ERG in this report whether it agrees with the company that the results of the SPIRIT trials are generalisable to UK practice. Another weakness in the submission is the lack of direct evidence available on ixekizumab in relation to the comparators in the scope, i.e. the main results in the CS came from a NMA.

The cost effectiveness model is well built and transparent. The treatment effectiveness estimates from a network of studies are a strength, as is the attempt to consider treatment sequences. The company performed many relevant sensitivity and scenario analyses to reflect uncertainty about the cost effectiveness results. The model was relatively robust to these changes, with some notable exceptions as detailed in the previous sections.

Health states in the model are based on a relative measure of response (based on reductions in symptoms), which leads to health states being composed of heterogeneous patient populations, for which it is arguably difficult to assign costs and HRQoL estimates. Further limitations are the exclusion of comparators identified in the scope and the omission of adverse events from the NMA and economic model. For b/tsDMARD-experienced patient population, only a limited network was used, which omitted PASI 50 as an outcome. The ERG considers a weakness the assumption of equal treatment discontinuation rates for all b/tsDMARD treatments. The representativeness of the patient population in the SPIRIT trial programme, excess mortality in this population, resource use and cost estimates associated with HAQ-DI and PASI pose areas of uncertainty.

8.3 Suggested research priorities

Research is lacking directly comparing the active comparators in the scope to determine the best treatment available for patients with PsA. The ERG notes that there is an ongoing trial (SPIRIT-H2H) due to complete in April 2019 which compares ixekizumab to adalimumab in bDMARD naïve patients. It should also be noted that using direct evidence rather than NMA results would give more reliable estimates for both, clinical as well as cost effectiveness.