Tofacitinib for treating Ankylosing spondylitis

Committee meeting – Part 1

Technology appraisal committee B [09 June 2022]

Chair: Charles Crawley

Lead team: Rhiannon Owen, James Fotheringham, Tony Wootton

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Company: Pfizer

NICE

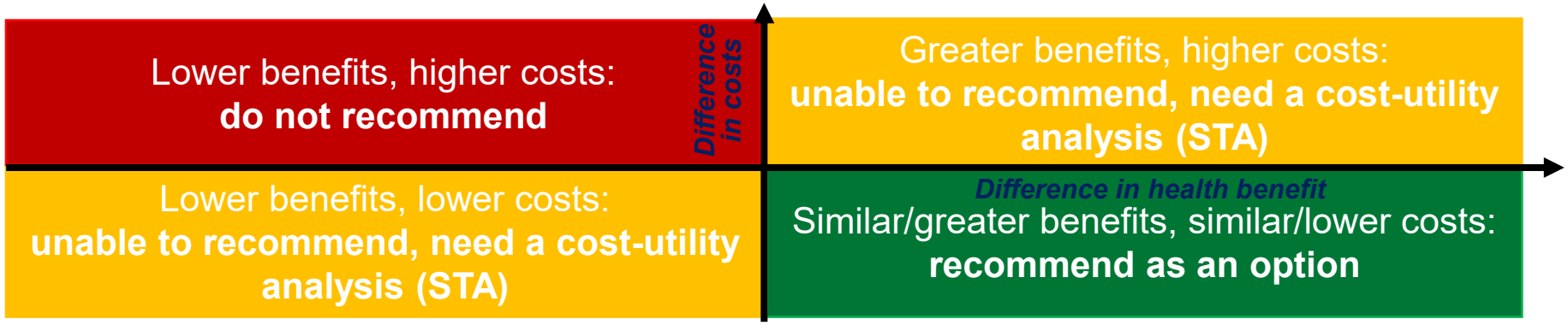
Cost comparison appraisal

- Cost comparison appraisals are considered if the technology provides similar or greater benefits at a similar or lower cost to a NICE recommended comparator

- A cost-comparison model by definition assumes that the compared technologies are equivalent in terms of efficacy and safety. A key question in an FTA is whether the clinical evidence is sufficient to support a claim of clinical equivalence between technology and comparator.

- As a new technology is only required to be equivalent, uncertainty around effect estimates can favour the new technology.

- There are three possible recommendations



  - If a technology is recommended through cost comparison, guidance states:
    - *"if patients and their clinicians consider both the technology and comparator/s to be suitable treatment, the least costly should be used"*

 Abbreviations: STA, single technology appraisal

Background on Ankylosing spondylitis (AS)

Causes

- AS is an inflammatory rheumatologic disease which is caused by chronic inflammation of the sacroiliac joints and spine
- Inflammation can lead to erosion, thickening of the bone or fusion of joints

Epidemiology

- Around 200,000 people in the UK have been diagnosed with ankylosing spondylitis
- There are thought to be around 2,300 new diagnoses each year in England and Wales
- AS is about 3 times more common in men than in women

Diagnosis and classification

- AS is also known as radiographic axial spondyloarthritis and it is diagnosed when there are signs of inflammation with x-ray evidence that there are abnormalities with the sacroiliac joints and spine
- If there is inflammation without x-ray evidence then this is classified as non-radiographic axial spondyloarthritis (this is outside the scope of this appraisal)

Symptoms and prognosis

- Back pain, arthritis, enthesitis, and can have extra-articular manifestations including uveitis, inflammatory bowel disease and psoriasis.
- Onset of symptoms usually occurs in the third decade of life, but it can be 7-10 years before a diagnosis is made

Background on Ankylosing spondylitis (AS) – Disease Outcomes

ASAS *(overall)* – A response criteria which includes a global assessment, a pain assessment (VAS), a functional score (BASFI) and a measure of inflammation (last two questions of the BASDAI) to give overall score from 0 (no disease)

BASDAI *(disease activity)* – A survey of six questions that assess tiredness, back and peripheral pain, discomfort from touch and discomfort and duration of stiffness in the morning. Gives an overall score out of 10 (higher score is worse)

BASFI – *(functional)* – A survey of ten questions that assesses ability to complete "everyday" physical tasks. Each question can be answered from 0 (easy) to 10 (impossible). Returns an overall score out of ten (higher score is worse)

Response rates – Each of the above outcomes may be measured as a response rate (ASAS20, BASDAI50 etc). For example ASAS20 would be the proportion of people with a 20% improvement in ASAS.

ASQoL *(Disease specific QoL)* - 18 question survey assessing quality of life. Overall score from good (0) to poor (18)

FACIT-F *(fatigue)* – A survey with 43 questions over 5 domains measuring physical, emotional, functional wellbeing and fatigue. Overall score out of 160. (higher scores represent worse outcomes)

Clinical experts: "What are considered clinically significant improvements in these outcomes?"

Abbreviations: ASAS, assessment in ankylosing spondylitis; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; ASQoL, ankylosing spondylitis quality of life; FACIT-T, functional assessment of chronic illness therapy – fatigue;

Patient perspectives – National Axial Spondylitis Society (NASS) and patient expert submissions

- 92% of NASS members interviewed said that AS has impacted their life either very negatively (49%) or somewhat negatively (43%)
- Pain and fatigue affects peoples ability to carry on with everyday life and affects their mental health, it can cause frequent night time waking
- Many people with AS have had to stop working, reduce working hours or apply for personal independence payments (PIP)
- Respondents were relatively satisfied with their current medications but 26% were either completely (6%) or somewhat (20%) unsatisfied
- 20% of people have disease that does not respond to the biologic drugs currently available (TNF and IL-17 inhibitors)
- As tofacitinib has a distinct mechanism of action, it may benefit people whose disease has not responded to previous treatments
- Storage and self administration of biologics causes extra anxiety
- A daily oral tablet may alleviate the issues and anxiety linked to storage of and travelling with biologic medications.

"My whole lifestyle has been impacted by AS, it has turned me from a healthy, active & happy person into the opposite"

"It is important to have a range of treatments, and new mechanisms of action to treat this disease, as for most people there is not a simple 'treatment journey'"

NICE Abbreviations: AS, ankylosing spondylitis; SpA, spondyloarthritis

Clinical perspectives – British Society for Rheumatology Spondyloarthritis Special Interest Group (SIG)

- Pathway of care generally well defined but there may be local variability
- There is an unmet need in those patients whose disease fails to respond to TNF inhibitors and/or IL-17 inhibitors
- Tofacitinib could provide clinically meaningful benefits- especially for people whose disease hasn't responded to currently approved therapies
- Simple oral administration provides convenience for people and may be easier for some people compared with subcutaneous treatments

"[There is an unmet need] in those patients who fail to respond to TNF inhibitors and/or IL-17 inhibitors. There is also a need for oral small molecule inhibitors for AS."

"As with all medical therapies used in AS, the risk of side effects will be weighed against the impact of uncontrolled disease"

Abbreviations: AS, ankylosing spondylitis; TNF, tumour necrosis factor; IL-17, Interleukin 17

Technology – Tofacitinib (Xeljanz, Pfizer)

Marketing authorisation	"Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy" - Granted September 2021
Mechanism of action	Small molecule inhibitor of the JAK1 and JAK3 enzymes which transmit signals from the cell surface to the nucleus to influence production of new blood vessels and immune cell function
Administration	Oral administration; 5mg twice per day.
Price	List price: £690.03 (56 5mg tablets) There is a confidential PAS for tofacitinib.

Tofacitinib MHRA safety warning (1)

Background

- MHRA released a binding safety warning for tofacitinib relating to its use in people with various risk factors
- The risk factors are: older than 65 years, current or past smoker, history of diabetes or of coronary artery disease (including past myocardial infarction, coronary heart disease, stable angina pectoris)
- *"Only consider use of tofacitinib in patients with these cardiovascular risk factors, **irrespective of indication**, if no suitable treatment alternative is available"*

Company

- Doesn't anticipate this to substantially affect the population addressed in the current NICE appraisal
- Anticipates that a significant proportion of patients with AS will still be eligible for tofacitinib

ERG comments

- ~50% of the BSRBR-AS population are current or former smokers, would only receive tofacitinib if there were no suitable alternatives
- For the remaining population there is uncertainty about which will have risk factors in the future and whether tofacitinib may cause some of the risk factors

Abbreviations: MHRA, medicines and healthcare products regulatory agency; AS, ankylosing spondylitis; BSRBR-AS, British society for rheumatology biologics register in ankylosing spondylitis

Tofacitinib MHRA safety warning (2)

Other considerations

- The safety warning effectively splits the population in the marketing authorisation in 2:
  - People with and people without MHRA risk factors.
- Tofacitinib would be used at different places in treatment pathways for the different populations.
- Only the position in the pathway for the non-MHRA risk factor population could displace a NICE recommended comparator and thus be eligible for a cost-comparison analysis
- Evaluation of tofacitinib in the MHRA risk factor population is thus beyond the scope of this appraisal

Patient experts: "What are your views on tofacitinib in light of the MHRA safety warning?"

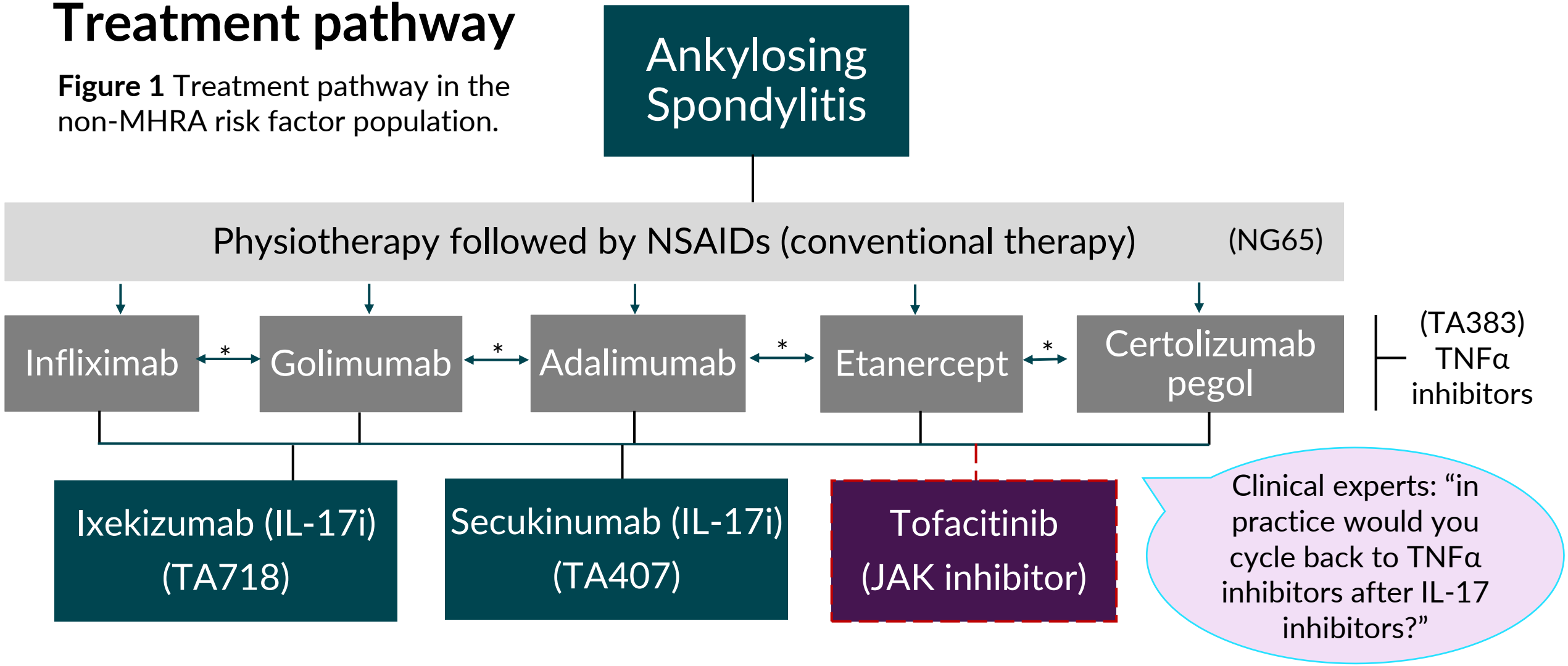
Clinical experts: " How would monitoring of patients on tofacitinib be different to those on IL-17 inhibitors?

Clinical experts: "Are any of the MHRA risk factors likely to be treatment effect modifiers for the disease outcomes used

Abbreviations: MHRA, medicines and healthcare products regulatory agency; AS, ankylosing spondylitis; BSRBR-AS, British society for rheumatology biologics register in ankylosing spondylitis

Treatment pathway

Figure 1 Treatment pathway in the non-MHRA risk factor population.



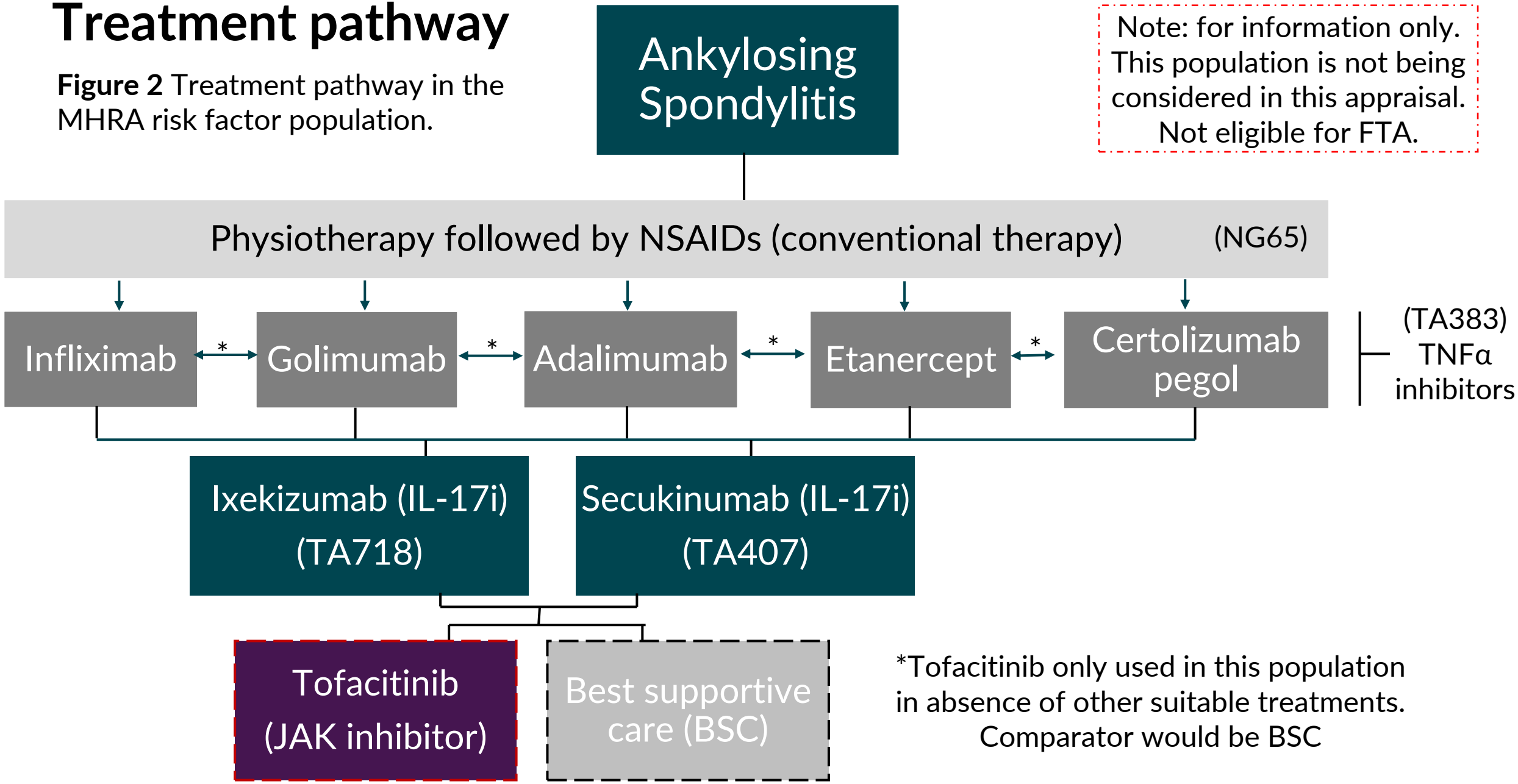
Are secukinumab and ixekizumab the most appropriate comparators for this appraisal?

*Note: TNFα inhibitors may be cycled through if one treatment provides inadequate response, but treatments are not repeated.

Abbreviations: TNF, tumour necrosis factor; IL-17, interleukin 17; NSAID, non-steroidal anti inflammatory drug

Treatment pathway

Figure 2 Treatment pathway in the MHRA risk factor population.



*Note: TNFα inhibitors may be cycled through if one treatment provides inadequate response, treatments are not repeated.
Abbreviations: TNF, tumour necrosis factor; IL-17, interleukin 17; NSAID, non-steroidal anti inflammatory drug

Comparator technologies

Table 2 Comparator technology details

	Secukinumab (Cosentyx, Novartis)	Ixekizumab (Taltz, Eli Lilly)
Marketing authorisation	"…is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy" – Granted 2014	"…is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy"
Mechanism of action	Secukinumab is a monoclonal antibody which binds and inhibits the IL-17A cytokine which promotes inflammation when it binds to immune cells.	Ixekizumab is a monoclonal antibody which binds and inhibits the IL-17A cytokine which promotes inflammation when it binds to immune cells.
Administration	Administered by subcutaneous injection; 150mg weekly for first four weeks then every four weeks.	Subcutaneous injection. 160mg starting dose and then 80mg every four weeks.
Price	List price: £1218.78 (2 X150mg syringes) There is a confidential PAS for secukinumab	List price: £1125 (1x 80mg syringe) There is a confidential PAS for ixekizumab.

 Abbreviations: IL-17, interleukin 17; PAS, patient access scheme

Recent NICE appraisals in ankylosing spondylitis

Evidence provided and modelling approaches

	TA718 (2021)	TA407 (2016)	TA383 (2016)
Evidence on people with bDMARD use	COAST-V: 0% experienced COAST-W: 100% experienced Ixekizumab n=212 Placebo n= 104	MEASURE-1: 61% experienced Secukinumab n=44, placebo n=45 MEASURE-2: 74% experienced Secukinumab n=92, placebo n=89	Some included studies had limited data on bDMARD experienced patients.
Evidence on long-term treatment efficacy and safety	COAST-V & W: 52 weeks COAST-Y: 116 weeks	MEASURE-1 and -2: 104-week follow up (52 weeks for some outcomes)	Included studies had 3-5 years of follow up.
Economic model	Cost utility	Cost utility	Cost utility
Time horizon	Lifetime	Lifetime (58 years)	Lifetime (except adalimumab, 40 years)
Adverse events included and costs	Tuberculosis reactivation and serious infection modelled, no disutility.	Tuberculosis reactivation or serious infection, no disutility.	Tuberculosis reactivation or serious infection
Discontinuation rates	Annual treatment discontinuation of 11% applied equally across treatments		

*COAST-Y is a rollover study from COAST-V and W, the 116 weeks follows on from week 52 of previous studies
Abbreviations: bDMARD, biological disease modifying anti-rheumatic drug

Key Issues

Table 4 Key issues

Issue	Action
Tofacitinib safety warning	Background info
Generalisability of evidence I (Cardiovascular risk factors)	For discussion
Generalisability of evidence II (Prior bDMARDs)	For discussion
Lack of evidence on long term efficacy, safety and discontinuation	For discussion
Time horizon	For discussion
Exclusion of costs associated with adverse effects	For discussion

Decision problem

Table 5 Population, intervention, comparators and outcomes from the scope

	Final scope	Company	ERG comments
Population	People with active ankylosing spondylitis whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs	As per scope	Due to the MHRA safety warning people in the target population with various cardiovascular risk factors would likely not receive tofacitinib.
Intervention	Tofacitinib	As per scope	No comments
Comparators	Secukinumab, Ixekizumab Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	Secukinumab, ixekizumab (second line)	"The most relevant comparator for most (though not all) patients would be established clinical management without biologics. . ."
Outcomes	Disease activity, functional capacity, disease progression, pain, peripheral symptoms, extra articular manifestations, adverse effects, HRQoL	ASAS20, ASAS40, BASDAI50, BASDAI, BASFI, ASDAS, ASQoL, SF-36 PCS, SAEs, AE related discontinuations	

Abbreviations: HRQoL, health related quality of life; ASAS, assessment in ankylosing spondylitis score ; BASDAI, bath ankylosing spondylitis disease activity index, BASFI, bath ankylosing spondylitis functional index; ASDAS, ankylosing spondylitis disease activity score; ASQoL, ankylosing spondylitis quality of life instrument; SF-36, short form 36; SAE, serious adverse effects

Clinical effectiveness

- A3921119 & A3921120 trials (tofacitinib)
- MEASURE2, MEASURE4 and MEASURE5 trials (secukinumab)
- COAST-W trial (ixekizumab)

NICE National Institute for Health and Care Excellence

Key clinical trials – two trials provide data for tofacitinib

Table 6 Clinical trial designs and outcomes

	A3921119	A3921120
Design	Phase II multicentre RCT	Phase III multicentre RCT
Population	Adults with active ankylosing spondylitis	Adults with active ankylosing spondylitis
Intervention	Tofacitinib (2mg, 5mg or 10mg BID) Each regimen n=52	Tofacitinib 5mg BID n = 134
Comparator(s)	Placebo n=52	Placebo (until 16 weeks, then whole population switched to tofacitinib 5mg BID) n=136
Duration	16 weeks - 12 weeks of treatment and four weeks follow up	48 weeks - 16 weeks of blinded treatment with comparator followed by 32 weeks 5mg BID for all participants
Primary outcome	ASAS20 response rate at 12 weeks	ASAS20 response rate at week 16
Key secondary outcomes	ASDAS-CRP, BASDAI, BASDAI50, BASFI, overall and AE related discontinuations	ASDAS-CRP, BASDAI, BASDAI50, BASFI, overall and AE related discontinuations
Use	To inform tofacitinib arm of the NMA	To inform tofacitinib arm of the NMA

Abbreviations: ASAS, assessment in ankylosing spondylitis; BASDAI, bath ankylosing spondylitis disease assessment index; SF-36 PCS, short form 36 physical component score; ASQoL, ankylosing spondylitis quality of life; cfb, change from baseline; NMA, network meta analysis

Key clinical trials – three trials provide data for secukinumab

Table 7 Clinical trial designs and outcomes

	MEASURE2 (NCT01649375)	MEASURE4 (NCT02159053)	MEASURE5 (NCT02896127)
Design	Phase 3 RCT	Phase 3 RCT	Phase 3 RCT
Population	Moderate to severe AS with at least 1 inadequate response to a TNFα inhibitor	Moderate to severe AS, inadequate response to NSAIDs	Moderate to severe AS, not responding to at least 2 NSAIDs
Intervention	Secukinumab 75mg or 150mg (4x weekly loading then Q4W)	Secukinumab 150mg (with and without loading)	Secukinumab 150mg (with loading dose)
Comparator(s)	Placebo	Placebo	Placebo
Duration	16 weeks (efficacy) 5 years (safety, discontinuation)	16 weeks (efficacy) 2 years (safety, tolerability)	16 weeks (efficacy) 1 years (safety)
Primary outcome	ASAS20	ASAS20	ASAS20
Key secondary outcomes	ASAS40, BASDAI (cfb), SF-36 PCS, ASQoL (cfb),	ASAS40, BASDAI (cfb), SF-36 PCS, ASQoL	ASAS40, BASDAI (cfb), SF-36 PCS, ASQoL
Use	To inform secukinumab arm of NMA	To inform secukinumab arm of NMA	To inform secukinumab arm of NMA

Abbreviations: ASAS, assessment in ankylosing spondylitis; BASDAI, bath ankylosing spondylitis disease assessment index; SF-36 PCS, short form 36 physical component score; ASQoL, ankylosing spondylitis quality of life; cfb, change from baseline;

Key clinical trials – one trial provides data for ixekizumab

Table 8 Clinical trial designs and outcomes

	COAST-W
Design	Phase 3 double blind RCT
Population	Patients with AS who have had treatment with 1-2 TNF inhibitors
Intervention	Ixekizumab (80mg Q2W or Q4W)
Comparator(s)	Placebo
Duration	16 weeks double blind 52 weeks follow up (single arm)
Primary outcome	ASAS40
Key secondary outcomes	ASAS20, ASDAS, BASDAI50, BASDAI, BASFI, ASDAS, SF-36 PCS, BASMI
Use	To inform ixekizumab arm of NMA

Abbreviations: ASAS, assessment in ankylosing spondylitis; BASDAI, bath ankylosing spondylitis disease assessment index; SF-36 PCS, short form 36 physical component score; ASQoL, ankylosing spondylitis quality of life; cfb, change from baseline;

Clinical trial results – Tofacitinib is more efficacious than placebo

Table 9 Clinical trial results

Outcome (efficacy/safety)	A3921119* (week 12)		A3921120 (week 16)	
	Tofacitinib 5mg (N=52)	Placebo (N=51)	Tofacitinib 5mg (N=134)	Placebo (N=136)
ASAS20 Actual Response % (SE)	80.8% ([redacted])	41.2% ([redacted])	56.4%	29.4%
ASAS40	46.2% ([redacted])	19.6% ([redacted])	40.6%	12.5%
BASDAI50	42.3% ([redacted])	23.5% ([redacted])	42.9%	17.7%
BASFI mean (SE)	-2.4 (0.3)	-1.4 (0.3)	-2.1 (0.2)	-0.8 (0.2)
Overall discontinuations	1/52	4/51	4/133	5/136
AE-related discontinuations	1/52	3/51	[redacted]	[redacted]

Outcome (QoL)	A3921119* (week 12)		A3921120 (week 16)	
	Tofacitinib 5mg	Placebo	Tofacitinib 5mg	Placebo
ASQoL Total score (SE)	-4.8 (0.6)	-2.5 (0.6)	-4.0	-2.0
SF-36v2 Physical Component (SE)	6.5 (0.9)	2.7 (0.9)	6.7 (0.6)	3.1 (0.6)
SF-36v2 Mental Component (SE)	4.1 (1.3)	2.4 (1.3)	[redacted]	[redacted]
FACIT-F Total Score (SE)	7.0 (1.1)	3.1 (1.2)	[redacted]	[redacted]

Abbreviations: ASAS, assessment in ankylosing spondylitis score ; BASDAI, bath ankylosing spondylitis disease activity index, BASFI, bath ankylosing spondylitis functional index; ASQoL, ankylosing spondylitis quality of life instrument; SF-36, short form 36; SAE, serious adverse effects; FACIT-F, functional assessment of chronic illness therapy fatigue score; SE, standard error.

Clinical trial results – subgroup analyses

- A range of subgroup analyses were planned and carried out in the A3921120 trial
- The results from the bDMARD naïve and bDMARD experienced subgroups for the primary outcome are shown below

Table 10 Clinical trial subgroup results

Population	Tofacitinib 5mg BID	Placebo	Difference (95%CI)	P value
ASAS20, response %				
All patients (N=269)	56.4%	29.4%	[redacted]	<0.0001
bDMARD naïve (N=207)	61.8%	33.3%	[redacted]	-
TNF-IR or bDMARD experienced (N=62)	38.7%	16.1%	[redacted]	-
ASAS40, response %				
All patients (N=269)	40.6	12.5	[redacted]	<0.0001
bDMARD naïve (N=207)	45.1	14.3	[redacted]	-
TNF-IR or bDMARD experienced (N=62)	25.8	6.5	[redacted]	-

Abbreviations: bDMARD, biological disease modifying anti-rheumatic drug; TNF-IR, tumour necrosis factor- inadequate response; 95%CI, 95% confidence intervals;

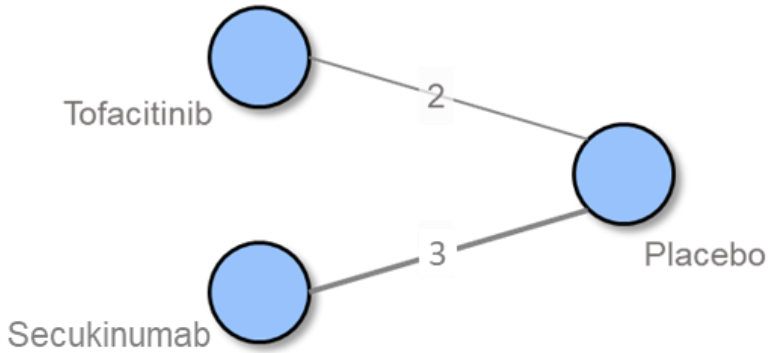
NMA/ITC methodology

- The company provided NMAs comparing tofacitinib with secukinumab and ixekizumab for various outcomes in both bDMARD naïve and experienced populations
- These NMAs included 6 studies.
    - A3921119 (12 weeks double blind) and A3921120 (16 weeks double blind) – to inform the tofacitinib 5mg BID arm
    - MEASURE2, MEASURE4 and MEASURE5 to inform secukinumab 150mg arm
    - COAST-W to inform ixekizumab 8mg arm
- Where possible, random effects and fixed effect models were provided, with or without baseline risk adjustment
- Outcomes:
    - Efficacy: ASAS20, ASAS40, BASDAI50, BASDAI (continuous), BASFI, ASDAS
    - Quality of life: ASQoL, SF-36 PCS
    - Adverse event related discontinuation
- Where possible separate NMAs were carried out for each outcome for both bDMARD naïve and experienced subgroups
- Relative effects reported as odds ratios and continuous outcomes as difference (with 95% CI)

Abbreviations: bDMARD, biological disease modifying anti-rheumatic drugs

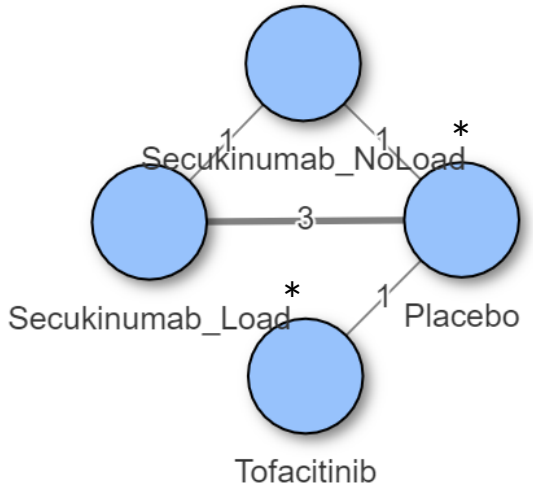
NMA/ITC network diagrams

Network diagram for all comparisons in the bDMARD naïve subgroup

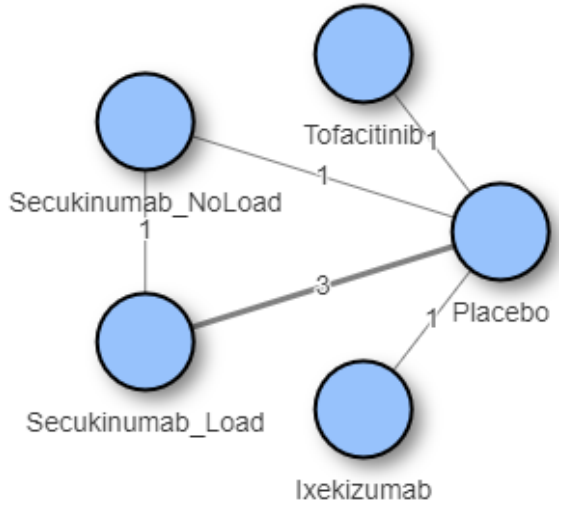


Network diagrams for the bMDARD experienced subgroup

For the ASQoL comparison



For all other outcome comparisons**



*"NoLoad" and "Load" refer to the secukinumab loading dose. The licence for use in the UK is with the loading dose
** Network diagram for BASFI and ASDAS outcomes in bDMARD experienced subgroup only contained two studies and is not shown here.

Abbreviations: NMA, network meta-analysis; ITC, indirect treatment comparison; ASQoL, Ankylosing spondylitis quality of life score; bDMARD, biological disease modifying anti-rheumatic drug

NMA/ITC results: tofacitinib versus secukinumab

Table 11 Clinical trial designs and outcomes

Outcome (dichotomous)	Tofacitinib vs secukinumab* - bDMARD naïve : Odds Ratio (95% CI)		Tofacitinib vs secukinumab* - bDMARD experienced : Odds Ratio (95% CI)	
	Fixed effect	Random effects	Fixed effect	Random effects
ASAS20	[redacted]	[redacted]	[redacted]	-
ASAS40	[redacted]	[redacted]	[redacted]	-
BASDAI50	NMA couldn't be conducted		-	-
AE related discontinuations	[redacted]	-	-	-
Serious adverse events	[redacted]	-	-	-
Outcome (continuous)	**Tofacitinib vs secukinumab* - bDMARD naïve : Difference (95% CI)**		**Tofacitinib vs secukinumab* - bDMARD experienced : Difference (95% CI)**	
BASDAI difference (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
ASQoL	[redacted]	[redacted]	[redacted]	-
SF36 PCS	[redacted]	-	[redacted]	-

ERG preferred model **in bold**
*All comparisons here are with the secukinumab loading dose regimen as this is licensed in the UK
**This model was with baseline risk adjustment (all others without)
Abbreviations: 95% CI, 95% confidence interval; bDMARD, biological disease modifying anti-rheumatic

NMA/ITC results: tofacitinib versus ixekizumab

Table 12 Clinical trial designs and outcomes

Outcome (dichotomous)	Tofacitinib vs ixekizumab* - bDMARD experienced : Odds Ratio (95% CI)	
	Fixed effect	Random effects
ASAS20	[redacted]	-
ASAS40	[redacted]	-
BASDAI50	[redacted]	-
AE related discontinuations	-	-
Serious adverse events	-	-
Outcome (continuous)	**Tofacitinib vs secukinumab* - bDMARD experienced : Difference (95% CI)**	
BASDAI difference	[redacted]	[redacted]
BASFI	[redacted]	-
ASDAS	[redacted]	-
ASQoL	Not measured by COASTW	-
SF36 PCS	[redacted]	-

ERG preferred model **in bold**
*All comparisons here are with the secukinumab loading dose regimen as this is licensed in the UK
**This model was with baseline risk adjustment (all others without)
Abbreviations: 95% CI, 95% confidence interval; bDMARD, biological disease modifying anti-rheumatic

NMA/ITC results – ERG opinion

ERG comments

- The ERG considers non-inferiority between tofacitinib and secukinumab plausible on the basis of the evidence presented, albeit caveated by a number of uncertainties
- The evidence provided by the NMA results support the assumption of equivalent efficacy against secukinumab (in the naïve or experienced subgroups) or ixekizumab (in the experienced subgroup)
- This was irrespective of the final model selected (for both naïve and experienced)
- However, relative effect estimates comparing tofacitinib to secukinumab are uncertain and the sparsity of safety evidence on the use of tofacitinib in a bDMARD-experienced population is of particular concern

 Abbreviations: bDMARD, biological disease modifying anti-rheumatic drug

Key issue: Generalisability of tofacitinib evidence I – Risk Factors

Background: the evidence for tofacitinib is from trials that did not restrict for the MHRA risk factors

- Around 50% of participants in the A3921120 trial were smokers and almost 20% had hypertension meaning they are covered by the MHRA safety warning. Differences in response could mean overestimation of efficacy

Company

- Presented ASAS40 data from A3921120 and stated that responses between over and under 65 and current, former or never smokers are similar. *(acknowledges study was not powered to detect subgroup differences)*

Category at Baseline		Tofacitinib 5 mg twice daily			Placebo			Difference (95% CI)
		N	n	R (%)	N	n	R (%)	
Age	<65 years	127	[redacted]	[redacted]	136	[redacted]	[redacted]	[redacted]
	≥65 years	6	[redacted]	[redacted]	0	[redacted]	[redacted]	-
Smoking Status	Never	75	[redacted]	[redacted]	73	[redacted]	[redacted]	[redacted]
	Former	24	[redacted]	[redacted]	19	[redacted]	[redacted]	[redacted]
	Current	34	[redacted]	[redacted]	44	[redacted]	[redacted]	[redacted]

ERG comments

- The evidence on risk factors and generalisability is limited in terms of outcomes and does not sufficiently resolve uncertainty around generalisability
- It is unclear whether any of the risk factors are effect modifiers.

Is the evidence on tofacitinib generalisable to the "non-MHRA risk factor" population?

Abbreviations: ASAS, assessment of ankylosing spondylitis score; MHRA medicines and healthcare products regulatory

Key issue: Generalisability of tofacitinib evidence II – prior treatment

Background

- There is limited evidence from the bDMARD experienced population in the A3921120 trial (n=62 [23%]), 31 per arm. Thus the evidence provided may not be generalisable to NHS clinical practice.

ERG comments

- That only 23% of participants in A3921120 were bDMARD experienced limits applicability of the trial populations to the NHS setting

Company

- MEASURE trials in TA407 had 126 bDMARD experienced participants combined (27% of MEASURE-1 and 39% of MEASURE-2). The committee concluded the results were comparable and generalisable to the UK population.

Other considerations (Note TA383 was a cost utility analysis, not cost comparison)

- **Tech Team**: TA383 recommended a second TNFα inhibitor be used after the first if there was inadequate response or it wasn't tolerated. The evidence in this appraisal was almost all in the bDMARD naive population.
- **TA383** "the committee concluded that, although there was limited cost-effectiveness evidence for subsequent TNFα inhibitor use. . . It considered the ICER would be within the range considered to be cost-effective. . ."

Is the evidence from the A3921120 trial sufficiently generalisable to support clinical comparability between tofacitinib and IL-17 inhibitors in a bDMARD experienced population?

 Abbreviations: bDMARD, biological disease modifying anti-rheumatic drug

Key issue: Generalisability of tofacitinib evidence II – prior treatment

Table 14 bDMARD experienced participants from trials for previous appraisals

	Tofacitinib		Secukinumab (TA 407)				Ixekizumab (TA 718)				
	A3921120		MEASURE-1		MEASURE-2		COAST-V		COAST-W		
	Tofa	Placebo	Secu	Placebo	Secu	Placebo	Ixe	Placebo	Ixe Q4W	Ixe Q2W	Placebo
bDMARD experienced, n=	31	31	34	33	28	31	0	0	98	90	93
% of trial population	23%	23%	27%	27%	39%	39%	0%		100%		

Table 15 bDMARD differences in primary response by prior treatment subgroup

Population	Tofacitinib 5mg BID	Placebo	Difference (95%CI)	P value
ASAS20, response %				
All patients (N=269)	56.4%	29.4%	[redacted]	<0.0001
bDMARD naïve (N=207)	61.8%	33.3%	[redacted]	-
TNF-IR or bDMARD experienced (N=62)	38.7%	16.1%	[redacted]	-

Is the evidence from the A3921120 trial sufficiently generalisable to support clinical comparability between tofacitinib and IL-17 inhibitors in a bDMARD experienced population?

NICE Abbreviations: bDMARD, biological disease modifying anti-rheumatic drug

Cost comparison

Cost-comparison issues and results

NICE National Institute for Health and Care Excellence

Key issue: lack of long term evidence on efficacy, safety and discontinuation

Background

- Despite there being no differences in efficacy detected at 12-16 weeks, it remains uncertain how tofacitinib will compare to secukinumab in the long term (beyond 48 weeks), in terms of both efficacy and discontinuation

ERG comments

- Lack of long term data means there is uncertainty around whether there is clinical equivalence
- "The ERG considers there to be a non-negligible risk that the long-term rates of treatment discontinuation experienced on tofacitinib will not be comparable to the chosen comparator"
- This could distort the differences in costs as the CCA model assumes that all people stay on treatment for the duration of the time horizon (I.e discontinuation is not modelled)

Other considerations (note, these appraisals were full cost-utility analyses)

- **TA383** (MTA) – Various studies had follow up of either 3 or 5 years, confirmed maintenance of efficacy results
- **TA407** – MEASURE 1 & 2 studies had 2 year follow up for most efficacy results and 1 year for others
- **TA718 –** COAST-V and W studies had one year of follow up which confirmed maintenance of efficacy results and then rolled over into the COAST-Y study which confirmed maintenance beyond 2 years.

What are the long term effects in terms of efficacy, safety and discontinuation rates of tofacitinib?

 Abbreviations: MTA, multiple technology appraisal

Key issue: time horizon

Background

- The FTA cost-comparison case requires accrued costs to be considered over a time horizon which covers a typical course of treatment.

Company

- After a request at clarification the company updated the cost-comparison model to allow specific time horizons to be analysed.
- The company presented results using time horizons of 2, 5 and 10 years.

ERG comments

- Noted that the time horizon does not account for treatment discontinuation (as it is assumed to be equivalent between treatments, and not modelled).
- The most relevant time horizon would be the mean duration of treatment, as this is uncertain, scenarios from 2 to 10 years are presented

Other considerations

- TA407 and 718 adopted a lifetime time horizon
- TA383, all the models provided in this MTA adopted either a lifetime or 40 year time horizon

What would be an appropriate time horizon to capture differences in costs between tofacitinib and the two comparators?

Key issue: exclusion of monitoring and adverse effect associated costs

Background

- Costs associated with adverse effects and monitoring (e.g annual lipid profile monitoring) were excluded
- The ERG requested inclusion of these costs at the clarification stage

Company

- The NMA did not show statistically significant differences in terms of safety outcomes between tofacitinib and secukinumab, therefore the cost of adverse events was not taken into account
- A scenario analysis with costs of annual lipid monitoring included was provided

ERG comments

- If long term safety profile of tofacitinib is worse than secukinumab or ixekizumab, exclusion of AE associated costs would favour tofacitinib in the cost-comparison. AE costs remains an important area of uncertainty
- Include lipid monitoring costs in their base case but note that it had a negligible effect on the results
- Notes that differences in adverse effect profiles could also have HRQoL impacts (which cannot be captured in a cost-comparison analysis)

Other considerations

- **Tech team** note that in TA383, 407 and 718 the only AEs modelled were TB reactivation and serious infection, no disutilities were modelled for these AEs

Is the adverse effect profile of tofacitinib (outside of the MHRA risk factor population) likely to be different to that of the comparators?

Abbreviations: AE, adverse effect; HRQoL, health related quality of life; TB, tuberculosis;

Equalities

Background

- No equalities issues were identified in the company submission, or raised during scoping consultation.

Summary of company and ERG base case assumptions

Minor differences between the two base cases

Table 16 Assumptions in company and ERG base case

Assumption	Company base case	ERG base case
Secukinumab dosing schedule	Assumed secukinumab administered once every four weeks, not once per month.	Corrected this which resulted in slightly fewer doses of secukinumab in the first and subsequent years.
Baseline and annual lipid profile assessment	Not included (scenario provided)	Included in base case

Table 17 Differences between company and ERG comparator costings

Number of doses	Company's model		ERG revised model	
	1st year	Subsequent years	1st year	Subsequent years
Secukinumab	16.79	13.04	16.08	12.00
Ixekizumab	13.79	13.04	15.04	13.04

Cost-comparison results

All results are reported in PART 2 slides because they include confidential comparator PAS discounts

Abbreviations: [for example, OS, overall survival; ICER, incremental-cost effectiveness ratio]

NICE National Institute for Health and Care Excellence

Thank you.

Supplementary slides follow

Recent NICE appraisals for ankylosing spondylitis

Table S1 Recent NICE appraisals

Technology appraisal	Drug	Recommendation
NICE TA383 (2016)	TNF alpha inhibitors (MTA): Adalimumab, etanercept, golimumab, certolizumab pegol, infliximab.	"Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are recommended as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to or who cannot tolerate NSAIDs."
NICE TA407 (2016)	Secukinumab	"Secukinumab recommended as option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to NSAIDs or TNF-alpha inhibitors"
NICE TA718 (2021)	Ixekizumab	"Ixekizumab is recommended as an option for treating active ankylosing spondylitis that is not controlled well enough with conventional therapy. . . Only if TNF-alpha inhibitors are not suitable or do not control the condition."

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor; MTA, multiple technology appraisal