Public observer slides – confidential data redacted

Lead team presentation

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

1st Appraisal Committee meeting

Committee D

Clinical effectiveness

Lead team: Nabeel Alsindi and Malcolm Oswald

ERG: Kleijnen Systematic Reviews

NICE technical team: Ross Dent, Nwamaka Umeweni

15 May 2018

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

- Any there any additional equalities issues?

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

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

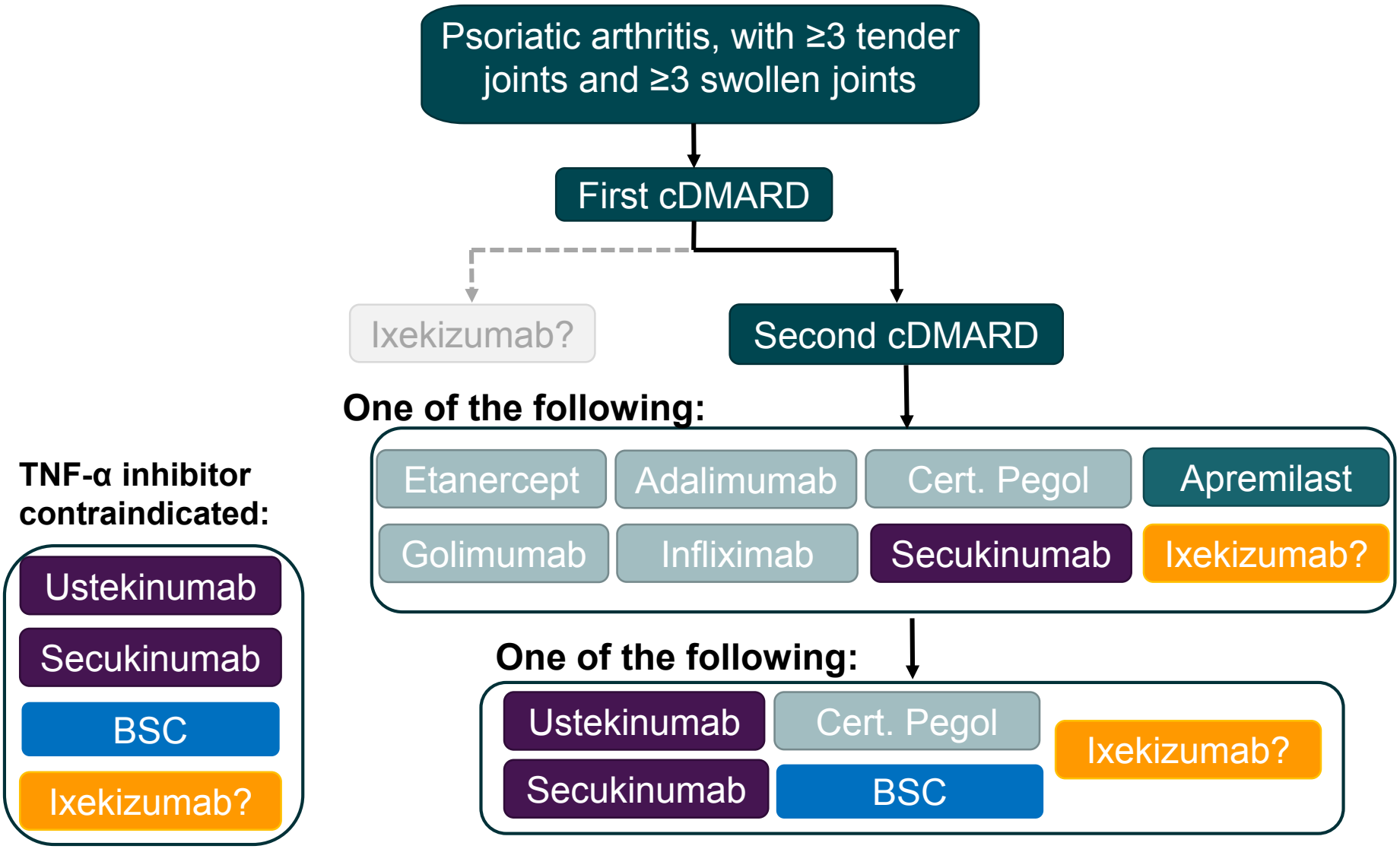
Patient perspectives

- Submissions from Psoriasis and Psoriatic Arthritis Alliance and Psoriasis Association
- 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
- 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 treatments that improve symptoms such as fatigue and nail disease
- 4-weekly ixekizumab injections beneficial – more frequent injections can prevent travel and be difficult for people with affected finger joints
- Ixekizumab can improve both psoriatic arthritis and concomitant psoriasis – 1 treatment is preferable to multiple

Clinical expert comments

- Submissions from British Society for Rheumatology and Rheumatology Pharmacists UK
- Aim of treatment is to reduce symptoms and improve quality of life
- There are 5 TNF-α inhibitors recommended in NICE guidance but only 1 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
- Ixekizumab inhibits IL17 which plays an important role in psoriatic arthritis - ixekizumab could improve multiple aspects of the disease
  - may 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-P1				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

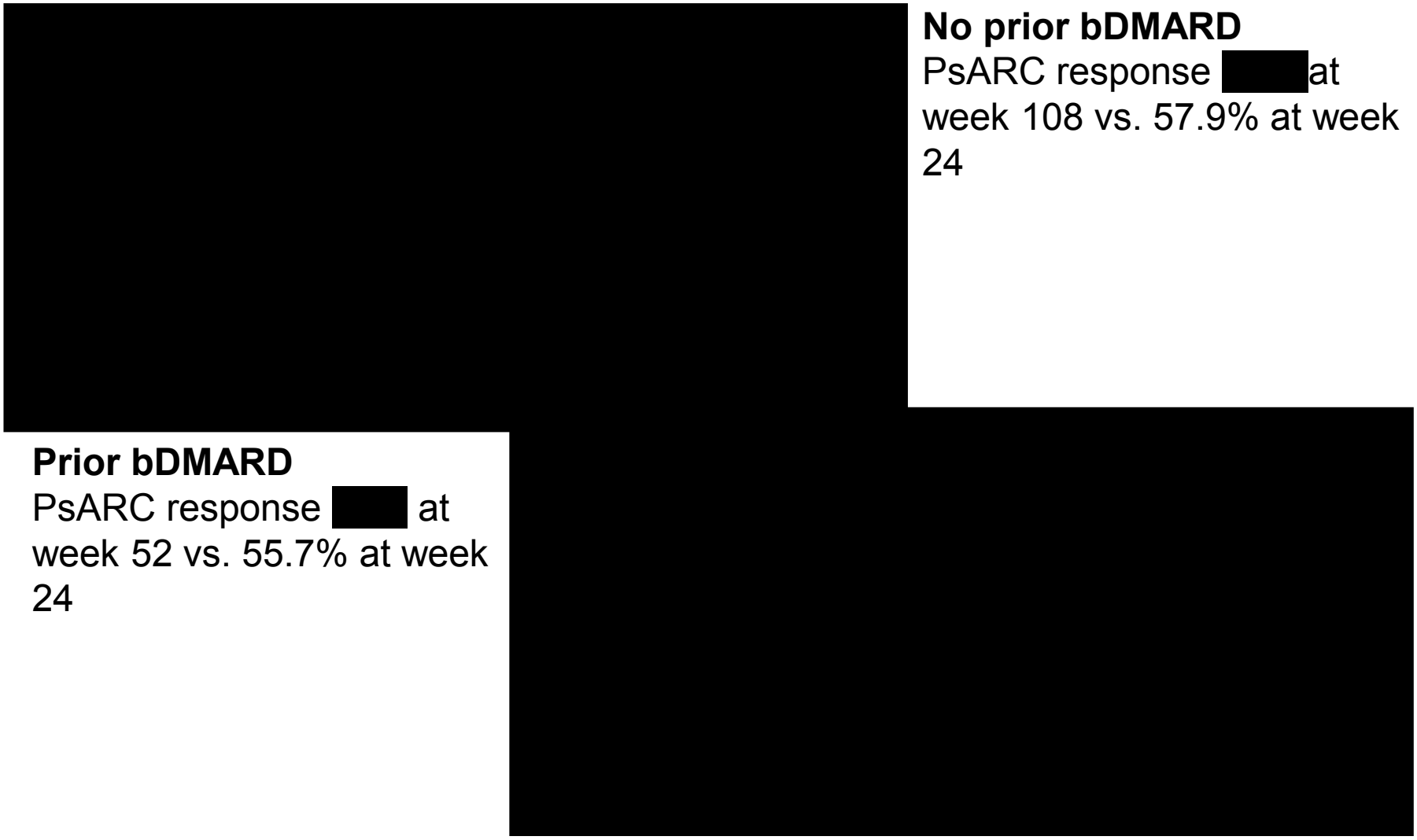
- 8 measures of daily activities, higher score indicates increased disability

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



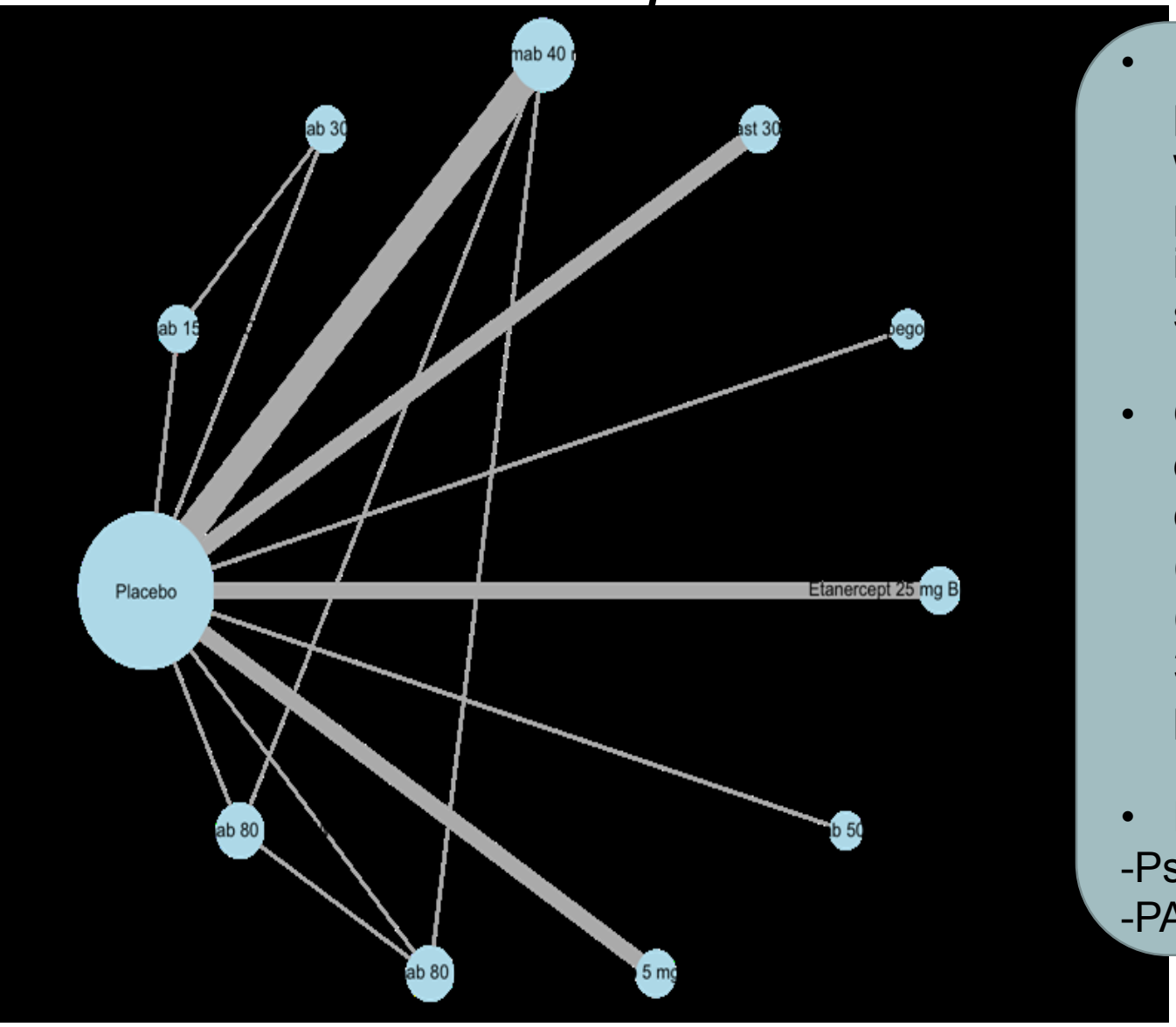
No prior bDMARD
PsARC response [redacted] at week 108 vs. 57.9% at week 24

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

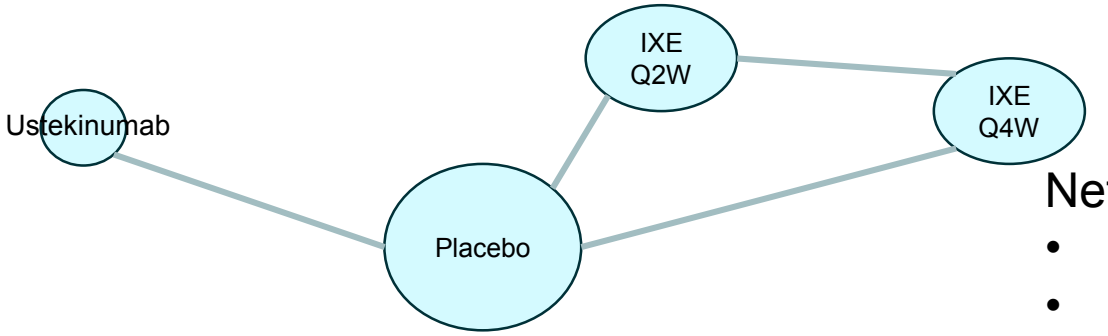
Key network meta-analysis results
no prior bDMARD

	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

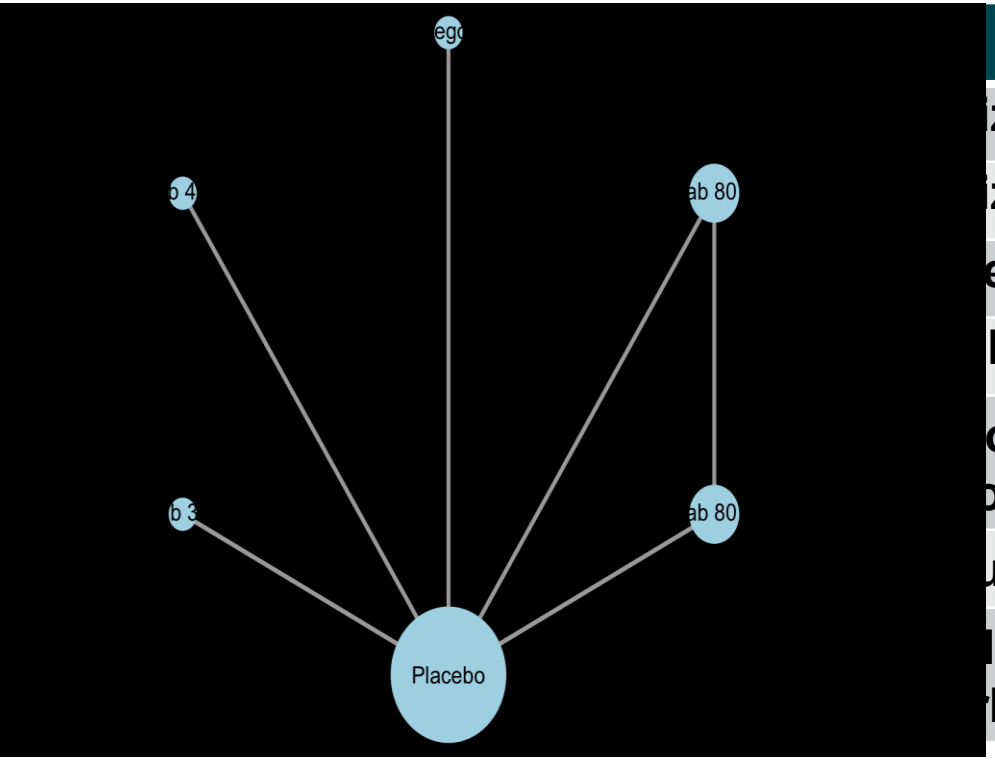
	PsARC	PsARC odds ratio vs. Ixe		PASI 75
		Ixe Q2W	Ixe Q4W	
Ixekizumab Q2W	[redacted]	-	-	[redacted]
Ixekizumab Q4W	[redacted]	-	-	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

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]
l = 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

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

- Any there any additional equalities issues?

Public observer slides – confidential data redacted

Lead team presentation

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

1st Appraisal Committee meeting

Committee D

Cost effectiveness

Lead team: Susan Dutton

ERG: Kleijnen Systematic Reviews

NICE technical team: Ross Dent, Nwamaka Umeweni

15 May 2018

Key cost effectiveness issues

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

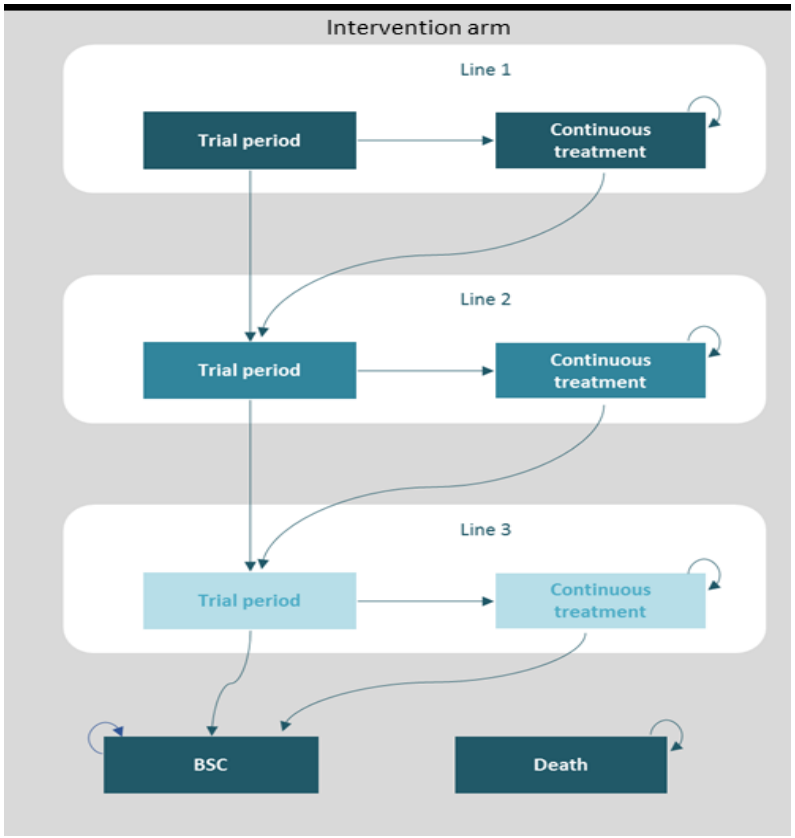
- Model based on TA445 (cert pegol and secukinumab), but results differ
  - likely to be due to different clinical effectiveness inputs (e.g. only overall population data available for NMAs)

- 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?

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 3) 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)

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 3)
  - 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 explores alternative sequences for no prior bDMARD group
- 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 part 2 session of the meeting
- 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

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)

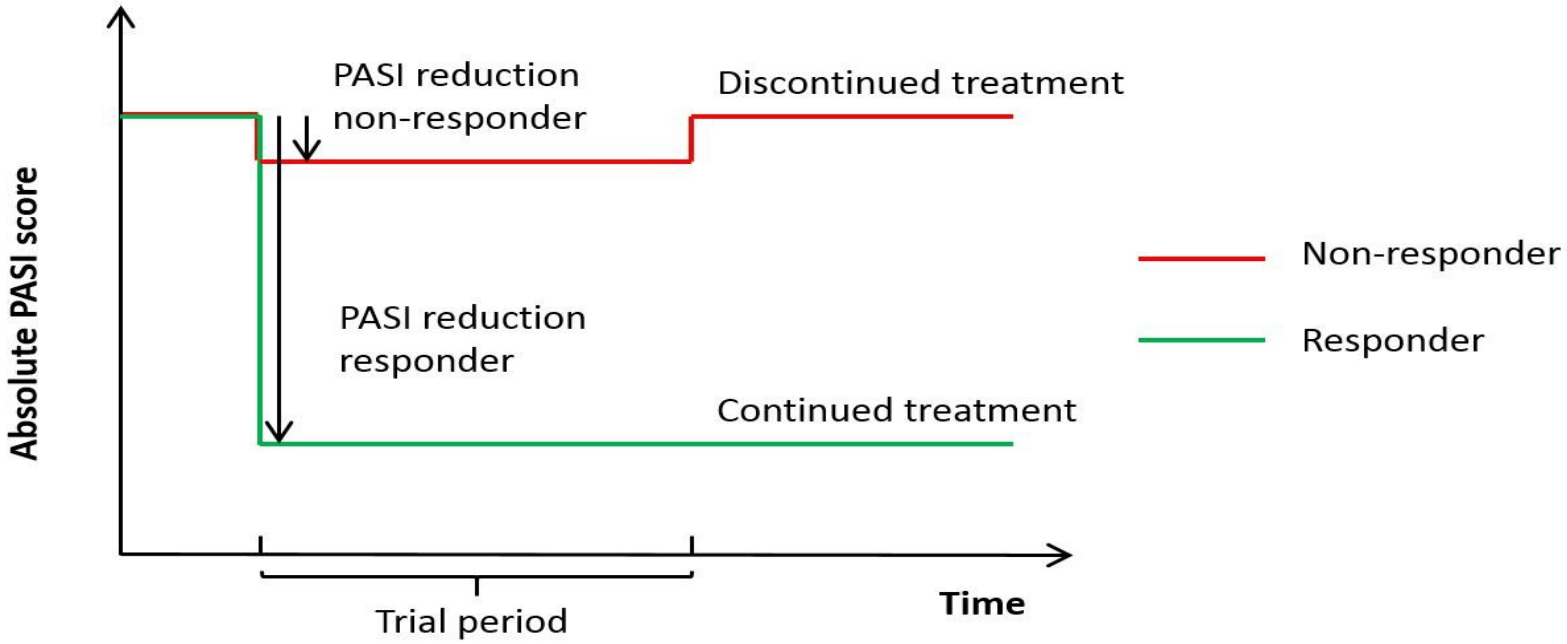
- Other key differences to model used in TA445:
  - utility algorithm based on data from SPIRIT trials
    - ◊ scenario using TA445 algorithm: ICERs vs. BSC decrease
  - baseline PASI scores for psoriasis severity subgroups from SPIRIT
    - ◊ scenario with TA445 values shows small effect on ICER vs.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

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

Background slides

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