Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Redacted

Technology appraisal committee B [13 October 2022]

Chair: Charles Crawley

Lead team: Charles Crawley (Chair), Baljit Singh (Clinical), Henry Edwards (Cost)

Evidence assessment group: Liverpool Reviews and Implementation Group

Technical team: Catherine Spanswick, Carl Prescott, Henry Edwards

Company: AbbVie

NICE National Institute for Health and Care Excellence

Key issues

Issue	Resolved?	Tech team view	ICER impact
No direct evidence vs comparators – *influenced by confidence in NMA results*	No – cannot be resolved	Company approach acceptable	Unknown
NMA statistical issues – *plausibility and suitability of NMA results*	No – for discussion	NMAs results plausible but some uncertainty	Unknown
Modelled treatment pathway – *does not represent NHS practice*	No – for discussion	Choice does not have big impact	Small
Utility values – *trial utilities available, but not used in company base case*	No – for discussion	Choice does not have big impact	Small
High and low doses of upadacitinib maintenance treatments – *different doses with different costs available; what is used in NHS?*	Yes	No further discussion needed	Small

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

Additional issue after technical engagement

Issue	Resolved?	Tech team view	ICER impact
Surgery rates – *only relates to company base case (not EAGs)*	No – for discussion	Choice does not have big impact	Moderate

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

NICE technical team suggested recommendation

Upadacitinib should be recommended

Upadacitinib should be recommended in line with other JAK inhibitors tofacitinib and filgotinib

Suggested wording: *"Upadacitinib is recommended as an option for treating moderately to severely active ulcerative colitis in adults when conventional or biological treatment cannot be tolerated, or if the disease has not responded well enough or has stopped responding to these treatments"*

Rationale:

- Upadacitinib has broadly similar total costs and QALYs vs existing NICE recommended treatments for moderately to severely active ulcerative colitis, including other JAK inhibitors, tofacitinib and filgotinib, with indirect analyses suggesting upadacitinib may be more effective than some treatments
- Where company and EAG base cases differ, the impact on ICERs are generally small
- Low risk to the NHS – many other drugs available, this will be another option

Risks and uncertainties in suggested recommendation

Some uncertainty and risks with suggested recommendation

Uncertainty:

- EAG identified some unresolvable statistical issues in NMA results that add uncertainty

Risks:

- In a limited number of pairwise comparisons, tofacitinib was more effective than upadacitinib
- In some comparisons, upadacitinib was not the most cost-effective option but it was broadly a cost-effective use of NHS resources
- Recommendation may need to be updated following EMA's safety review of tofacitinib:

EMA's safety committee (PRAC) is carrying out a review to determine whether risks associated with tofacitinib are associated with all JAK inhibitors authorised in EU (including upadacitinib) for the treatment of inflammatory disorders, and whether marketing authorisations for these medicines should be amended

- For now there is nothing to be done so in the interim period it should be recommended alongside tofacitinib (TA547) with any NICE recommendations updated post EMA investigation

Abbreviations: PRAC, Pharmacovigilance Risk Assessment Committee

Background

Moderately to severely active UC is a severe, chronic and burdensome disease with many different treatment options

Upadacitinib is a potential additional treatment option for patients who have already had conventional therapy or a biologic agent

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Disease background

Ulcerative colitis:

- Lifelong, progressive disease characterised by relapsing and remitting episodes of inflammation of the rectal and colonic mucosa
- Tiny ulcers develop on the surface of the lining of the colon (bleed and produce pus)

Epidemiology:

- Around 115,000 people in England have UC (52% moderate to severe disease - defined as Mayo clinic score - 6 to 12)
- Incidence peaks between 15 and 25 years. Smaller peak between 55 and 65 years

Risk factors:

- Unknown cause. Hereditary, infectious and immunological factors possible

Symptoms:

- Bloody diarrhoea, colicky abdominal pain, urgency and tenesmus; extra-intestinal manifestations (joints, eyes, skin and liver)

Complications:

- Haemorrhage, perforation, stricture formation, abscess formation and anorectal disease

Treatments:

- Pharmacological: conventional therapy (aminosalicylates, corticosteroids or thiopurines) and biologics (adalimumab, golimumab, infliximab, vedolizumab, tofacitinib or ustekinumab)
- Surgery: colectomy

Abbreviations: UC, ulcerative colitis

Mayo clinic score (MCS) for ulcerative colitis

Used for diagnosis and to assess disease activity

Component	Description	Points
Stool frequency subscore	Normal	0
	1–2 stools more than usual	1
	3–4 stools more than usual	2
	≥ 5 stools more than usual	3
Rectal bleeding subscore	No blood	0
	Streaks of blood < 50% of time with stool	1
	Obvious blood most of time with stool	2
	Blood alone passed	3
Endoscopic findings subscore	Normal/inactive disease	0
	Mild disease	1
	Moderate disease	2
	Erosions	3
Physician's global assessment	Normal	0
	Mild	1
	Moderate	2
	Severe	3

Adapted Mayo score:
- Total score of 0-9
- Primary and key secondary outcome measure in upadacitinib trials based on recommendation by regulatory agency

Full Mayo score:
- Total score of 0-12
- Moderate to severely active ulcerative colitis has total score of 6 to 12

Abbreviations: UC, ulcerative colitis

Upadacitinib (Rinvoq, AbbVie)

Marketing authorisation	• Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent • Granted in July 2022 • Contraindications – hypersensitivity to active substance or excipients, active tuberculosis, active serious infections, severe hepatic impairment, pregnancy
Mechanism of action	• Selective and reversible Janus kinase (JAK) inhibitor that preferentially inhibits JAK1 • Modulates the signalling of the JAK-dependent cytokines, which reduces inflammation in the gut and improves signs and symptoms of UC
Administration	Once-daily oral dosing: • Induction: 45 mg for 8 weeks, continued for a further 8 week if inadequate response • Maintenance: 15 mg or 30 mg based on patient presentation
Price	• List price (28 tablets per pack): £805.56 for 15 mg tablets; £1,281.54 for 30 mg tablets; £2087.10 for 45 mg tablets • Patient access scheme (PAS) discount in place (confidential)

Decision problem (1)

	Final scope	Company	EAG comments
Population	People with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent	*As per scope.* Subpopulations: • Non-Bio IR*, hereafter referred to as '**bio naïve population**' and defined as: *patients who had an inadequate response or intolerance to CT but had not failed biologic therapy* • Bio IR, hereafter referred to as '**bio exposed population**' and defined as: *patients who had an inadequate response or intolerance to CT or a biologic treatment*	*As per scope*

*Only 2% of non-Bio-IR population had previously been exposed to a biologic treatment and had stopped for reasons other than inadequate response, loss of response, or intolerance

Abbreviations: CT, conventional therapy; IR, inadequate response; UC, ulcerative colitis

Decision problem (2)

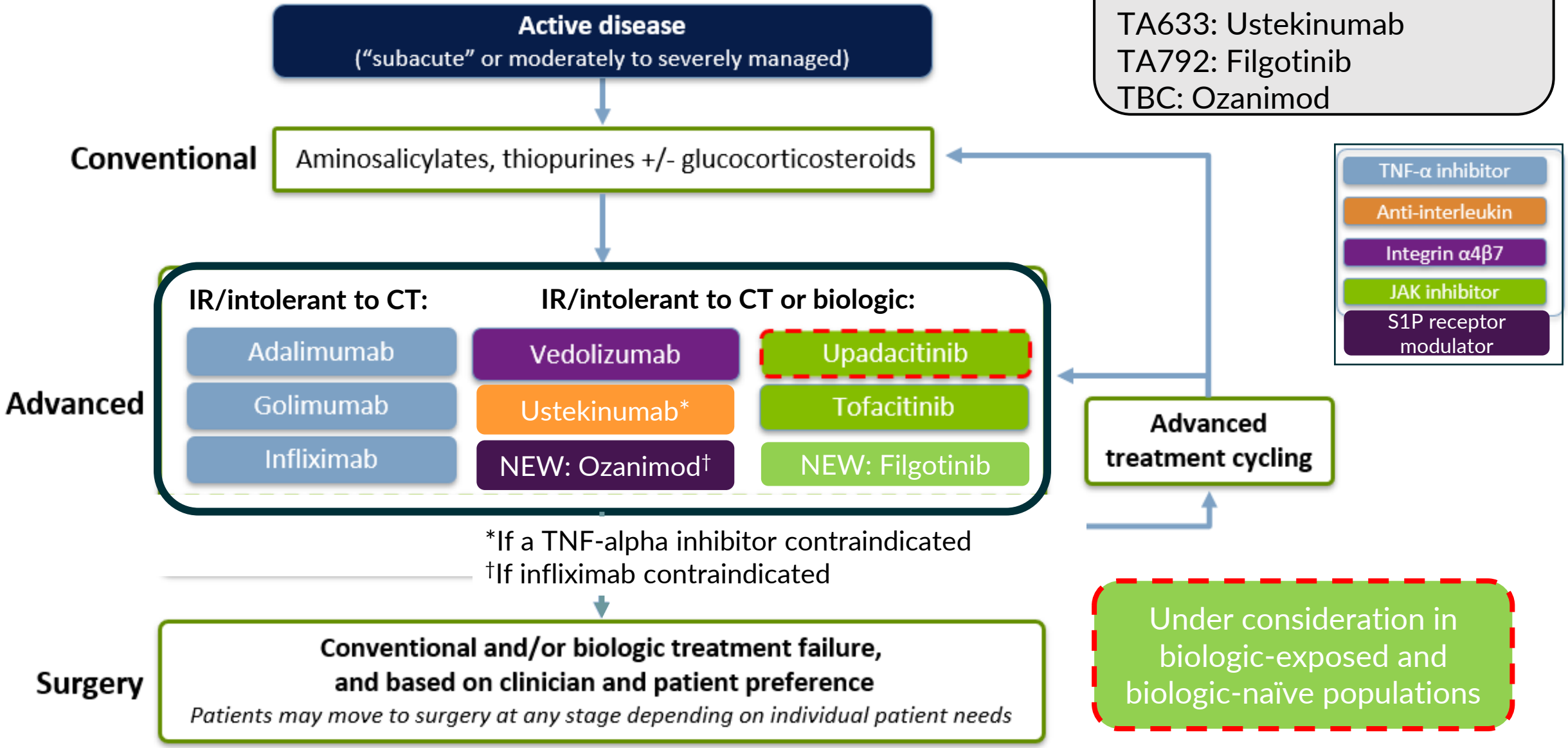
	Final scope	Company	EAG comments
Intervention	Upadacitinib	*As per scope*	*As per scope*
Comparators	• TNF-alpha inhibitors (adalimumab, golimumab, infliximab) • Tofacitinib • Ustekinumab • Vedolizumab • Filgotinib (ongoing NICE appraisal [TA792]) • Ozanimod (ongoing NICE appraisal [ID3841] expected publication 5 Oct) • Conventional therapies (including aminosalicylates, oral corticosteroids and/or immunomodulators), without biological treatments	• TNF-alpha inhibitors (adalimumab, golimumab, infliximab) • Tofacitinib • Ustekinumab • Vedolizumab Excludes: • Filgotinib and ozanimod – at time of submission, both subject to ongoing NICE appraisal and do not represent standard of care • Conventional therapies – given earlier in treatment pathway	Agrees with company approach

Decision problem (3)

	Final scope	Company	EAG comments
Outcomes	• Mortality • Measures of disease activity • Rates of and duration of response, relapse, and remission • Rates of hospitalisation (including readmission) • Rates of surgical intervention • Endoscopic healing • Endoscopic remission combined with histological improvement • Corticosteroid-free remission • Achieving mucosal healing • Adverse effects of treatment • Health-related quality of life	*As per scope* Note: Endoscopic remission combined with histological improvement corticosteroid-free remission is addressed as 2 separate outcomes in submission • Endoscopic healing combined with histological improvement • Corticosteroid-free remission	*As per scope* Note: Rate of relapse not presented as a clinical outcome but is estimated from NMA results

Ulcerative colitis treatment pathway

TA329: TNF-alpha inhibitors
TA342: Vedolizumab
TA547: Tofacitinib
TA633: Ustekinumab
TA792: Filgotinib
TBC: Ozanimod



Abbreviations: IR, inadequate response; JAK, Janus kinase; S1P, sphingosine 1-phosphate; TNF-α, tumour necrosis factor-α

Recent NICE appraisals: tofacitinib

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults …	Pathway positioning
TA547 (2018)	Janus kinase (JAK) inhibitor	Tofacitinib	…when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment	Biologic naïve Biologic exposed

Position in pathway:

- Committee concluded tofacitinib used in the same place in pathway as biological therapies, instead of or after biologic therapy

Rationale for recommendation:

- Indirect comparison suggests that for people who have not had a TNF-alpha inhibitor, tofacitinib is more effective than adalimumab and golimumab as maintenance treatment. For people who have had a TNF-alpha inhibitor, tofacitinib is more effective than adalimumab as induction treatment.
- Compared with conventional therapy and biologicals, tofacitinib was considered cost effective

Recent NICE appraisals: ustekinumab

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults ...	Pathway positioning
TA633 (2020)	Anti-interleukin	Ustekinumab	...when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if: • a TNF-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) or • a TNF-alpha inhibitor cannot be tolerated or is not suitable	Biologic exposed

Position in pathway:

- TNF-alpha inhibitors most commonly used biological treatment
- People who cannot have TNF-alpha inhibitors usually offered vedolizumab, so this is the most relevant comparator for ustekinumab

Rationale for recommendation:

- When compared with vedolizumab, ustekinumab was considered cost effective
  - Ustekinumab not cost effective in people who have TNF-alpha inhibitors as a treatment option

Recent NICE appraisals: filgotinib

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults …	Pathway positioning
TA792 (2022) *recommended after current submission*	JAK inhibitor	Filgotinib	…when conventional or biological treatment cannot be tolerated, or if the disease has not responded well enough or has stopped responding to these treatments	Biologic naïve Biologic exposed

Position in pathway:

- Filgotinib positioned 3 ways: biologic-naïve, biologic experienced after 1 line, biological experience after 2 lines

Rationale for recommendation:

- Indirect comparison suggests filgotinib likely to be as effective as most treatments offered after conventional therapy
- Filgotinib was likely to be cost effective compared with these other treatments

Upadacitinib: most similar to approach taken in filgotinib TA: biologic-naïve, biologic experienced (any line)

Recent NICE appraisals: ozanimod

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults …	Pathway positioning
ID3841 (2022)	Sphingosine-1-phosphate inhibitor	Ozanimod	…only if: • conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable, or • biological treatment cannot be tolerated or is not working well enough	TNF-alpha inhibitor naïve TNF-alpha inhibitor experienced

Position in pathway:

- Company presented 2 positions: TNF-alpha inhibitor naïve and TNF-alpha inhibitor experienced because TNF-alpha inhibitors more commonly used after conventional therapy than other biological treatments, so
  - Ozanimod can be used after conventional treatment or after a TNF-alpha inhibitor

Rationale for recommendation:

- Standard treatments after conventional therapy are biological treatments or tofacitinib
- Indirect comparison suggests ozanimod likely to be as effective as some treatments offered after conventional therapy
- When conventional therapy is not tolerated or not working well enough, infliximab is more cost effective than ozanimod
- When compared with most other treatments ozanimod was likely to be cost effective

Patient expert perspectives

Submissions from Crohn's & Colitis UK and patient testimony

Living with ulcerative colitis

- Disease severity is wide-ranging and each individual has own experience: embarrassed, frustrated, sad and fear need for surgery or developing cancer
- Symptoms include frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations, affecting ability to work, study and socialise

UC is a horrible disease, with a huge impact on personal, professional and family life

Unmet need in moderate to severe ulcerative colitis

- Range of treatments available but people who experience a lack of response face the prospect of surgery with considerable anxiety
- Dissatisfaction with current treatments, side effects from steroids extremely unpleasant, concern about long-term safety profile of other treatments including biologics
- Allowing the earlier introduction of biologic / JAK treatments to the treatment plan may increase quality of life for UC sufferers, reduce hospital admissions and the need for surgery

Upadacitinib

- An oral therapy, gives patients a treatment option to be taken at home
- Additional option with a different mode of action that may reduced likelihood of loss of response

Abbreviations: UC, ulcerative colitis

Clinical expert perspectives

Submissions from UKPCA and British Society of Gastroenterology

Aim of drug treatment for moderately to severely active ulcerative colitis

- To induce clinical, steroid-free and endoscopic remission, prevent flares, hospitalisations and surgery, and improve QoL

Unmet need

- Approximately 1/3rd people relapse during first 12 months on treatment
- In up to ~50% of patients there is a lack of response or loss of response over time
- TNF-α inhibitors are affected by primary failure of induction therapy (19-58%) and secondary loss of response (17-22%) or need for dose escalation (~40%); treatment failure even higher if given 2nd-line

Upadacitinib

- Step change – NMA suggests best performing agent for induction of clinical remission in moderate to severe UC
- Easier for patients: a once-daily oral agent, so ↓ risk of hospital derived infection and injection site reactions
- No special temperature storage conditions (vs other options such as adalimumab which needs to be stored in a fridge – less wastage)
- Like with current treatments, additional monitoring is required
- High response rates seen suggest it should not be reserved for *after* failure of anti-TNF-α, vedolizumab or ustekinumab
- Use caution in patients with risk factors for venous thromboembolism

Abbreviations: NMA, network meta-analysis; UKCPA, UK Clinical Pharmacy

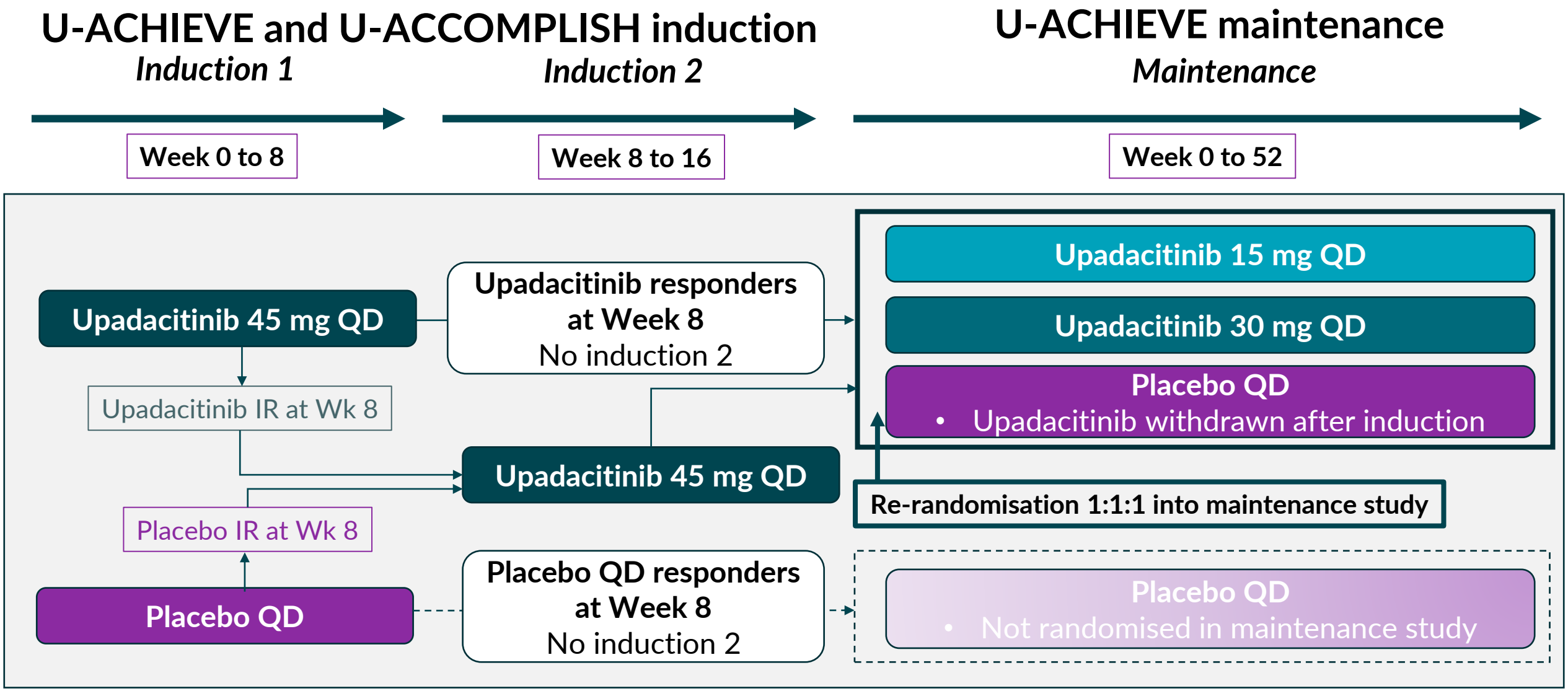
Clinical effectiveness

In clinical trials, upadacitinib is more effective than placebo for key outcomes

In indirect comparisons, NMA results show upadacitinib is more effective than comparators and has similar AEs

Clinical trial results

Key clinical trials



Note: Any IR patients at Week 16 did not enter maintenance study

Key clinical trials of upadacitinib versus placebo

	U-ACHIEVE induction	U-ACCOMPLISH induction	U-ACHIEVE maintenance
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial		
Population	Moderately to severely active UC with inadequate response, loss of response or intolerance to aminosalicylates, immunomodulators, corticosteroids, or biologic therapies		Moderately to severely active UC who achieved clinical response in induction studies
Intervention	Upadacitinib 45 mg		Upadacitinib 15 mg or 30 mg
Comparator(s)	Placebo		Placebo
Duration	8 weeks (+8 weeks open label if no adequate response)		52 weeks
Primary outcome	Clinical remission by adapted Mayo score at week 8		
Key secondary outcomes	Endoscopic improvement / remission Clinical response Histologic-endoscopic mucosal improvement Lack of bowel urgency / abdominal pain		Endoscopic improvement / remission Maintenance of clinical remission Corticosteroid-free maintenance of clinical remission
Locations	International including UK		
Used in model?	Yes	Yes	Yes

Abbreviations: UC, ulcerative colitis

Baseline characteristics

Endpoint	U-ACHIEVE induction		U-ACCOMPLISH induction		U-ACHIEVE maintenance		
	Upadacitinib 45 mg (n=319)	Placebo (n=154)	Upadacitinib 45 mg (n=341)	Placebo (n=174)	Upadacitinib 15 mg (n=148)	Upadacitinib 30 mg (n=154)	Placebo (n=149)
Male, %	62	63	63	62	64	56	57
Age, mean, years	44	44	42	42	43	43	43
Bio-IR, %	53	51	50	51	48	47	54
Mayo score >9, %	49	49	53	51	49	52	50
Medication use, % Yes:							
Corticosteroid	39	40	35	41	37	37	40
Immunomodulator	1	2	0	2	1	1	0
Aminosalicylates	69	67	68	69	67	69	66

NICE

Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; SD, standard deviation

Summary of trial efficacy data

A summary of slides 26 to 28

Upadacitinib more effective than placebo for key outcomes

Overall population:

- Primary endpoint (clinical remission) and key secondary endpoints*: significantly more people treated with upadacitinib than placebo had improvement in induction (week 8) and maintenance studies (all $p<0.001$)

Biologic experienced and biologic naïve subpopulations:

- In line with overall population. Some differences between biologic experienced and biologic naïve but no clear trends (all CIs overlap suggesting no significant differences between subgroups)

Ranges of adjusted treatment difference (upadacitinib vs placebo) across studies and upadacitinib doses:

- Clinical remission: 17.5% to 31.6% following induction, 26.3% to 41.6% following maintenance
- Clinical response: 39.7% to 51.6% following induction, 41.0% to 56.6% following maintenance
- Endoscopic improvement: 25.3% to 39.2% following induction, 31.1% to 48.3% following maintenance
- Maintenance of clinical remission (from induction): 21.3% to 62.8%
- Corticosteroid-free maintenance of clinical remission (from induction): 21.3% to 59.4%
- Maintenance of endoscopic improvement (from induction): 29.2% to 61.7%

*Clinical response, endoscopic improvement and measured at week 52 only, maintenance of clinical remission, corticosteroid-free maintenance of clinical remission, maintenance of endoscopic improvement

Results of induction studies at Week 8

Endpoint, %		U-ACHIEVE induction		U-ACCOMPLISH induction	
		Upadacitinib 45 mg		Upadacitinib 45 mg	
		Adjusted treatment difference vs placebo, % (95% CI)	p value	Adjusted treatment difference vs placebo, % (95% CI)	p value
Clinical remission (by adapted Mayo score)	Overall population	21.6 (15.8, 27.4)	<0.001	29.0 (23.2, 34.7)	<0.001
	Biologic experienced	17.5 (11.4, 23.6)	-	27.1 (19.6, 34.7)	-
	Biologic naïve	26.0 (16.0, 36.1)	-	31.6 (22.8, 40.5)	-
Clinical response (by adapted Mayo score)	Overall population	46.3 (38.4 to 54.2);	<0.001	49.4 (41.7 to 57.1)	<0.001
	Biologic experienced	51.6 (41.2 to 61.9)	-	50.1 (39.4 to 60.8)	-
	Biologic naïve	39.7 (27.0 to 52.4)	-	48.0 (36.4 to 59.6)	-
Endoscopic improvement	Overall population	29.3 (22.6 to 35.9)	<0.001	35.1 (28.6 to 41.6)	<0.001
	Biologic experienced	25.3 (17.8 to 32.7)	-	32.3 (23.7 to 40.8)	-
	Biologic naïve	33.6 (22.5 to 44.7)	-	39.2 (29.0 to 49.5)	-

Results of maintenance study at Week 52 (1)

Endpoint, %		U-ACHIEVE maintenance			
		Upadacitinib 15 mg		Upadacitinib 30 mg	
		Adjusted treatment difference vs placebo, % (95% CI)	p value	Adjusted treatment difference vs placebo, % (95% CI)	p value
Clinical remission (by adapted Mayo score)	Overall population	30.7 (21.7 to 39.8);	<0.001	39.0 (29.7 to 48.2)	<0.001
	Biologic experienced	33.0 (20.1, 45.9)	-	41.6 (28.6, 54.7)	-
	Biologic naïve	26.3 (11.9, 40.6)	-	36.3 (22.1, 50.6)	-
Clinical response (by adapted Mayo score)	Overall population	44.6 (34.5 to 54.7)	<0.001	56.6 (47.2 to 66.0)	0.001
	Biologic experienced	41.2 (27.2 to 55.3)	-	52.5 (39.0 to 66.0)	-
	Biologic naïve	41.0 (26.2 to 55.9)	-	54.9 (41.3 to 68.6)	-
Endoscopic improvement	Overall population	34.4 (25.1 to 43.7)	<0.001	46.3 (36.7 to 55.8)	<0.001
	Biologic experienced	35.5 (25.1 to 43.7)	-	48.3 (36.7 to 55.8)	-
	Biologic naïve	31.1 (15.9 to 46.4)	-	44.1 (29.4 to 58.8)	-

Results of maintenance study at Week 52 (2)

Endpoint, %		U-ACHIEVE maintenance			
		Upadacitinib 15 mg		Upadacitinib 30 mg	
		Adjusted treatment difference vs placebo, % (95% CI)	p value	Adjusted treatment difference vs placebo, % (95% CI)	p value
Maintenance of clinical remission (from induction)	Overall population	37.4 (20.3 to 54.6)	<0.001	47.0 (30.7 to 63.3)	-
	Biologic experienced	62.8 (38.1 to 87.6)	-	59.4 (34.6 to 84.1)	-
	Biologic naïve	21.3 (-2.5 to 45.2)	-	39.9 (18.3 to 61.5)	-
Corticosteroid-free maintenance of clinical remission (from induction)	Overall population	35.4 (18.2 to 52.7)	<0.001	45.1 (28.7 to 61.6)	<0.001
	Biologic experienced	57.0 (31.0 to 82.9)	-	59.4 (34.6 to 84.1)	-
	Biologic naïve	21.3 (-2.5 to 45.2)	-	37.2 (15.4 to 59.0)	-
Maintenance of endoscopic improvement (from induction)	Overall population	42.0 (27.9 to 56.2)	<0.001	48.7 (35.6 to 61.8)	<0.001
	Biologic experienced	61.7 (41.1 to 82.4)	-	51.6 (30.9 to 72.3)	-
	Biologic naïve	29.2 (8.1 to 50.2)	-	47.8 (29.1 to 66.5)	-

Summary of AEs

A summary of slides 30 to 31

Upadacitinib no current concerns with safety profile but safety review underway for all JAK inhibitors

Most common AEs with upadacitinib:

- Inductions trials: blood CPK increase, acne and nasopharyngitis and leading to discontinuation, GI disorders
- Maintenance trial: nasopharyngitis, worsening of UC, and blood CPK increase and leading to discontinuation, GI disorders, infections and infestations

EAG clinical advisors:

- No concerns with safety profile of upadacitinib compared to other targeted therapies for inflammatory bowel disease; no need for additional monitoring during treatment

Note: TA792 (filgotinib) noted that cardiovascular AEs should have been included in model due to association

[redacted]

EMA safety review tofacitinib (June 2022)

Final results from a clinical trial of tofacitinib in rheumatoid arthritis showed people who were at risk of heart disease were more likely to experience a major cardiovascular problem and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors

As a result, EMA safety committee is carrying out a review to determine whether risks associated with tofacitinib are also associated with all JAK inhibitors authorised in the EU (including upadacitinib) for the treatment of inflammatory disorders, and whether marketing authorisations for these medicines should be amended

Adverse events

Category, %	U-ACHIEVE induction		U-ACCOMPLISH induction		U-ACHIEVE maintenance		
	Upadacitinib 45 mg (n=319)	Placebo (n=155)	Upadacitinib 45 mg (n=344)	Placebo (n=177)	Upadacitinib 15 mg (n=148)	Upadacitinib 30 mg (n=154)	Placebo (n=149)
Any AE	56	62	53	40	78	79	76
Serious adverse events	3	6	3	5	7	6	13
AE leading to discontinuation	2	9	2	5	4	6	11

- No deaths in any group
- Most common AEs with upadacitinib were blood CPK increase, acne and nasopharyngitis in induction trials and nasopharyngitis, worsening of UC, and blood CPK increase in maintenance trial
- Most common AEs leading to discontinuation were GI disorders in induction trials and GI disorders, infections and infestations in maintenance trial, all with higher rates for placebo than upadacitinib

EAG:
- Induction studies have short follow up (8 weeks)
- Clinical advisors: no concerns with safety profile of upadacitinib compared to other targeted therapies for inflammatory bowel disease; no need for additional monitoring during treatment

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; GI, gastrointestinal

JAK inhibitor safety review underway by EMA

EMA safety review tofacitinib (June 2022)

Final results from a clinical trial of tofacitinib in rheumatoid arthritis showed people who were at risk of heart disease were more likely to experience a major cardiovascular problem and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors

As a result, EMA safety committee is carrying out a review to determine whether risks associated with tofacitinib are also associated with all JAK inhibitors authorised in the EU (including upadacitinib) for the treatment of inflammatory disorders, and whether marketing authorisations for these medicines should be amended

Note: TA792 (filgotinib) noted that cardiovascular AEs should have been included in model due to association

Company has ongoing study that may provide data:

- U-ACTIVATE is a multicentre, long-term extension study to evaluate the safety, tolerability, and efficacy of upadacitinib in patients with UC up to Week 288. The study population includes patients who previously participated in completed or ongoing trials, including U-ACHIEVE and U-ACCOMPLISH induction studies, and U-ACHIEVE maintenance study

[redacted]

Summary of key issue – no direct evidence vs comparators

Trial demonstrates effectiveness, but only vs placebo

A summary of slide 33

Clinical evidence:

- Upadacitinib studied versus placebo in clinical trial, so no direct comparison against relevant comparators
- Not uncommon for this to be the case in clinical studies

Is committee satisfied that a lack of direct evidence versus relevant comparators is not unique to upadacitinib?

Tech team recommendation: company's approach is acceptable – issue is not unique to this appraisal and conducing placebo-controlled trial in line with NICE methods.

Key issue: Lack of direct evidence for the comparison of upadacitinib versus relevant comparators

EAG

- Clinical effectiveness evidence for upadacitinib is from placebo-controlled trials with no direct evidence for comparison of upadacitinib versus any relevant comparators in NICE scope
- Company NMAs generate indirect clinical effectiveness evidence for the comparisons

Company technical engagement response

- Approach in line with NICE manual; placebo controlled clinical trial design adopted in several comparator trials for therapies that have been assessed and recommended by NICE for use in UC
- Acknowledges lack of direct evidence for the comparison of upadacitinib versus relevant comparators and that the use of indirect evidence is a source of uncertainty
- Large number of relevant treatment options means that even if upadacitinib had a comparator in the control arm, this would not provide direct evidence against all relevant comparators

Stakeholder comments – UKPCA

- Lack of direct evidence between majority of relevant comparators– issue not unique to upadacitinib
- To-date only direct comparison is VARSITY trial of vedolizumab versus adalimumab

Is committee satisfied that a lack of direct evidence versus relevant comparators is not unique to upadacitinib?

Abbreviations: UC, ulcerative colitis; UKCPA, UK Clinical Pharmacy

Indirect treatment comparison

Summary of NMA methods

A summary of slide 36

Company did 9 NMAs for outcomes of clinical remission, clinical response and serious infection

Included studies:

- 2 RCTs of upadacitinib and 18 RCTs of comparators (5 of infliximab, 4 adalimumab, 3 golimumab, 2 vedolizumab, 1 ustekinumab, 3 tofacitinib); all vs placebo
- Considered bio exposed and bio naïve subpopulation for efficacy and overall population for safety
- Considered induction and maintenance studies separately

NMA outcomes:

- Odds ratio vs placebo: values closer to 1 suggest smaller difference from placebo
- SUCRA (surface under the cumulative ranking) score, which is used to rank treatments. Higher SUCRA scores correlates with better efficacy or better safety
- Predicted absolute outcome rate, which shows the predicted probability of the outcome being considered. Higher rates correlate with better efficacy, whereas lower rates correlate with better safety
- Pairwise comparisons (slides in back up): median odds ratio (OR) and credible intervals presented for each comparator versus upadacitinib, where OR of <1, favours upadacitinib

Company NMA methods

Performed 9 NMAs:

Population	Induction phase data (duration: 6-10 weeks)	Maintenance phase data (duration: 44-54 weeks)
Bio-naïve	Clinical remission, Clinical response	Clinical remission, Clinical response
Bio-experienced	Clinical remission, Clinical response	Clinical remission, Clinical response
Overall population	Serious infection	-

- NMAs included 20 RCTs (5 of infliximab, 4 adalimumab, 3 golimumab, 2 vedolizumab, 1 ustekinumab, 3 tofacitinib, 2 upadacitinib); all with common comparator – placebo
- Base case models: random effects used for all analyses except clinical response in the bio-naïve population in induction, where fixed effects with baseline-risk adjustment used
- Bio-naïve defined as: patients who had an inadequate response or intolerance to conventional therapy but had not failed biologic therapy
- Bio-exposed defined as: patients who had an inadequate response or intolerance to conventional therapy or a biologic treatment
- Sensitivity analyses of these did not materially change the results

Abbreviations: IR, inadequate response; NMA, network meta-analysis; RCT, randomised controlled trial

Summary of NMA results

A summary of slides 38 to 50

Upadacitinib point estimates often more effective than comparators, sometimes with statistical significance, but with similar low risk of serious infection

Efficacy endpoints of clinical remission and clinical response:

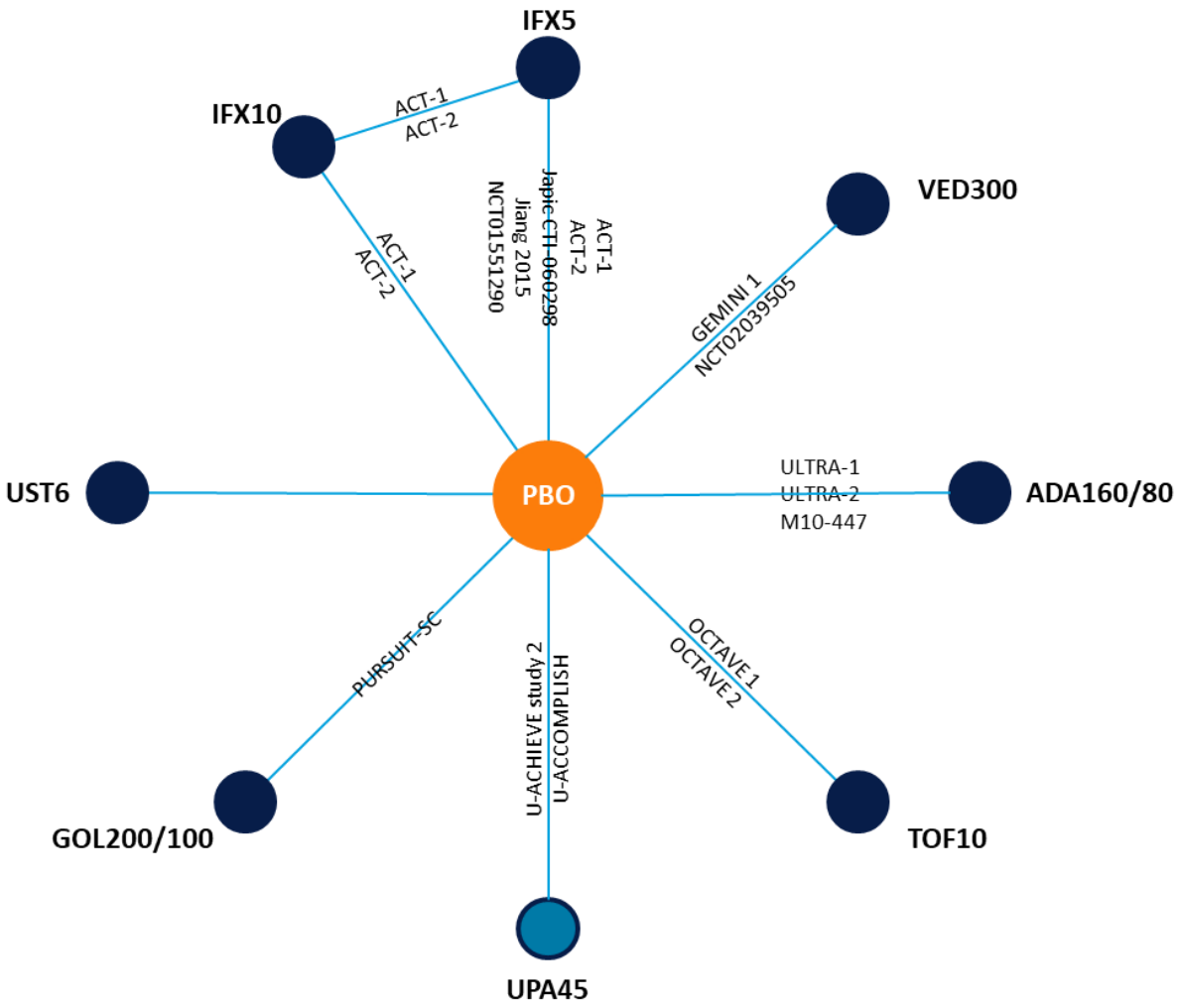
- Induction: upadacitinib is more effective than all comparators (bio naïve and bio exposed)
    - Credible intervals non-overlapping for some comparisons, so difference is statistically significant
- Maintenance: upadacitinib is more effective than most comparators in achieving clinical remission and clinical response, with some difference being statistically significant. Taking account of company and EAG analyses of pairwise comparisons, a 3 comparisons favoured tofacitinib:
    - bio naïve subpopulation – in maintenance phase, tofacitinib 5 mg or 10 mg is more effective than upadacitinib for clinical remission, and for other comparisons upadacitinib is the same or more effective
    - bio exposed subpopulation – in maintenance phase, tofacitinib 10 mg is [redacted] for clinical response, and for other comparisons upadacitinib is more effective for clinical remission and more effective than most comparators for clinical response

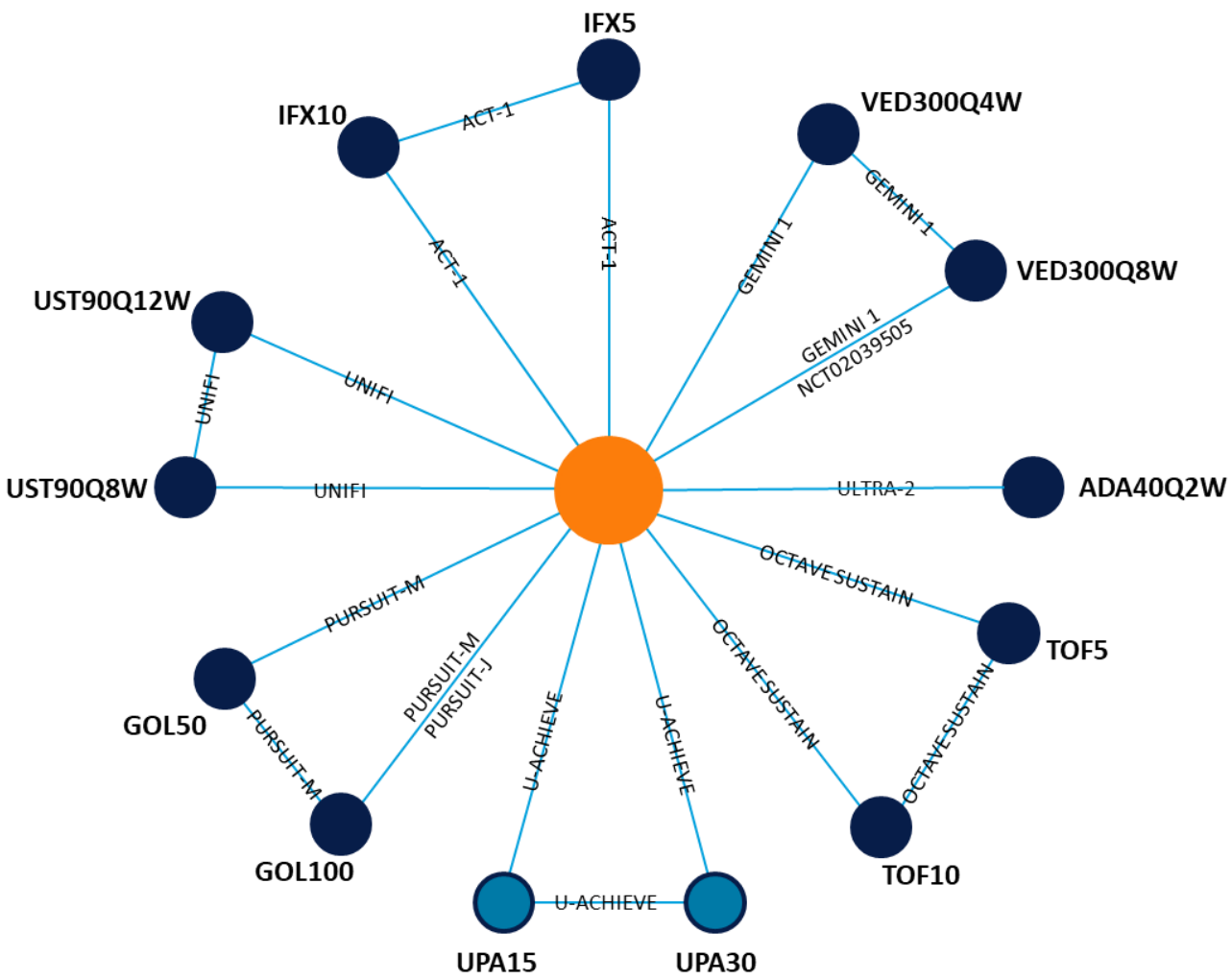
Safety endpoint of serious infections:

- Induction (only): upadacitinib has a low risk of serious infections ([redacted] probability). [redacted]

Company NMAs: bio-naïve

- **Induction:**
  - (1) Clinical remission, (2) Clinical response
- **Maintenance:**
  - (3) Clinical remission, (4) Clinical response





Abbreviations: NMA, network meta-analysis

NMA 1: clinical remission in bio-naïve induction

Upadacitinib has highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Golimumab 200/100 mg	[redacted]	[redacted]	[redacted]
Infliximab 10 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 2: clinical response in bio-naïve induction

Upadacitinib has highest probability of clinical response

- Fixed effects adjusted model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Infliximab 10 mg/kg	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Golimumab 200/100 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 3: clinical remission in bio-naïve maintenance

Upadacitinib 30 mg has 3rd highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg			
Upadacitinib 30 mg			
Vedolizumab 300 mg Q4W			
Vedolizumab 300 mg Q8W			
Upadacitinib 15 mg			
Golimumab 100 mg			
Golimumab 50 mg			
Ustekinumab 90 mg Q8W			
Ustekinumab 90 mg Q12W			
Infliximab 10 mg/kg			
Infliximab 5 mg/kg			
Adalimumab 40 mg Q2W			
Placebo			

*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

NMA 4: clinical response in bio-naïve maintenance

Upadacitinib 30 mg has highest probability of clinical response

- Random effects model

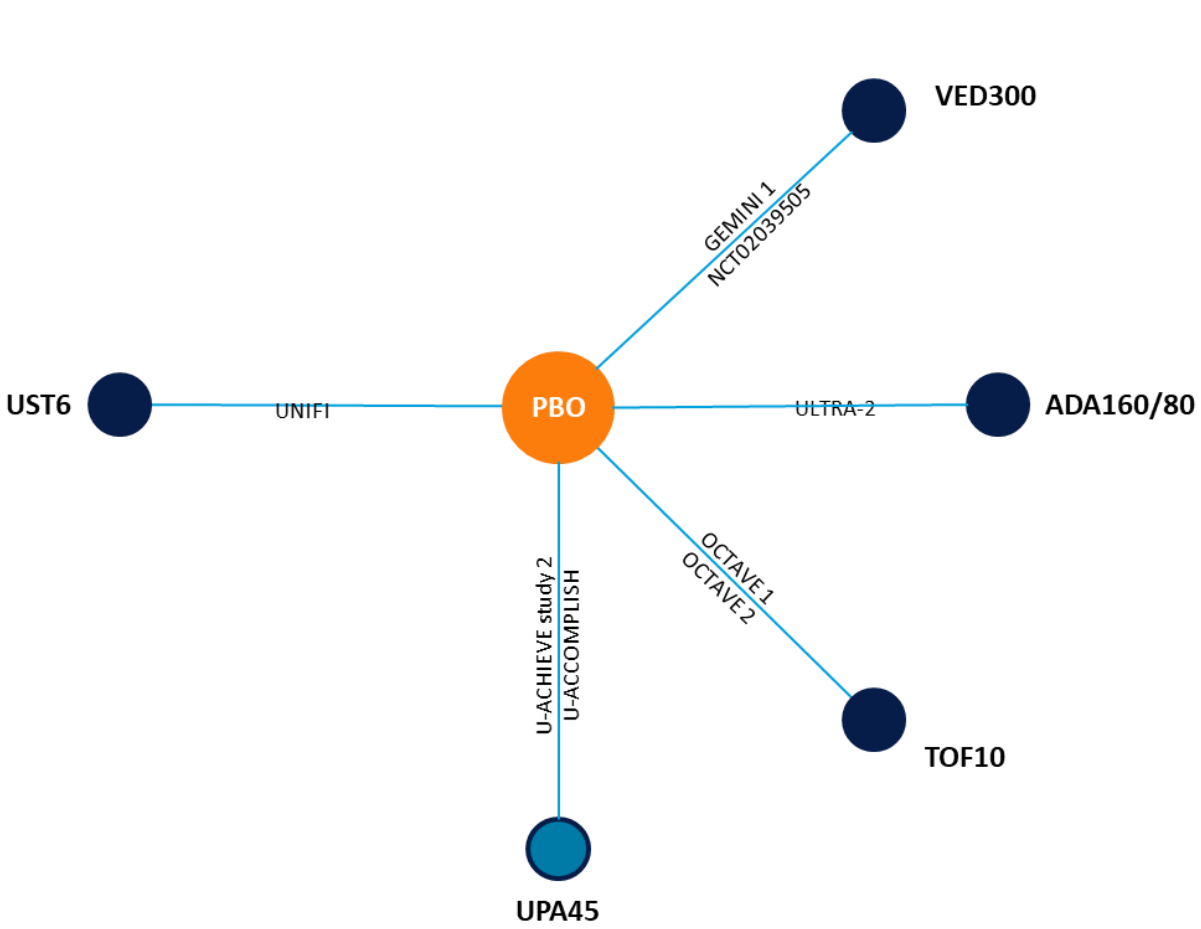
Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg			
Vedolizumab 300 mg Q8W			
Upadacitinib 15 mg			
Tofacitinib 5 mg			
Vedolizumab 300 mg Q4W			
Ustekinumab 90 mg Q8W			
Ustekinumab 90 mg Q12W			
Golimumab 100 mg			
Infliximab 10 mg/kg			
Golimumab 50 mg			
Infliximab 5 mg/kg			
Adalimumab 40 mg Q2W			
Placebo			

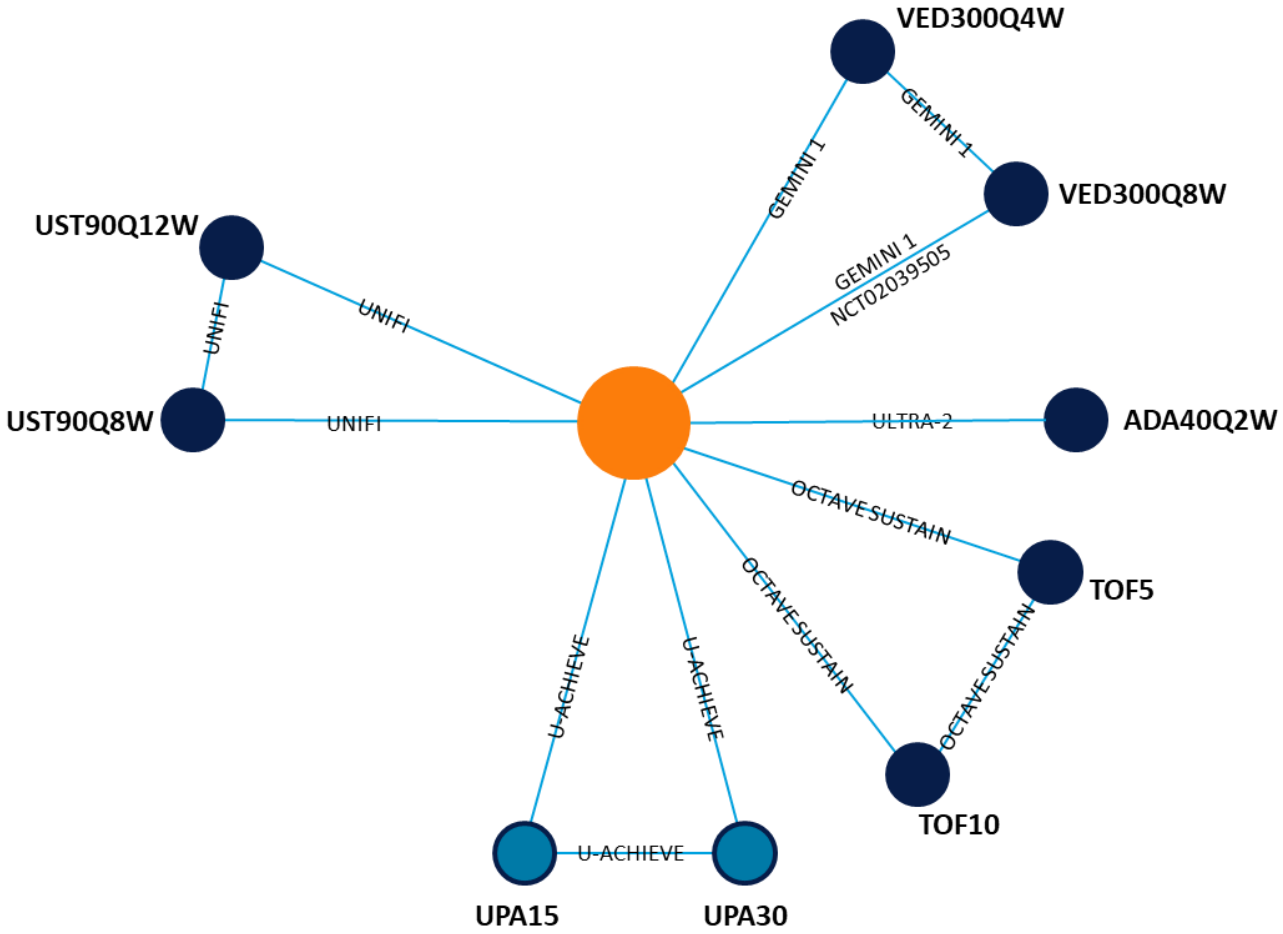
*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

Company NMAs: bio-exposed

- **Induction:**
  (5) Clinical remission, (6) Clinical response
- **Maintenance:**
  - (7) Clinical remission, (8) Clinical response





Abbreviations: NMA, network meta-analysis

NMA 5: clinical remission in bio-exposed induction

Upadacitinib has highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 6: clinical response in bio-exposed induction

Upadacitinib has highest probability of clinical response

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 7: clinical remission in bio-exposed maintenance

Upadacitinib has highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg			
Vedolizumab 300 mg Q8W			
Vedolizumab 300 mg Q4W			
Tofacitinib 10 mg			
Ustekinumab 90 mg Q8W			
Adalimumab 40 mg Q2W			
Tofacitinib 5 mg			
Ustekinumab 90 mg Q12W			
Placebo			

*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

NMA 8: clinical response in bio-exposed maintenance

Upadacitinib 30 mg has highest probability of clinical response

- Random effects model

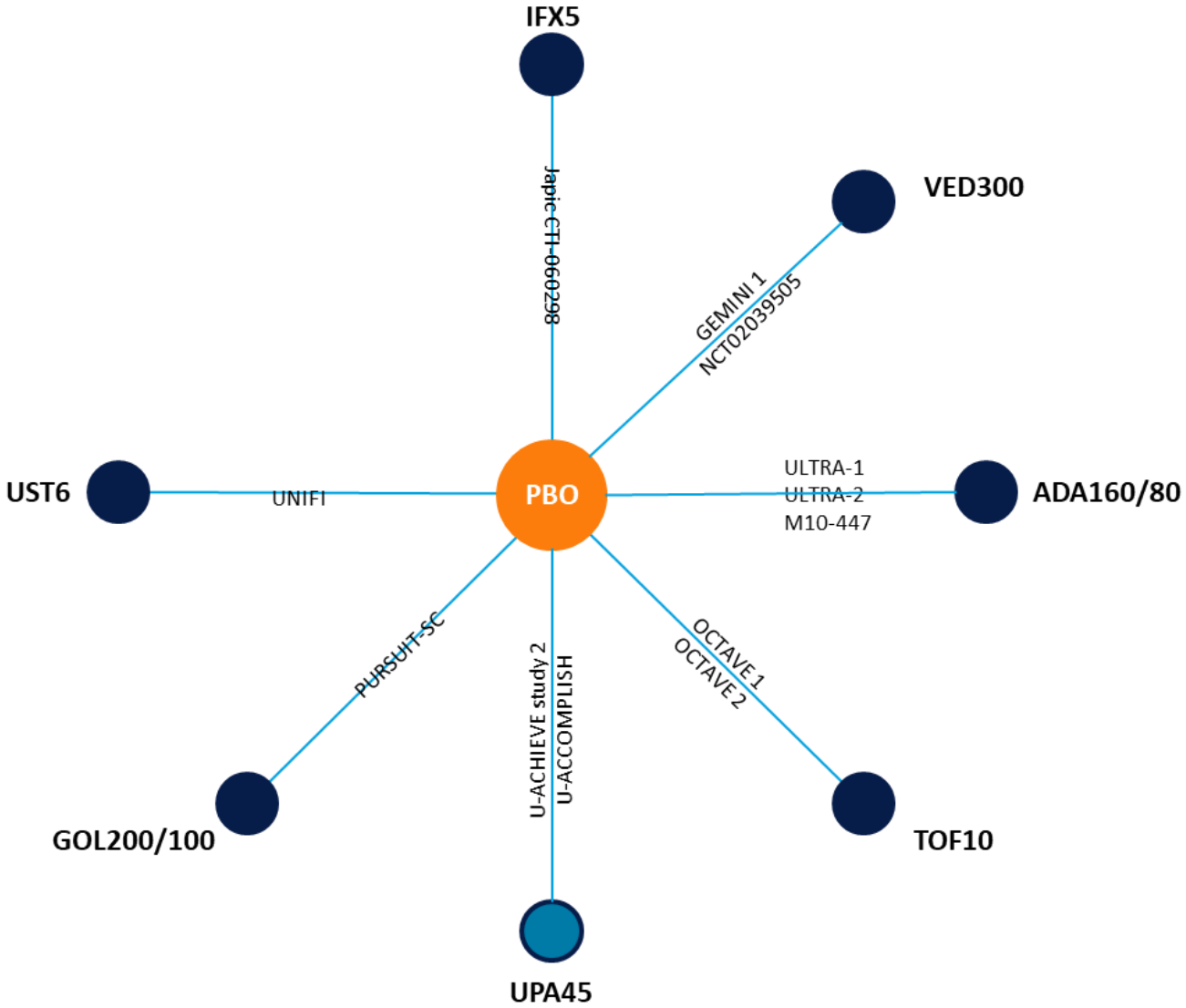
Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg			
Upadacitinib 15 mg			
Tofacitinib 5 mg			
Vedolizumab 300 mg Q8W			
Vedolizumab 300 mg Q4W			
Ustekinumab 90 mg Q8W			
Adalimumab 40 mg Q2W			
Ustekinumab 90 mg Q12W			
Placebo			

*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

Company NMA: overall population

- **Induction:** (9) Serious infection



Abbreviations: NMA, network meta-analysis

NMA 9: serious infections in overall induction

Upadacitinib has a low risk of serious infections

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Golimumab 200/100 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better safety

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

EAG's comments on company NMA results

- Induction NMAs: upadacitinib best performing vs placebo for clinical remission and clinical response
- Maintenance NMAs:
    - Upadacitinib 30mg ranked within top 3 for all outcomes
    - Upadacitinib 15mg ranked within top 4 for all outcomes (apart from maintenance/bio-naïve/clinical remission where it ranked 6th with a non-statistically significant odds ratio versus placebo)
- Company used random effects models for all NMAs except for induction/bio-naïve/response comparison where company used fixed effects adjusted (FEA) NMA model
- At clarification, company provided pairwise comparisons and EAG presented these alongside its own analyses. These identified some comparisons with other treatments that did not favour upadacitinib:
    - Maintenance/bio-exposed population, upadacitinib 15 mg: for clinical response point estimates favoured tofacitinib 10 mg
    - Maintenance phase/bio-naïve population, upadacitinib 30 mg: for clinical remission point estimates favoured tofacitinib 10 mg and tofacitinib 5 mg
- Conclusion from company's and EAG's NMAs:
    - Upadacitinib induction & maintenance treatments compared favourably with all comparators in bio-naïve and bio-exposed populations for clinical remission and clinical response
    - For most comparisons, point estimates similar, and all results that were statistically significantly different favoured upadacitinib. For many comparisons, no statistically significant differences

Abbreviations: NMA, network meta-analysis; RCT, randomised controlled trial

Summary of key issue – NMA statistical issues

A summary of slides 52 to 53

NMAs results plausible but with some uncertainty

Unresolvable issue of unclear impact:

- EAG raised 3 issues with the NMA method but was unable to suggest an alternative approach
  - consistency assumption could not be tested formally – reliability of NMA unknown
  - maintenance phase NMA results less reliable than those of induction phase – trial design and descriptions of the intervention and placebo treatments of the trials included raise unresolvable issues
  - company and EAG preferred approaches to generating NMA results differ; however, outputs similar
- EAG suggested clinical opinion is sought on plausibility and robustness of NMA results – if 3 issues of no major concern, then company NMA results should be used to inform decision making
  - Company cited 2 new published NMAs and clinical opinion to support findings that upadacitinib is consistently more effective than comparators

UKPCA and British Society of Gastroenterology: also cited evidence from the 2 new published NMAs noting these "*reached the same conclusions for moderate-severe UC… Upadacitinib ranked highest in both NMA for clinical remission and response*"

Is committee satisfied that the results of the company's NMA are plausible and suitable for decision making?

Tech team recommendation: NMAs results are plausible, so we consider upadacitinib is effective in UC, but the EAG has identified unresolvable issues which adds uncertainty.

Abbreviations: UKCPA, UK Clinical Pharmacy

Key issue: Network meta-analysis statistical issues

EAG

- Identified 3 methodological issues which cast doubt on the robustness of NMA results:
  - for all networks (induction and maintenance), the consistency assumption could not be tested formally
  - maintenance phase NMA results less reliable than those of induction phase – trial design and descriptions of the intervention and placebo treatments of the trials included raise unresolvable issues
  - company and EAG preferred approaches to generating NMA results differ; however, outputs similar
- EAG unable to suggest an alternative approach – effect of these issues on cost effectiveness is not known
- Suggest clinical opinion is sought on the plausibility and robustness of NMA results
- If 3 issues are of no major concern, then company NMA results should be used to inform decision making

Company technical engagement response

- Upadacitinib consistently shown to be most efficacious at inducing and maintaining clinical response and remission in both biologic-exposed and biologic-naïve populations, in 4 separate NMAs – Company's, EAG's, and NMAs published by Burr (2022) & Lasa (2022) (see next slide)
- Notes submission from British Society of Gastroenterology: *'The rapidity of response to treatment is impressive with upadacitinib'* and *'In addition, the high remission rates at 8 weeks are impressive'*
- Clinical advice: the RCTs included in NMAs were appropriate sources of clinical data for decision-making
- Clinical statements included: *'had 7 patients on upadacitinib in UC, all are still on drug, which is unique. Upadacitinib for the treatment of UC is as effective as most effective (infliximab) and more durable'*

References: Burr NE, et al. Gut 2022;71:1976–1987. Lasa JS, et al. Lancet Gastroenterol Hepatol 2022; 7: 161–70.
Abbreviations: RCT, randomised controlled trial; UC, ulcerative colitis; UKCPA, UK Clinical Pharmacy

Key issue: Network meta-analysis statistical issues

Stakeholder comments – UKPCA and British Society of Gastroenterology

- 2 peer reviewed published NMAs of biologics and small molecule drugs have broadly reached the same conclusions as company / EAG NMAs for moderate to severe UC:

Published NMA	Conclusions
Burr et al 2022 (28 trials)	• Upadacitinib 45 mg once daily ranked first for clinical remission in all patients, patients naïve to anti-TNF-α drugs and patients previously exposed
Lasa et al 2022 (29 trials)	• Upadacitinib best performing agent for efficacy outcomes in the overall population • Upadacitinib was more likely to be associated with non-serious AEs than comparators (but not serious AEs)

- These published NMAs also include filgotinib which has now been approved by NICE
- In clinical practice, in addition to generally sequencing the therapies, a key question is how to sequence the 3 JAK inhibitors licensed (tofacitinib, filgotinib and upadacitinib)
  - These 2 NMAs could inform the current appraisal

Is committee satisfied that the results of the company's NMA are plausible and suitable for decision making?

References: Burr NE, et al. Gut 2022;71:1976–1987. Lasa JS, et al. Lancet Gastroenterol Hepatol 2022; 7: 161–70.
Abbreviations: RCT, randomised controlled trial; UC, ulcerative colitis; UKCPA, UK Clinical Pharmacy

Cost effectiveness

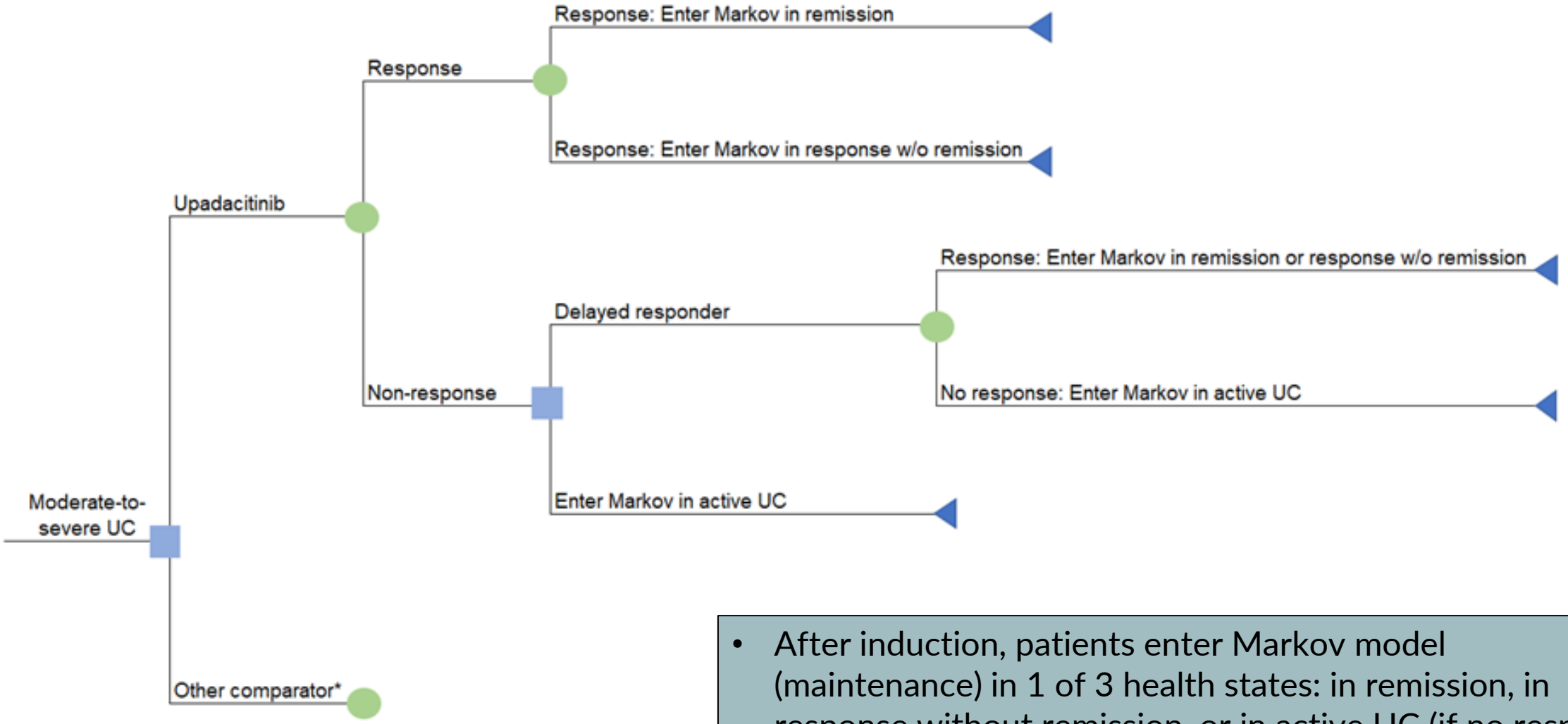
Company's hybrid decision tree (induction) and Markov model (maintenance) generally in line with previous appraisals

Company and EAG differ in base case assumptions relating to modelled treatment pathway and source for utility values

Key issues where company and EAG differ generally do not have big impact on ICER

Company's model structure (1)

- **Induction – decision tree:**

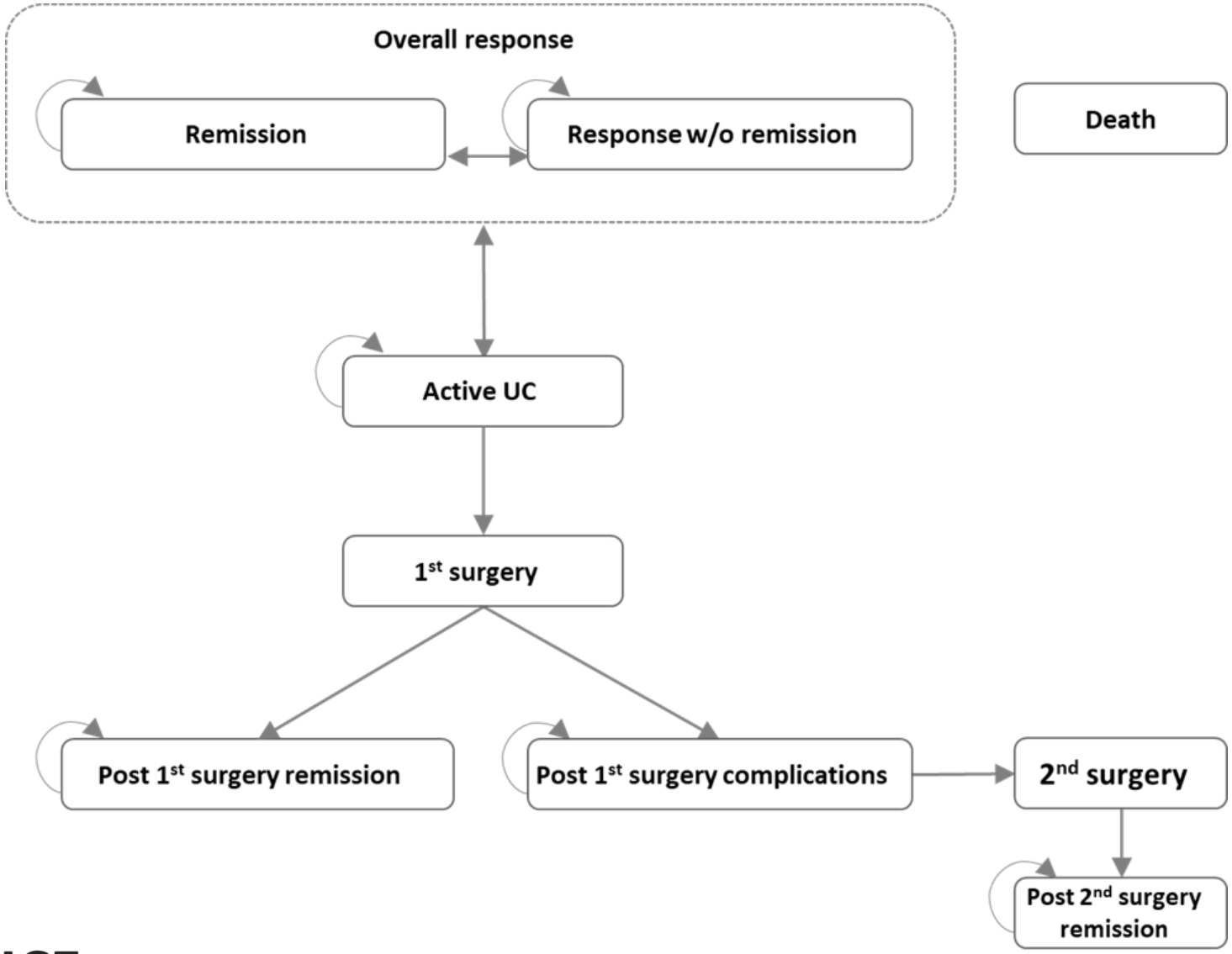


- After induction, patients enter Markov model (maintenance) in 1 of 3 health states: in remission, in response without remission, or in active UC (if no response)

Abbreviations: CT, conventional therapy; UC, ulcerative colitis; w/o without

Company's model structure (2)

- **Maintenance phase – Markov model:**



- At the end of each 4-week cycle, responders either remain on maintenance treatment (in remission or in response without remission), lose response and transition to active UC (where they receive surgery), or die

Upadacitinib affects **costs** by:

- More people with response /remission - fewer in 'active UC' accruing costs associated with this health state

Upadacitinib affects **QALYs** by:

- More people with response /remission - fewer in 'active UC' losing QALYs associated with this health state

Abbreviations: CT, conventional therapy; UC, ulcerative colitis; w/o without

Company's model *continued*
Model features generally in line with previously appraisals

Assumptions:

- Base case: patients who do not achieve a response after induction, discontinue treatment and enter maintenance in 'active UC'
- Scenario analyses for: a further line of (non-CT) treatment after treatment failure; and spontaneous remission

Features of model are generally in line with previous UC appraisals:

- Lifetime horizon (consistent with most previous appraisals)
- Model structure is hybrid decision tree-Markov model (consistent with previous appraisals)
- Cycle length of 4 weeks (previous appraisals consider 2 to 8 weeks)
- Treatment waning effect – no (consistent with previous appraisals)
- Source of utilities was published literature (consistent with most recent TA633 of ustekinumab)
- Source of costs consistent with previous appraisals and updated to most recent year
- Discounting: costs and QALYs accrued after the first year are discounted at an annual rate of 3.5%
- Adverse effects of treatment considered serious infection (consistent with previous appraisals, although TA792 (filgotinib) noted that cardiovascular AEs should also have been included)
- Stopping rule – no (consistent with recent appraisals)
- Spontaneous remission – no (consistent with previous appraisals)

Abbreviations: CT, conventional therapy; UC, ulcerative colitis; w/o without

Summary of company and ERG base case assumptions and key scenarios after technical engagement

Assumption	Company base case	ERG base case	Company and EAG agree?
Modelled treatment pathway (induction or maintenance)	Non-responders enter 'active UC' health state • Scenario analyses of second line treatment option, and time horizons of 2 years and 5 years	Non-responders enter 'on subsequent treatment' health state • Scenario analysis of company's base case but assuming higher rates of surgery	No
Source of utility values for response, remission and active UC health states	Published evidence (Woehl 2008) • Scenario analyses of other published evidence sources and upadacitinib trial-based data	Upadacitinib trial-based data (higher values than in published evidence)	No
Upadacitinib given at 70:30 ratio of 15 mg (standard) to 30 mg (high) maintenance doses	Adopts 70:30 ratio	Adopts 70:30 ratio	Yes

Abbreviations: UC, ulcerative colitis

How company incorporated evidence into model

Input	Company	EAG comment
Baseline characteristics	Upadacitinib induction trials	Agrees with approach
Efficacy estimates	Induction phase – NMA results Maintenance phase – NMA results	Has concerns with maintenance phase NMAs but has not been able to identify more certain estimates
Adverse events	Modelled serious infections only due to high costs, consistent with TA547 and TA633 Induction phase only – NMA results	Agrees with approach
Utilities	From Woehl et al (2008), except surgery and post-surgery complications (Arseneau 2006) • Adjusted for age and gender • Applied disutility for effect of serious infections on HRQoL	Not in line with NICE reference case. Prefers EQ-5D data from upadacitinib trials • Effect of serious infections on HRQoL already incorporated
Costs and resource use	From published literature, previous NICE submissions, NHS Reference Costs for 2019/20 and BNF Includes drug acquisition, administration, management of adverse events, surgery, and background disease management	Number of consultant contacts in response / remission health states are likely overestimated but negligible effect on cost effectiveness results
Mortality	UK general population (ONS data), with 30% excess risk of death for surgery health states	Agrees with approach

Abbreviations: BNF, British National Formulary; NMA, network meta-analysis; ONS, Office for National Statistics SC, subcutaneous

Description of Company's modelled health states

Health state	Definition
Remission	Full Mayo score of 0-2 points with no individual subscore >1
Response without remission	• Not meeting remission definition, and • Decrease from baseline in Mayo score of ≥30% and ≥3 points, and • Decrease from baseline in the rectal bleeding subscore of ≥1, or an absolute rectal bleeding subscore of 0 or 1
Active ulcerative colitis	Full Mayo score of 6-12 (remission or remission without response not achieved)
First surgery	First surgical intervention to resolve UC (assumed duration of 6 months); could include acute complications
Post-first surgery remission	No chronic complications from first surgery
Post-first surgery complications	Chronic complications from first surgery such as wound infection, bowel obstruction, intra-abdominal abscess, or anastomotic leak
Second surgery	Second surgical intervention due to pouch failure (assumed duration of 6 months); could include acute complications
Post-second surgery remission	No chronic complications from second surgery
Death	Absorbing state

Abbreviations: UC, ulcerative colitis

Summary of key issue – modelled treatment pathway (1)

Company and EAG differ although does not have big impact on ICER

A summary of slides 63 to 69

Company vs EAG approach:

- Company consider only 1 line of treatment. If this fails, patients enter 'active UC' health state
  - Consistent with newest appraisal at time of submisssion – TA633 (ustekinumab) – however, here committee would have preferred additional health states in the model to account for patients who had long-term treatment with corticosteroids
  - Different approach in recent filgotinib appraisal (TA792) – model included a 'last line of conventional therapy' for people who failed advanced treatment and were in active UC – committee considered model appropriate
- Company explored adding 2nd line of treatment (ustekinumab) after failure in a scenario analysis – no big impact on ICER
- EAG note that by the end of 2 years, most patients who received any treatment end up in 'active UC' health state. The only way to leave then is by having surgery or dying, and surgery rates are low
  - Company's model treatment pathway does not reflect NHS clinical practice and results in most modelled patients, regardless of treatment, ending up in active UC health state for many decades with no active treatment and with low HRQoL
  - Instead models 'On subsequent treatment' health state for any subsequent therapy (but not surgery), which more accurately reflects NHS practice

Summary of key issue – modelled treatment pathway (2)

Company and EAG differ although does not have big impact on ICER

A summary of slides 63 to 69

Company disagrees with EAG's approach in 3 areas:

- (a) Inclusion of further drug after failure
  - In EAG model, people who fail treatment move to a 'basket of treatments' instead of active UC
  - Company notes that when modelling treatment sequences, each additional line of treatment introduces uncertainty. It has explored a 2nd line treatment option in a scenario analysis
- (b) Validity of efficacy estimates for further drug treatment after failure:
  - Company disagrees with the way EAG has incorporated efficacy estimates into its model when considering people receiving 'basket of treatments' and disagrees that surgery is not included
- (c) Utility values unrealistic particularly in longer term
  - Company notes that any reduction in quality of life that patients who fail treatment may experience is not taken into account for people receiving 'basket of treatments'
- Overall impact of EAG's preferred approach on ICER – upadacitinib dominates

Which modelled health state most reflects NHS clinical practice for patients who lose response, 'active UC' (company) or 'on subsequent treatment' (EAG)?

Tech team recommendation: company's approach in line with recent appraisals, pros and cons to both company and EAG approach. Company and EAG base cases differ on this issue, but has little impact on ICER overall

Key issue: Modelled treatment pathway not a good reflection on NHS practice

Background

- Company's model considers only 1 line of treatment, so patients who have not had an adequate response (induction) or who stop responding (maintenance) enter the active UC health state
- Same maintenance treatment pathway used in models that informed previous NICE appraisals (TA342 [vedolizumab] and TA633 [ustekinumab]), but committee have expressed a preference for modelling of subsequent therapy (TA633) including conventional therapy 9TA792 [filgotinib])
  - Annual probability of 1st and 2nd surgery of 0.5% from Misra et al (2016) and proportion of surgeries that resulted in post-surgery complications (33.5%) from UK clinical audit

ERG comments

- Company's modelled treatment pathway does not reflect NHS clinical practice and results in most patients, regardless of treatment, ending up in active UC health state for many decades with no active treatment
  - By the end of 2 years, most patients (bio-naïve or bio-exposed) who received any treatment end up in active UC health state
  - The only way for a patient to leave the active UC state is by having surgery or dying
  - As only 1 in ~200 (0.5%) patients in active UC health state have surgery each year, this means that most people in the active UC health state remain there until they die
  - Patients in active UC health state experience a low HRQoL (0.41) and are likely to be hospitalised

Abbreviations: HRQoL, health-related quality of life; UC, ulcerative colitis

Key issue: Modelled treatment pathway not a good reflection on NHS practice

ERG comments *continued*

- Clinical advice: patients with active UC treated in NHS clinical practice are either offered surgery within 12 months or are prescribed the treatment which previously gave them the best symptom alleviation, even if the patient was not considered to have responded to this treatment
- EAG has modelled an alternative pathway that more closely represents NHS clinical practice, to replace the company's 'active ulcerative colitis' heath state:

EAG's alternative 'On subsequent treatment' modelled heath state
• Patients who have achieved remission on a treatment after having failed to achieve remission on earlier treatment(s), and • Patients who have failed to achieve long-term remission on any drug and are unwilling or unsuitable for surgery and therefore are indefinitely prescribed the treatment which gave them the most symptom alleviation (without achieving remission) • Patients can receive a basket of biologic treatments, but not surgery

- This approach negates the need for the second-line therapy option within the company model (scenario analysis) or the introduction of a model with multiple lines of biologic treatments
  - Proportions of treatments used in EAG modelled pathway based on company's market share data
  - Efficacy assumptions based on NMA results for those treatments (response, remission)

Abbreviations: UC, ulcerative colitis

Key issue: Modelled treatment pathway not a good reflection on NHS practice

Company technical engagement response

- Company model suitable for addressing NICE decision problem and is aligned with previous appraisals in UC
  - Scope of appraisal is not to determine the most cost-effective treatment sequence among hundreds of possible permutations
- Provides new scenarios including those considering shorter time horizons of 2 years and 5 years, time points at which a large proportion of the patient cohort has entered the active UC health state
  - Upadacitinib remained dominant or highly cost effective versus all comparators in both the bio-naïve and bio-exposed scenarios – expected since clinical and quality-of-life benefits from upadacitinib treatment are accrued in the remission and response health states
  - Incremental benefit of upadacitinib derived from disease control through clinically important outcomes documented in clinical trials – BSG submission describes it as a step change in management
- Concerns about EAGs approach regarding: (a) treatment sequencing; (b) efficacy estimates; (c) utility values (more detail on next slides)

ERG critique

- Clinical advice: company's model does not capture current experience of NHS patients and describes a treatment pathway that may be considered unethical by patients and health care professionals

Abbreviations: BSG, British Society of Gastroenterology; UC, ulcerative colitis

Key issue: Modelled treatment pathway
(a) inclusion of further drug after failure:

Background
- Company consider only 1 line of treatment. If this fails, patients enter 'active UC' health state
- Consistent with newest appraisal at time of submisssion – TA633 (ustekinumab) – however, here committee would have preferred additional health states in the model to account for patients who had long-term treatment with corticosteroids
- Different approach in recent filgotinib appraisal (TA792)– model included a 'last line of conventional therapy' for people who failed advanced treatment and were in active UC – committee considered model appropriate

Company technical engagement response
- Choice of treatment after 1st biologic is complex clinical decision and individualised to patient
- When modelling treatment sequences, each additional line introduces uncertainty into decision making
- Company's model allows treatment sequencing to be explored in a scenario analysis

ERG critique
- While 'basket of treatments' is not perfect, clinical advice is that it more accurately represents NHS clinical practice than company's model
- Lifetime time horizon and including subsequent treatments in line with NICE reference case
- 'Basket of treatments' is not treatment sequencing
- Clinical advice: most patients do not spend long in 'active UC', instead managed with drug treatments

Abbreviations: UC, ulcerative colitis

Key issue: Modelled treatment pathway
(b) validity of efficacy estimates for further drug treatment:

Company technical engagement response

- EAG approach lacks face validity:
  - Assumes bio exposed population has same levels of clinical efficacy and utility as bio-naïve population
  - Assumes patients who have failed all treatments default back to 'the best one' and achieve same level of efficacy as first time they received it before failing
  - No consideration of surgery from this 'basket' health state, so not aligned with clinical practice, and assumes that patients will be on drug treatment until death
- Clinical experts state, and trial data show, that each additional line of treatment has a reduction in efficacy
  - Use of bio-naïve efficacy data inaccurate, overestimates effectiveness of subsequent biologic treatment
  - Since EAG's 'on subsequent treatment' health state includes all treatments, this benefits treatments with worse efficacy as it will be beneficial to fail 1st treatment in sequence
  - Also cancels out any benefit gained by more effective treatment, such as upadacitinib, when calculating ICERs, as upadacitinib is included in 'basket of treatments'
- Biologic-exposed population in upadacitinib UC trials included subjects who had ≥1 biologic previously of whom 37.5%, 37.9%, 19.5% and 5% had failed 1, 2, 3 or ≥4 biologics, respectively
  - Therefore, bio-exposed population data used in company's model is representative of clinical efficacy across multiple lines of biologic treatments and is a conservative interpretation of cost effectiveness

Abbreviations: UC, ulcerative colitis

Key issue: Modelled treatment pathway
(b) validity of efficacy estimates for further drug treatment:

ERG critique

- EAG has produced a scenario where treatment efficacy data for the bio-exposed population (where available) have been used to estimate the efficacy of the basket of treatments
- Clinical advice: surgery is a rare event for people who start on biologic therapy and inclusion in the model is therefore unlikely to make a significant difference to the estimates of cost effectiveness
  - Cost of surgery and the utility benefit from surgery mean that surgery is a highly cost effective treatment option
  - More patients treated with a comparator end up in basket of treatment health state than patients treated with upadacitinib, so if surgery was incorporated into basket of treatments health state, the ICERs per QALY gained for the comparison of upadacitinib versus all treatments would increase
- Modelling a basket of treatments is not without limitations; however, EAG consider that this approach more closely reflects NHS practice than company's modelling approach, and therefore provides more reliable ICERs per QALY gained
  - Proportions of treatments used in EAG modelled pathway based on company's market share data
  - Efficacy assumptions based on NMA results for those treatments (response, remission)

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UC, ulcerative colitis

Key issue: Modelled treatment pathway
(c) utility values after treatment failure:

Background
- Company's base case model uses an 'active UC' health state after treatment failure, while the EAG model uses an alternative 'on subsequent treatment' health state it its base case

Company technical engagement response
- Utility value applied to EAG's 'on subsequent treatment' health state is a weighted average of values for remission and response without remission from upadacitinib UC trials. As such, all patients in the EAG model have a utility value at least equal to the utility value associated with response to treatment until death
- Company considers that patients who lose response to treatment (relapse) would have experienced a decrease in their quality of life due to disease symptoms, more aligned with the 'active UC' health state
  - Clinicians noted: 'If untreated, a 40-50% reduction in quality of life would be expected for moderate-to-severe UC. Work will be severely impacted …increased impact on joblessness, social life, relationships'

ERG critique
- Clinical advice: in contrast to company model outcomes, most NHS patients who are treated with pharmacological treatment do not have 'active UC'
  - Therefore, they will not incur the QALYs (and costs) modelled by the company for patients with active UC – EAG considers the use of remission and response utility values is appropriate

Which modelled health state most reflects NHS clinical practice for patients who lose response, 'active UC' (company) or 'on subsequent treatment' (EAG)?

Abbreviations: QALY, quality-adjusted life year; UC, ulcerative colitis

Summary of key issue – utility values

A summary of slides 71 to 72

Company and EAG have different preferences although does not have a big impact on ICER

Company vs EAG approach:

- Company use utility values from published sources and explore impact of alternative using alternative published sources for the data and using upadacitinib trial data = all have little impact on ICER
    - In most recent appraisal at time of submisssion – TA633 (ustekinumab) – the NICE committee noted patient expert's reflections on utility values, stating that it is possible some effects on quality of life (such as feeling out of control) may not be captured in trials
- EAG uses higher utility values, from upadacitinib trail base data in its preferred base case – in line with NICE reference case. Impact of EAG's preferred approach – small increase in ICER
- Note: in previous appraisals, the committee have questioned use of utility data from published sources when trial data is available (e.g. TA547 [tofacitinib] and TA633 [ustekinumab]), and in TA633 noted the Woehl et al. 2008 data had been a source of controversy in all the previous appraisals

Which source of utilities data does the committee prefer?

Tech team recommendation: company and EAG base cases differ on this issue, and previously company approach has been preferred, but it has little impact on ICER overall, so choice does not have big impact.

Key issue: Company choice of utility values

ERG comments

- In line with NICE reference case, EAG provides scenario using EQ-5D data collected in 3 upadacitinib trials – this is adopted as EAG preferred base case
- Clinical opinion needed to determine most realistic utility values for use in company model

Health state	Subgroup	Company preferred: published utility values (Woehl 2008)	EAG preferred: upadacitinib trial-based utility values
Remission	Bio-naïve	0.87	[redacted]
Response without remission		0.76	[redacted]
Active UC		0.41	[redacted]
Remission	Bio-exposed	0.87	[redacted]
Response without remission		0.76	[redacted]
Active UC		0.41	[redacted]

Company technical engagement response

- Clinical experts and company consider utility data collected in a trial is likely to underestimate true quality of life burden experienced by patients with UC, especially in active UC health state with limited trial follow-up
  - *'being in a trial [benefits] QoL … patients feel rewarded by increased interactions with a dedicated team'*
  - *'would like to see multiple years of QoL data… reasonable to use observational data where this not available'*

Abbreviations: QoL, quality of life; UC, ulcerative colitis

Key issue: Company choice of utility values

Company technical engagement response *continued*

- In TA633 (ustekinumab), the NICE committee noted patient expert's reflections on utility values, stating that it is possible some effects on quality of life (such as feeling out of control) may not be captured in trials
  - Also reflected in the statements on patient experience of UC in Crohn's and Colitis UK's TE submission
- New scenarios to support company submission, testing several utility data sources: Swinburn et al (2012), Vaizey et al (2014), and utility data collected in upadacitinib UC trials
  - Upadacitinib remained dominant or highly cost effective versus all comparators in these scenario analyses in both the bio-naïve and bio-exposed populations

Tech team note

- In several previous appraisals, the committee have questioned use of utility data from published sources when trial data is available (e.g. TA547 [tofacitinib] and TA633 [ustekinumab]), and in TA633 noted the Woehl et al. 2008 data had been a source of controversy in all the previous appraisals

Which source of utilities data does the committee prefer?

Abbreviations: UC, ulcerative colitis

Company's model – intervention and comparators

- **Intervention:**
  - Induction: upadacitinib 45 mg once daily
  - Maintenance: upadacitinib 15 mg ('standard') and 30 mg ('high') once-daily
- **Comparators:**

Comparator	Bio-naïve population	Bio-exposed population
Adalimumab (and biosimilar)	Included	Included
Golimumab	Included	Excluded
Infliximab (and biosimilar)	Included	Excluded
Tofacitinib	Included	Included
Ustekinumab	Included	Included
Vedolizumab†	Included	Included

†Data for vedolizumab IV applied to vedolizumab SC

- All comparator drugs assumed to be prescribed in 70:30 ratio of 'standard' to 'high' maintenance doses
  - Consistent with the assumption made in TA633 (ustekinumab) that 30% of patients have escalated doses of maintenance treatment
- Upadacitinib also assumed to be prescribed in 70:30 ratio of 'standard' to 'high' maintenance doses – *Key issue resolved after TE*

Abbreviations: IV, intravenous; NMA, network meta-analysis; SC, subcutaneous

Summary of key issue – high / low doses of upadacitinib

Note: issue now resolved

A summary of slide 75

Company presented high/low maintenance dose as 2 separate analyses, EAG considered there would be a mix of doses in practice, company agreed

Upadacitinib maintenance doses:

- Company initially presented separate analyses for 15 mg and 30 mg maintenance doses of upadacitinib
- EAG assumed a 70:30 ratio of these upadacitinib doses would be used, in line with what was being assumed for standard and high doses of comparators
- Company agreed and presented subsequent analyses adopting 70:30 ratio for upadacitinib maintenance dosing

Tech team recommendation: no further discussion needed.

Key issue: high and low doses of upadacitinib maintenance treatments – *resolved after technical engagement*

EAG comments

- All comparator drugs assumed to be prescribed in 70:30 ratio of 'standard' to 'high' maintenance doses in company's model
- Assumption reasonable for comparators treatments, but results in inconsistency for comparison with upadacitinib
- Clinical advice to EAG is that whilst the proportion of patients who will be prescribed high dose upadacitinib maintenance therapy in clinical practice is currently unknown, an assumption of 70:30 ratio of standard to high maintenance doses is not unreasonable
- EAG prefers results from company scenario using this ratio for all treatments is relevant to decision makers

Company technical engagement response

- Provided updated probabilistic base-case analyses with a 70:30 dose split between the 15 mg and 30 mg upadacitinib maintenance doses to align with comparators
- Clinical advisors to company considered this assumption was plausible
- Deterministic analysis of 15 mg and 30 mg were conducted for completeness and as recognition that the Committee may find these useful as supporting information for decision making.

Summary of additional issue – surgery rates

A summary of slides 77 to 79

Company and EAG have different preferences, which has a moderate impact on ICER in company's preferred base case only
However, no surgery in EAG's preferred approach so not relevant here

Company vs EAG approach:

- Note: EAG's preferred model uses an alternative 'on subsequent treatment' health state in its base case which does not include surgery as an option (was not possible with the modelling), so this issue relates only to company's preferred model where people enter the 'active UC' health state
- EAG and company differ in the rates of surgery that should be assumed for patients who leave the company's modelled 'active UC' health state
    - Company assumes 0.5% of patients in 'active UC' health state will have surgery each year
    - EAG prefers to assume that ~50% of patients in 'active UC' health state will have surgery because 0.5% assumed by company relates to *all* patients with UC (not just those in active UC)
- EAG notes that new published evidence provided by company that colectomy rates are declining, provide further support for EAG's preferred model where an 'on subsequent treat' health state is used

Which source of surgery data does the committee prefer?

Tech team recommendation: In company's base case (only), the issue has a moderate impact on ICER overall but upadacitinib remains a cost-effective treatment so choice does not have big impact. If committee prefers the EAG base case and modelled treatment pathway (see earlier key issue) then no further discussion needed.

Additional issue: Surgery rates assumed by EAG higher than assumed by company

EAG comments

- In the company model, 0.5% of patients in the active UC health state receive surgery each year
  - The company converted this rate to a probability per cycle of 1st surgery for patients in the active UC health state. The same rate was also used for the probability of a patient undergoing a 2nd revision surgery after being left with complications following the 1st surgery
- Clinical advice to EAG is that:
  - ~50% of patients who do not respond to active treatments will undergo surgical procedures, and
  - the other ~50% of patients are offered surgery but choose not to have it – these patients are likely to continue the treatment that provided best symptom alleviation, even if it did not constitute response
- EAG considers that, in the company's modelled treatment pathway, the rate of surgical procedures used for patients in the active UC health state is too low - 0.5% is the rate for *all* people with UC (not just those in active UC)
  - Assessed impact of using higher surgery rates for patients in active UC state, by running scenarios using a 50% annual rate of 1st surgery and a 100% annual rate of 2nd revision surgery

Company technical engagement response

- EAG's scenario analysis in which 50% of patients with active UC progress to surgery each year conflicts with published literature
  - Clinical expert opinion: lifetime risk of colectomy associated with UC is ~25%

Abbreviations: UC, ulcerative colitis

Additional issue: Surgery rates assumed by EAG higher than assumed by company

Company technical engagement response *continued*

- Company's assumption that 0.5% of patients in the active UC health state receive surgery each year is based on based on HES data, is further validated by clinical expert opinion, and is the most reliable data source to inform the probability of surgery in the model
- There has been a reduction in colectomy rates over time, likely due to more advanced treatments, indicating that the surgical rates assumed by the company could be higher than they would be in 2022
  - Worsley et al (2020) showed that patients with UC, admitted for active disease during 2013-2016 had significantly lower cumulative probability of colectomy compared to patients admitted during 2003-2007 or 2008-2012 (based on HES data)
  - Another study looked at the reduction of surgery for UC, showing that between 2005 and 2018 yearly colectomy rates per 100 UC patients fell from 1.47 to 0.44 ($p<0.001$) (Jenkinson 2021)
  - Therefore, the EAG scenario for surgery is not relevant for this decision problem

EAG comments after technical engagement

- To estimate a colectomy rate, the company used HES data from patients who were admitted to hospital and had a UC diagnosis, but the 'active UC' health state in the company model represents patients who are not responding to pharmacological therapy, have a low quality of life and high resource use

Abbreviations: HES, Hospital Episode Statistics; UC, ulcerative colitis

Additional issue: Surgery rates assumed by EAG higher than assumed by company

EAG comments after technical engagement *continued*

- Clinical advice to the EAG is that all patients in the active UC health state (unless contraindicated) would be offered surgery in NHS clinical practice, of these ~50% would be ineligible or choose not to have surgery
- The Jenkinson (2021) study identified by the company highlights how increasingly rare colectomy rates have become for patients with UC since the introduction of biological therapies in the NHS
  - This provides evidence to support the EAG's 'basket of treatments' modelling approach as it indicates that most patients with UC are managed with pharmacological therapy
- EAG's preferred model using 'on subsequent treatment' health state does not include surgery as an option as it was not possible with the modelling

Which source of surgery data does the committee prefer?

Abbreviations: HES, Hospital Episode Statistics; UC, ulcerative colitis

Key issues

Issue	Resolved?	Tech team view	ICER impact
No direct evidence vs comparators – *influenced by confidence in NMA results*	No – cannot be resolved	Company approach acceptable	Unknown
NMA statistical issues – *plausibility and suitability of NMA results*	No – for discussion	NMAs results plausible but some uncertainty	Unknown
Modelled treatment pathway – *does not represent NHS practice*	No – for discussion	Choice does not have big impact	Small
Utility values – *trial utilities available, but not used in company base case*	No – for discussion	Choice does not have big impact	Small
High and low doses of upadacitinib maintenance treatments - *different doses with different costs available; what is used in NHS?*	Yes	No further discussion needed	Small

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

Additional issue after technical engagement

Issue	Resolved?	Tech team view	ICER impact
Surgery rates – *only relates to company base case (not EAGs)*	No – for discussion	Choice does not have big impact	Moderate 

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

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Thank you.