For public – contains no confidential information

Upadacitinib for treating active non-radiographic axial spondyloarthritis [ID3958]

Technology appraisal committee B

Technical briefing – Part 1

Chair: Charles Crawley

Lead team: Rhiannon Owen, James Fotheringham, Tony Wootton

Evidence assessment group: Liverpool Reviews and Implementation Group (LRiG)

Technical team: Emily Leckenby, Caron Jones, Janet Robertson

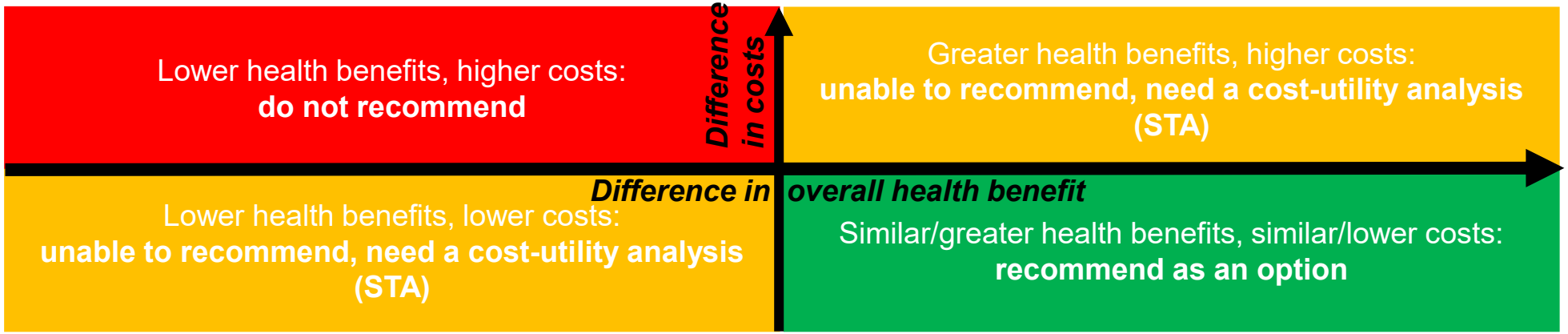
Company: AbbVie

Chair/Lead Team Summary

- **Cannot definitively state that upadacitinib is similar OR different to ixekizumab or secukinumab, however based on results/estimates, happy to say that they are sufficiently similar**
- Acknowledge uncertainty around sequencing, however can assume that upadacitinib would be cost-effective at any level of the pathway
- Clear preference for oral treatment vs current SC options
- Agree with EAG around safety profiles - difficult to compare as followed up at different times means different levels of risk between trials.
    - Formal modelling would have been helpful for decision making but not mandatory
- Upadacitinib is clinically more effective than placebo
- Uncertainties relating to heterogeneity within NMA are unlikely to be solved by cost-utility analysis; would provide a large range of ICERs with one that is correct

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 cost comparison 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
- 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*"



Background on active non-radiographic axial spondyloarthritis

Chronic, inflammatory disease affecting the spine and sacroiliac joints

Epidemiology

- Onset commonly occurs between ages of 20 and 30 years, 95% of patients <45 years
- Prevalence largely undetermined; equal ratio of men and women affected

Diagnosis and classification

- Part of spectrum of diseases known as axial spondyloarthritis
- Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)
    - 44% present with nr-axSpA; over 2-10 years, 10-40% of nr-axSpA patients progress to AS
- Similar disease characteristics with similar disease burden between two conditions

Symptoms and prognosis

- Back pain, arthritis, enthesitis, fatigue plus extra-articular manifestations (IBD, uveitis, psoriasis)
- Condition is currently incurable with irreversible damage; 59% experience mental health problems

Abbreviations: **AS**: ankylosing spondylitis; **IBD**: inflammatory bowel disease; **nr-axSpA**: non-radiographic axial spondyloarthritis

Patient perspectives

Upadacitinib received well by people with nr-axSpA and their carers

Submission from National Axial Spondyloarthritis Society (survey)

- 92% said that having axial spondyloarthritis had impacted their life very (49%) or somewhat negatively (43%)
- Pain and fatigue can leave people with nr-axSpA unable to work, and impacts mental health greatly
- Satisfaction level with medications available is good, but few are completely satisfied, and 26% are unsatisfied.
    - Clear unmet need for those who cannot tolerate non-steroidal anti-inflammatories, or do not respond to other biologics
- Tablet form negates current issues had with other biologics, e.g. needle phobia, shared accommodation/do not have access to own fridge
    - Oral administration more convenient for those with nr-axSpA
- 75% of people were concerned about the side effects
- 58% of people worried it wouldn't be as effective as current medications

"I am in pain, every day. I suffer with severe fatigue and "brain fog" regularly. I can no longer work full time and am considering medical retirement at 45"

"I lost my home and my career... rationally considering suicide before being prescribed anti-TNF in 2004… finally switched to Humira in 2015… still have a lot of nerve pain."

 Abbreviations: **nr-axSpA**: non-radiographic axial spondyloarthritis; **TNF**: tumour necrosis factor

Clinical perspectives

Unmet need for people who do not respond to current treatments

Submission from Spondyloarthritis Special Interest Group, British Society of Rheumatology

- Main aim of treatment for nr-axSpA is to reduce disease activity, improve pain and functioning, improve quality of life, reduce fatigue and reduce structural progression
- Unmet need in people who fail to respond to TNF inhibitors and/or IL-17 inhibitors; also a need for oral small molecule inhibitors in nr-axSpA
    - More convenient for people with nr-axSpA because of **oral administration** compared to injections
- Pathway of care is generally well defined; may be local variability depending on local expertise, resources and funding agreements for targeted therapies
- Would expect upadacitinib to provide clinically meaningful benefits

"Significant unmet need for patients who fail to respond, or lose response, to TNF/IL-17 inhibitors; upadacitinib offers an alternative treatment option"

"For some patients, active disease impairs their quality of life significantly and justifies the use of new medication with potential side effects"

Abbreviations: **IL**: interleukin; **nr-axSpA**: non-radiographic axial spondyloarthritis; **TNF**: tumour necrosis factor

Upadacitinib (RINVOQ, AbbVie)

Table 1 Technology details
(**Source**: company submission, table 2)

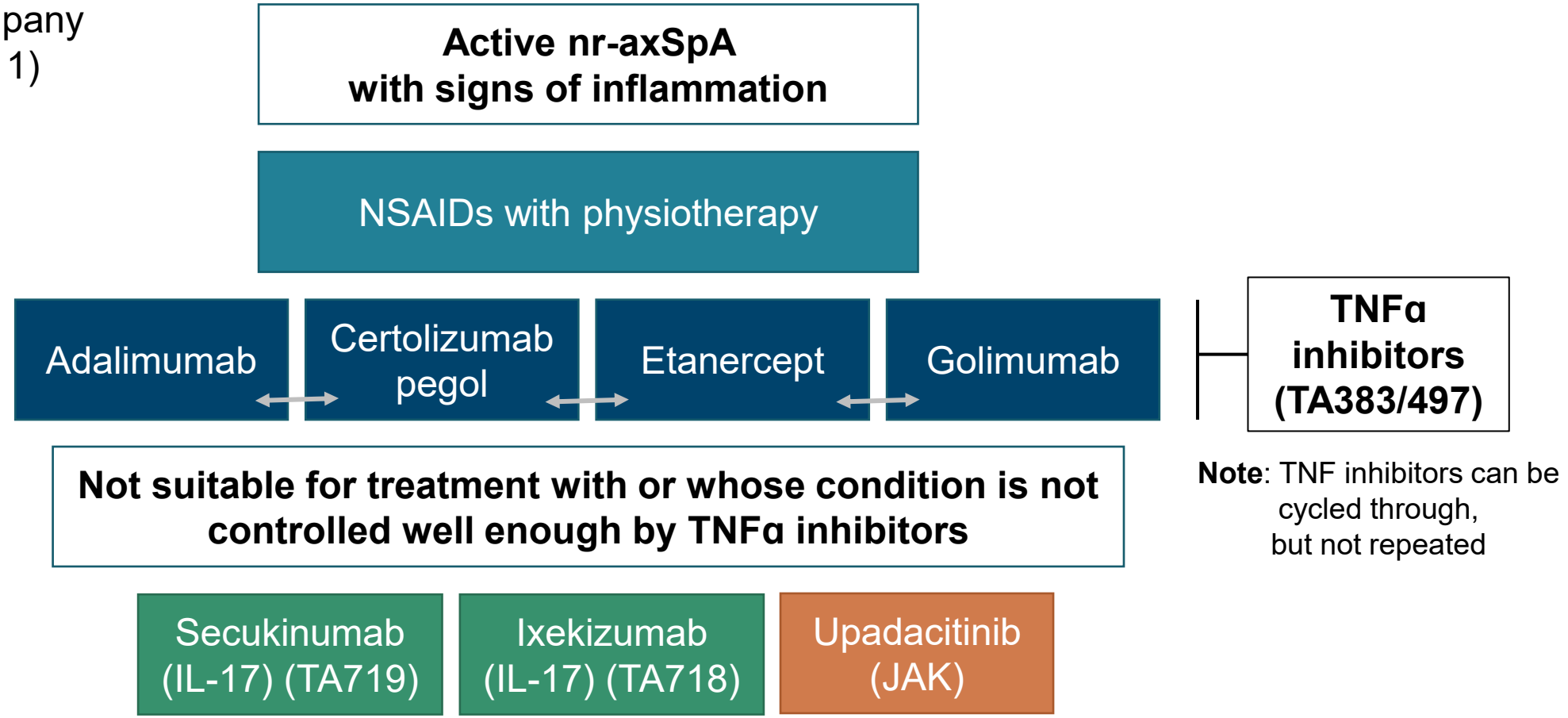
Marketing authorisation	• Upadacitinib "is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging, who have responded inadequately to nonsteroidal anti-inflammatory drugs"
Mechanism of action	• Selective and reversible JAK inhibitor • Preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2
Administration	• Oral administration • 15 mg prolonged-release tablet once daily with or without food • May be taken at any time of day
Price	• Unit price: [redacted] • Pack of 28 tablets: [redacted] • Annual maintenance treatment at 15 mg: [redacted] • Company has agreed a confidential **patient access scheme - simple discount**

 Abbreviations: **JAK**: janus kinase

Treatment pathway (1)

Upadacitinib positioned after, or for those intolerant to TNFα inhibitors

Figure 1 Treatment pathway (adapted from company Submission, figure 1)



Abbreviations: **IL**: interleukin; **JAK**: janus kinase; **nr-axSpA**: non-radiographic axial spondyloarthritis; **NSAID**: non-steroidal anti-inflammatory drug; **TNFα**: tumour necrosis factor alpha

Treatment pathway (2)

- **Clinical advice to EAG: secukinumab is used more often than ixekizumab**
  - Available as treatment option in separate AS indication for longer than ixekizumab
  - Unusual for patient to switch from secukinumab to ixekizumab (or vice versa) except for AEs
  - Patients who stop responding to IL-17 inhibitors have limited options
- **Clinical advice to EAG: upadacitinib, ixekizumab and secukinumab should be available as second- and third-line treatment options**
  - Choice whether to offer upadacitinib or IL-17 inhibitor depends on other factors:
    - Needle phobia, dexterity issues
    - Shorter half life of upadacitinib would enable patients to continue treatment for nr-axSpA when IL-17 inhibitors would be unsuitable due to longer half-life
    - Post-marketing safety concerns relating to JAK inhibitors would mean IL-17 inhibitors are preferred for those with a history, or risk of developing cardiovascular events and malignancy
    - IL-17 inhibitors preferred for those with uveitis and psoriasis
    - Upadacitinib preferred for those with a history of IBD (already has positive opinion for ulcerative colitis)
- **If upadacitinib, ixekizumab and secukinumab are all still viable treatment options, key consideration would be cost, with the cheapest treatment option being preferred**

Abbreviations: **AE**: adverse event; **AS**: ankylosing spondylitis; **IBD**: inflammatory bowel disease; **IL**: interleukin; **JAK**: janus kinase; **nr-axSpA**: non-radiographic axial spondyloarthritis

Comparators: secukinumab and ixekizumab

Table 2 Comparator details (**Source**: EAG report, tables 1 and 2)

	Secukinumab (TA719) (Cosentyx, Novartis)	Ixekizumab (TA718) (Taltz, Eli Lilly)
Marketing authorisation	• Indicated for the treatment of active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs	
Mechanism of action	• Monoclonal antibody which binds and inhibits the IL-17A cytokine → promotes inflammation when it binds to immune cells	
Administration	• SC injection; 150 mg weekly for first four weeks, then 150 mg every four weeks	• SC injection; 160 mg at week 0, then 80 mg every four weeks
Price	• List price: £1,218.78 (2 x 150 mg syringes) • There is a confidential PAS for secukinumab	• List price: £1,125 (1 x 80 mg syringe) • There is a confidential PAS for ixekizumab

Abbreviations: **IL**: interleukin; **mg**: milligram; **nr-axSpA**: non-radiographic axial spondyloarthritis; **PAS**; patient access scheme; **SC**: subcutaneous

Upadacitinib for treating active ankylosing spondylitis [ID3848]

Upadacitinib recently received positive recommendation via cost comparison route

Final appraisal document

- Upadacitinib is recommended as an option for treating active ankylosing spondylitis (AS) that is not controlled well enough with conventional therapy in adults, only if:
    - tumour necrosis factor (TNF)-alpha inhibitors are not suitable or do not control the condition well enough, and
    - the company provides upadacitinib according to the commercial arrangement…
- … if people and their clinicians consider upadacitinib to be one in the range of suitable treatments which includes secukinumab and ixekizumab, **the least expensive should be chosen**

Why committee made this recommendation

- Evidence from clinical trials: upadacitinib more effective than placebo.
  Indirect comparisons: upadacitinib likely to provide similar health benefits to secukinumab
- Upadacitinib compared with secukinumab most relevant comparison in line with NHS practice
- Total costs associated with upadacitinib similar to or lower than those for secukinumab/ixekizumab

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Background on disease-specific 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) to an unlimited amount (based on level of C-reactive protein [CRP])

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)

BASMI – (*functional)* - used to assess clinically significant changes in spinal mobility. The scale of the BASMI ranges from 0 to 10, where 0 is no mobility limitation and 10 is a very severe limitation

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

Abbreviations: ASAS: assessment in ankylosing spondylitis; **ASQoL**: ankylosing spondylitis quality of life; **BASDAI/FI/MI**: Bath ankylosing spondylitis disease activity/functional/mobility index; **VAS**: visual analogue scale

Key clinical trials

Evidence to support upadacitinib derived from SELECT-AXIS 2, study 2

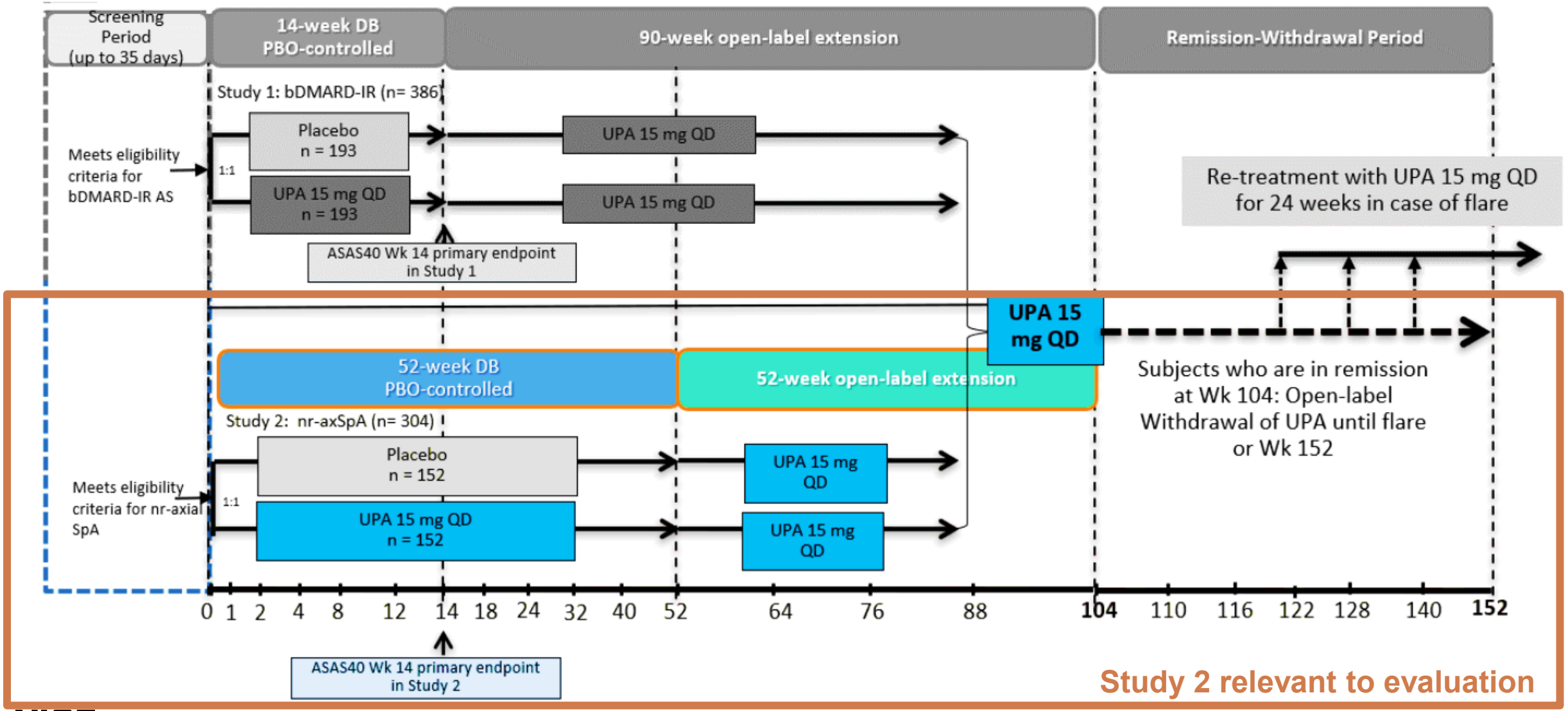
Table 3 SELECT-AXIS 2, study 2 study design (**Source**: company submission, figure 2, tables 6 and 7)

	SELECT-AXIS 2, study 2
Design	Phase III, multicentre, randomised, double-blind, placebo-controlled trial, with open label extension
Population	Patients ≥18 years with a clinical diagnosis of nr-axSpA meeting the 2009 ASAS classification criteria for axial spondyloarthritis. Patients **could have previous or no previous bDMARD exposure** (1 TNF inhibitor or 1 IL-17 inhibitor), ≥2 NSAIDs inadequate responses across ≥4 weeks or NSAID intolerance or contraindication.
Intervention	Upadacitinib 15 mg (n=156)
Comparator(s)	Placebo (n=157)
Duration	35 days screening, 52-week double blind, 52-week open label extension
Primary outcome	ASAS40 response at week 14, 40% improvement in disease activity
Key secondary outcomes	BASDAI 50, BASFI CFB, Patient's Assessment of Total Back Pain CFB (see slide 12 for information on disease-specific outcomes)
Locations	North America, South/Central America, Eastern Europe, Western Europe ([redacted]), Asia

NICE **Abbreviations: bDMARD**: biologic disease-modifying antirheumatic drug; **CFB**: change from baseline; **IL**: interleukin; **mg**: milligram; **nr-axSpA**: non-radiographic axial spondyloarthritis; **NSAID**: non-steroidal anti-inflammatory drug; **TNF**: tumour necrosis factor

SELECT-AXIS 2 study design

Figure 2 SELECT-AXIS 2 study design (**Source**: company submission, figure 2)



Abbreviations: **ASAS**: assessment in ankylosing spondylitis **DB**: double-blind; **mg**: milligram; **nr-axial SpA**: non-radiographic axial spondyloarthritis; **PBO**: placebo; **QD**: daily; **UPA**: upadacitinib; **wk**: week

SELECT-AXIS 2, study 2 results

Upadacitinib is more efficacious than placebo in multiple key disease areas

Table 4 SELECT-AXIS 2, study 2 results (**Source**: company submission, table 13)

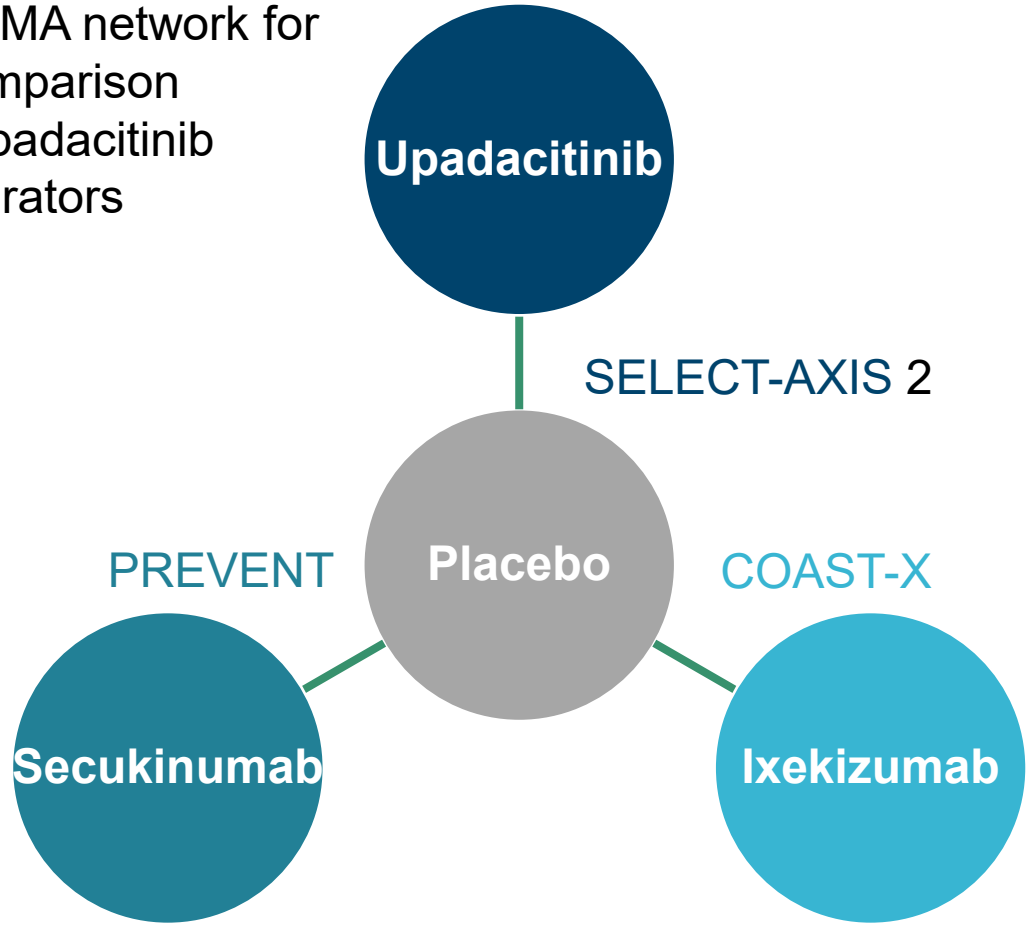
		Endpoint (week 14)	Placebo	UPA	Difference (95% CI)	p value
Primary	Disease activity	ASAS40 response	22.5%	44.9%	22.4% (12.1, 32.3)	<0.0001*
Key secondary endpoints		ASDAS (CRP) CFB	-0.71	-1.36	-0.65 (-0.85, -0.45)	<0.0001*
		ASDAS (CRP) inactive disease	5.20%	14.10%	8.8 (2.5, 15.2)	0.0063*
		ASDAS (CRP) low disease activity	18.30%	42.30%	23.8 (14.2, 33.4)	<0.0001*
		BASDAI50 response	22.10%	42.30%	20.1 (10.1, 30.1)	0.0001*
		ASAS20 response	43.80%	66.70%	22.8 (12.2, 33.4)	<0.0001*
		ASAS partial remission	7.60%	18.60%	10.9 (3.6, 18.3)	0.0035*
	Function	BASFI CFB	-1.47	-2.61	-1.14 (-1.60, -0.68)	<0.0001*
		BASMI (Mobility) CFB	-0.19	-0.29	-0.10 (-0.25, 0.05)	0.1781
	Inflammation	MRI SPARCC Score (SI joint) CFB	0.57	-2.49	-3.06 (-4.08, -2.04)	<0.0001*
	Pain	MASES (enthesitis) CFB	-1.6	-2.3	-0.7 (-1.3, -0.1)	0.0193
		Total back pain CFB	-2	-2.91	-0.92 (-1.42, -0.41)	0.0004*
		Nocturnal back pain CFB	-1.84	-2.96	-1.12 (-1.68, -0.55)	0.0001*
	Quality of life	ASQoL CFB	-3.15	-5.38	-2.23 (-3.26, -1.21)	<0.0001*
		ASAS Health Index	-1.48	-3.26	-1.78 (-2.56, -1.00)	<0.0001*

Abbreviations: **ASAS**: Assessment in Ankylosing Spondylitis; **ASDAS**: Ankylosing Spondylitis Disease Activity Score; **ASQoL**: Ankylosing Spondylitis Quality of Life; **BASDAI/FI/MI**: Bath Ankylosing Spondylitis Disease Activity/Functional/Mobility Index; **CFB**: change from baseline; **CRP:** c-reactive protein; **MASES**: Maastricht Ankylosing Spondylitis Enthesis Score: **MRI**: magnetic resonance imaging; **SI**: sacro-iliac; **SPARCC**: Spondyloarthritis Research Consortium of Canada; **UPA**: upadacitinib

NMA network

Unable to conduct NMAs in biologic-naïve or biologic-experienced populations separately due to limitations in data available

Figure 3 NMA network for indirect comparison between upadacitinib and comparators



- Initial NMA included 9 placebo-controlled trials
  - Included TNFα inhibitors which are not considered relevant comparators
  - Introduced unnecessary complexity
- NMA simplified following EAG critique at clarification
  - EAG considers simplified NMAs more appropriate for decision making

 Abbreviations: **NMA:** network meta-analysis; **TNF:** tumour necrosis factor

Comparator trials

Evidence for comparators derived from COAST-X (ixe) and PREVENT (sec)

Table 5 COAST-X and PREVENT study design (**Source**: company submission, table 15; appendix, table 5)

	COAST-X (n=303)	PREVENT (n=555)
Design	Phase III, multicentre, randomised, double-blind, placebo-controlled trial, with option 2yr open label extension (COAST-Y)	Phase III, multicentre, randomised, double-blind, placebo-controlled trial, with open label extension to week 100, optional 2yr extension
Population	bDMARD-naïve (see EAG report, table 13)	bDMARD-mixed (see EAG report, table 13)
Intervention	Ixekizumab 80 mg Q2W (n=102) Ixekizumab 80 mg Q4W (n=96)	Secukinumab 150 mg, loading dose (n=185) Secukinumab 150 mg, no loading dose (n=184)
Comparator	Placebo (n=105)	Placebo (n=186)
Duration	52-week double blind, 52-week open label extension	52-week double blind, 48-week open label extension
Primary outcome	ASAS40 response at weeks 16 and 52, 40% improvement in disease activity	ASAS40 response at weeks 16 and 52, 40% improvement in disease activity
Locations	Europe, Asia, North America, South America	Europe, Asia, North America, Central America, Australia

NICE **Abbreviations: ASAS:** Assessment of SpondyloArthritis international Society; **bDMARD**: biologic disease-modifying antirheumatic drug; **mg**: milligram; **Q2W/4W:** every 2/4 weeks

NMA results – clinical effectiveness

Medians favour upadacitinib versus comparators, but wide credible intervals

Table 6 NMA results, upadacitinib versus comparators (**Source**: company response to clarification, q. A7, Table 6-9)

Outcome	Placebo	Ixekizumab	Secukinumab (no loading dose)
ASAS40 (OR)[a]	[redacted]	[redacted]	[redacted]
BASDAI50 (OR)[a]	[redacted]	[redacted]	[redacted]
BASDAI CFB (MD)[b]	[redacted]	[redacted]	[redacted]
BASFI CFB (MD)[b]	[redacted]	[redacted]	[redacted]

Note: a: OR>1.00, result favours upadacitinib; **b**: Mean difference<0.00, results favour upadacitinib

- Results suggest statistical significance for upadacitinib vs placebo; not relevant
- Median values favour upadacitinib versus ixekizumab (except BASDAI50) and secukinumab
  - Credible intervals are wide, include unity for both binary outcomes (ASAS40, BASDAI50) and include zero for both continuous outcomes (BASDAI CFB and BASFI CFB)
- Health benefits for all treatments could be similar, but they could also be greater for any
- Likely that results for secukinumab with correct dose (no loading dose) would be similar

Abbreviations: ASAS40: assessment of ankylosing spondylitis 40; **BASDAI**: Bath ankylosing spondylitis disease activity index; **BASFI**: Bath ankylosing spondylitis functional index; **CFB**: change from baseline; **MD**: mean difference; **OR**: odds ratio

EAG comments on NMA - heterogeneity

Heterogeneity may impact validity of NMA, but no head-to-head studies available

Table 7 Heterogeneity between trials, plus clinical advice (**Source**: EAG report, section 4.4.3)

Heterogeneity between trials	Clinical advice to EAG
Outcomes measured at different timepoints across trials	-
Number and proportion of biologic-experienced patients different across included trials • SELECT-AXIS 2 (103/313, 32.9%), COAST-X (0/303), PREVENT (54/555, 9.7%)	No reason to assume difference in response to upadacitinib between people who are biologic-naïve or biologic-experienced **Contradicted by data in CS, appendix J**
Mean duration from diagnosis and duration of symptoms were shorter in PREVENT	Shorter duration of disease may have better response to treatment
Mean CRP level lower in SELECT-AXIS 2, but all three trials used same threshold for elevated CRP	Higher CRP levels may have better response to treatment
Less HLA-B27 positive patients lower in SELECT-AXIS 2	HLA-B27 is marker of disease severity
Proportion of patients who showed sacroiliac joint inflammation of MRI lower in SELECT-AXIS 2	Joint inflammation on MRI is marker of disease severity
Proportion of patients on concomitant NSAIDs lower in SELECT-AXIS 2	NSAID use can lower inflammatory markers and reduce MRI scan signal of inflammation

Abbreviations: **CRP:** C-reactive protein; **HLA-B27:** human leukocyte antigen B27; **MRI:** magnetic resonance imaging; **NSAID:** non-steroidal anti-inflammatory drug

EAG comments on NMA – heterogeneity (2)

Heterogeneity may impact validity of NMA, but no head-to-head studies available

Heterogeneity between trials	Clinical advice to EAG
Number and proportion of biologic-experienced patients different across included trials • SELECT-AXIS 2 (103/313, 32.9%), COAST-X (0/303), PREVENT (54/555, 9.7%)	No reason to assume difference in response to upadacitinib between people who are biologic-naïve or biologic-experienced **Contradicted by data in CS Appendix J, table 14**

- Responder: biologic-naïve = [redacted]; biologic-experienced = [redacted]
- Reason to assume that upadacitinib is less efficacious in those who are biologic-experienced
- SELECT-AXIS 2 had more biologic-experienced than biologic-naïve compared to COAST-X and PREVENT

	SELECT-AXIS 2		COAST-X			PREVENT		
	PBO (n=157)	UPA (n=156)	PBO (n=105)	IXE Q2W (n=102)	IXE Q4W (n=96)	PBO (n=186)	SEC (n=185)	SEC (no LD) (n=184)
bDMARD-experienced, n (%)	54 (34.4)	49 (31.4)	0 (0.0)	0 (0.0)	0 (0.0)	15 (8.1)	21 (11.4)	18 (9.8)

Safety comparisons between trials (1)

EAG: safety profiles of all treatments similar

Table 8a AEs, upadacitinib versus comparators (**Source**: company submission, table 21)

SA2: Week 14 COAST-X: Week 16 PREVENT: Week 20	SELECT-AXIS 2		COAST-X			PREVENT		
	PBO (n=157)	UPA (n=156)	PBO (n=104)	IXE Q2W (n=102)	IXE Q4W (n=96)	PBO (n=186)	SEC (n=185)	SEC (no LD) (n=184)
Length of follow-up	Week 14		Week 52			Up to Week 20		
Any TEAE, n (%)	72 (45.9)	75 (48.1)	60 (57.7)	79 (77.5)	63 (65.6)	101 (54.3)	119 (64.3)	107 (58.2)
Nasopharyngitis, n (%)	[redacted]	[redacted]	8 (7.7)	16 (15.7)	18 (18.8)	23 (12.4)	27 (14.6)	19 (10.3)
Injection site reaction, n (%)	[redacted]	[redacted]	4 (3.8)	17 (16.7)	11 (11.5)	--	--	--
Headache, n (%)	[redacted]	[redacted]	4 (3.8)	5 (4.9)	7 (7.3)	7 (3.8)	17 (9.2)	5 (2.7)
Upper respiratory tract infection, n (%)	[redacted]	[redacted]	4 (3.8)	6 (5.9)	4 (4.2)	7 (3.8)	11 (5.9)	11 (6.0)

Note: Different thresholds used for reporting AE data as follows: TEAEs >2% patients treated with PBO or UPA in SELECT-AXIS 2, TEAEs ≥5% patients treated with IXE (Q2W and Q4W combined) in COAST-X, AEs >5% patients treated with SEC in PREVENT. '--' denotes where data not reported, because threshold not met in trial (could mean there were fewer/no events)

NICE

Abbreviations: **AE:** adverse event; **IBD**: inflammatory bowel disease; **IXE**: ixekizumab; **LD**: loading dose; **PBO**: placebo; **Q2/4W**: every 2/4 weeks; **SE**: standard error; **SEC**: secukinumab; **TEAE**: treatment-emergent adverse event; **UPA**: upadacitinib

Safety comparisons between trials (2)

EAG: safety profiles of all treatments similar

Table 8b AEs, upadacitinib versus comparators (**Source**: company submission, table 21)

SA2: Week 14 COAST-X: Week 16 PREVENT: Week 20	SELECT-AXIS 2		COAST-X			PREVENT		
	PBO (n=157)	UPA (n=156)	PBO (n=104)	IXE Q2W (n=102)	IXE Q4W (n=96)	PBO (n=186)	SEC (n=185)	SEC (no LD) (n=184)
Length of follow-up	Week 14		Week 52			Up to Week 20		
Hypertension, n (%)	[redacted]	[redacted]	4 (3.8)	4 (3.9)	6 (6.3)	--	--	--
Diarrhoea, n (%)	[redacted]	[redacted]	--	--	--	7 (3.8)	14 (7.6)	9 (4.9)
Neutropenia, n (%)	[redacted]	[redacted]	9 (8.7)	13 (12.7)	12 (12.5)	--	--	--
IBD, n (%)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.5)
Uveitis, n (%)	0 (0.0)	1 (0.6)	2 (1.9)	2 (1.0)	1 (1.0)	1 (0.5)	2 (1.1)	0 (0.0)

Note: Different thresholds used for reporting AE data as follows: TEAEs >2% patients treated with PBO or UPA in SELECT-AXIS 2, TEAEs ≥5% patients treated with IXE (Q2W and Q4W combined) in COAST-X, AEs >5% patients treated with SEC in PREVENT. '--' denotes where data not reported, because threshold not met in trial (could mean there were fewer/no events)

Abbreviations: **AE:** adverse event; **IBD**: inflammatory bowel disease; **IXE**: ixekizumab; **LD**: loading dose; **PBO**: placebo; **Q2/4W**: every 2/4 weeks; **SE**: standard error; **SEC**: secukinumab; **TEAE**: treatment-emergent adverse event; **UPA**: upadacitinib

Safety comparisons between trials (3)

Post-marketing safety concerns with another JAK inhibitor, tofacitinib

- Adverse events (AEs) are not included in company's model
  - **EAG: from naïve comparisons, safety profiles of upadacitinib, ixekizumab and secukinumab are broadly similar**
    - Differences in the incidences of AEs between trials likely to be influenced by differences in trial design, length of follow-up, differences in AE definitions
    - Difficult to draw any definitive conclusions

- Given recent safety warnings issued to other JAK inhibitors (tofacitinib) which may be applicable to upadacitinib, inclusion of AE costs in cost comparison may be appropriate
  - Any potential differences in incidence of AEs between upadacitinib and IL-17 inhibitors cannot be fully dealt within the scope of a cost comparison
  - Would require cost-utility analysis to capture impact of AEs on cost-effectiveness

- **Clinical advice to EAG:** IL-17 inhibitors preferred for those with cardiovascular issues

Clinical effectiveness – EAG conclusion

Company has not provided sufficient justification to prove upadacitinib is similar or better

- **Company has not provided sufficient justification to conclude that upadacitinib is similar to ixekizumab or secukinumab**
  - Absence of evidence is not the same as evidence of absence
  - True effect of upadacitinib versus ixekizumab and upadacitinib versus secukinumab could lie anywhere in 95% credible intervals
    - Could indicate clinically important effects in both directions

- **Clinical advice to the EAG:**
  - Those who are currently unsuitable for treatment with IL-17 inhibitors could benefit from treatment with upadacitinib. These include:
    - Patients with needle phobia
    - Patients with dexterity issues
    - Patients with inadequate response to IL-17 inhibitors
    - Patients at higher risk of IBD/recurrent infections

Cost comparison

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Summary of costs and assumptions (1)

Considers upadacitinib, ixekizumab and secukinumab

Table 9 Summary of costs (**Source**: company submission, tables 23 and 24)

Input name	Base case value	Source
Upadacitinib cost (every 28 days, PAS price)	[redacted]	AbbVie

- Company assumed adverse events can be ignored; similar for all treatments
- Monitoring costs are identical for all treatments
- Excluding drug costs, the only difference between treatments is that for patients treated with ixekizumab and secukinumab, there is a one-hour nurse consultation before the first administration to instruct the patient on use of self-injectable treatments
- **Assumptions are consistent with ID3848, except for discontinuation rate (6% vs 11%)**

Summary of costs and assumptions (2)

Considers upadacitinib, ixekizumab and secukinumab

Table 10 Summary of assumptions and relevant scenario analysis (**Source**: company submission, section B.4.2)

Assumption	Rationale for assumption	Relevant scenario analysis
Time horizon of the analysis is 5 years	This is long enough to capture all treatment-related costs	Time horizon of 1 year and 10 years
Adverse events are not included in the model	Safety profile suggests few serious adverse events for upadacitinib and similar rates of events for upadacitinib, ixekizumab and secukinumab	None undertaken
Monitoring costs are the same for all treatments	Clinical feedback and previous NICE appraisals	None undertaken
Annual discontinuation rate of 6% for all treatments	This rate is consistent with the approach taken in recent NICE technology appraisals for nr-axSpA and considered appropriate by ERG in NICE (TA383 and TA719) and by clinical experts whose opinion was sought during interviews (CS, Section B.4.2.6)	Annual discontinuation rate of 11%
Training for one hour is required for ixekizumab and secukinumab injections	Required as treatments are self-administered injections	Removal of training costs

NICE **Abbreviations**: **nr-axSpA:** non-radiographic axial spondyloarthritis

Cost-effectiveness results

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

Equalities

- Not anticipated that any equality issues will arise if upadacitinib is recommended
  - Company highlighted that during the NICE appraisal of TNFα inhibitors as treatment options for AS and nr-axSpA treatment (TA383), an equality concern arose regarding the use of BASDAI and spinal pain VAS scores for assessing response to treatment
  - Guidance issued by NICE for TA383 states:

> "When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate"

  - This recommendation is also repeated in NICE guideline 65 (Spondyloarthritis in over 16s: diagnosis and management)
- Clinical experts highlight that access to current treatments can be unequal due to local variability
  - Oral technology may address this inequality because of convenient administration

Abbreviations: **AS:** ankylosing spondylitis; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **nr-axSpA:** non-radiographic axial spondyloarthritis; **TNF**: tumour necrosis factor; **VAS**: visual analogue score

Summary of EAG critique of cost-comparison

Clinical effectiveness

- Heterogeneity may impact treatment outcomes, and cast doubt on NMA validity
- NMAs show upadacitinib is not statistically significantly superior to ixekizumab or secukinumab for efficacy outcomes presented
- Unclear if outcomes reported are similar, greater or worse for those taking upadacitinib
- Naïve comparison of safety data is possible; difficult to draw definition conclusions

Cost comparison

- When using PAS price for upadacitinib and list prices for ixekizumab and secukinumab, cost comparison provides robust estimates for likely cost savings over 5-years
    - Cost comparison only appropriate where similar or greater health benefits for upadacitinib versus ixekizumab and secukinumab can be demonstrated

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Thank you.