For committee only – contains ACIC

Mirikizumab for treating moderately to severely active ulcerative colitis

Briefing for streamlined cost comparison

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Company: Eli Lilly

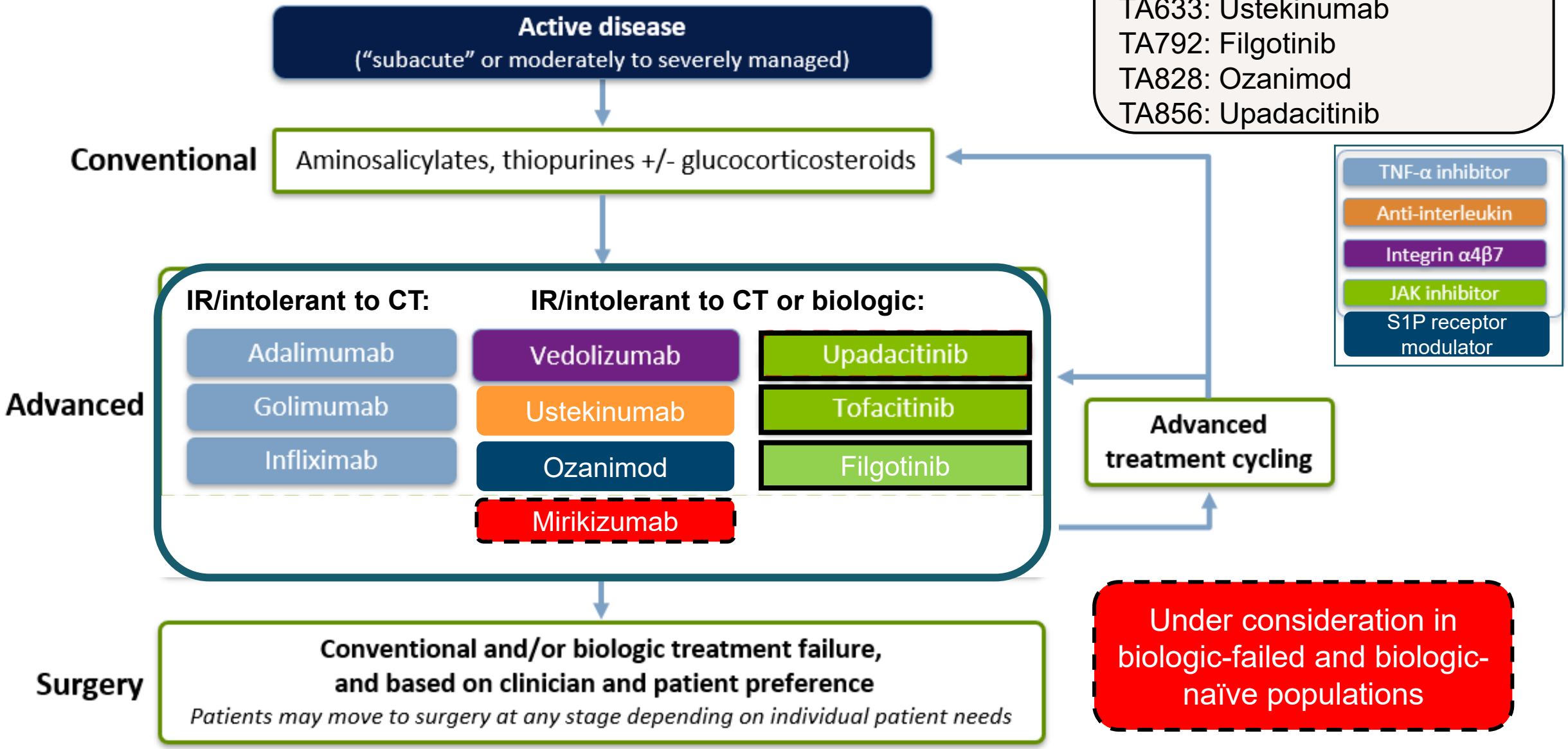
Mirikizumab (Omvoh, Eli Lilly)

Marketing authorisation (GB)	For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment
Mechanism of action	Humanized monoclonal antibody that inhibits the activity of interleukin-23 to reduce the inflammatory processes underlying ulcerative colitis
Administration	Induction: 300 mg by intravenous infusion at weeks 0, 4 and 8 Maintenance: 200 mg by subcutaneous injection every 4 weeks following induction phase
Price	• The list price is [redacted] per 300 mg vial for intravenous infusion (induction) or [redacted] per 2-pack of 100 mg pre-filled syringes or pens for subcutaneous injection • Company has a confidential commercial arrangement (simple discount PAS)

Abbreviations: GB: Great Britain; PAS: Patient access scheme

Ulcerative colitis treatment pathway

TA329: TNF-alpha inhibitors
TA342: Vedolizumab
TA547: Tofacitinib
TA633: Ustekinumab
TA792: Filgotinib
TA828: Ozanimod
TA856: Upadacitinib



Under consideration in biologic-failed and biologic-naïve populations

NICE

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

Overview of suitability for streamlined cost comparison

- Mirizumab was routed as a PATT cost comparison – similar or better clinical efficacy for treating moderately to severely active ulcerative colitis (UC) than the company's chosen comparators, ustekinumab and vedolizumab
- Suitability for cost-comparison routing was not assessed during scoping stage but the EAG confirms that company's argument is supported by the evidence in the company submission
- **No critical issues** have been identified by the EAG to prevent a streamlined cost comparison approach
- Based on the results of a network meta-analyses (NMA), mirikizumab appears to have [redacted], treatment effects in induction and maintenance and a similar safety profile to, vedolizumab and ustekinumab
- Model structure and key assumptions are appropriate (consistent with NICE ustekinumab appraisal, TA633)
- Cost differences between mirikizumab and comparators most sensitive to assumptions about re-induction rates and delayed response assessment – explored in scenario analysis
- A positive recommendation would not incur a significant budget impact. It is believed that the [redacted]

Abbreviations: PATT: Proportionate approach to technology appraisals; TA: Technology appraisal

Mirikizumab clinical effectiveness – LUCENT-1

- Phase 3, randomised controlled trial (RCT) evaluating efficacy and safety of mirikizumab versus placebo over a **12-week induction period**
- Primary outcome: **Clinical remission at week 12**

Clinical remission at week 12 (mITT population)

Source: Company submission document B, B.3.6.1.1, figure 7

A statistically significant greater percentage of patients achieved clinical remission at week 12 with mirikizumab group versus placebo

- **Clinical remission at week 12** is defined as achieving a modified Mayo score (MMS) subscore for rectal bleeding=0, stool frequency=0 or 1 with ≥ 1 point decrease from baseline, and endoscopy=0 or 1 (excluding friability), excluding consideration of Physician's Global Assessment
- **mITT** is defined as all randomized participants who received at least one dose of study drug and who had the MMS measured correctly at baseline. Participants were analysed per their assigned treatment arm regardless of the actual treatment received

NICE

Abbreviations: mITT: modified intention-to-treat

Mirikizumab clinical effectiveness – LUCENT-2

- Phase 3, RCT evaluating efficacy and safety of mirikizumabversus placebo in **maintaining a treatment response to week 40**
- Primary outcome: **Clinical remission at week 40**

Clinical remission at week 12 (mITT population)

Source: Company submission document B, B.3.6.2.1, figure 11

A statistically significant greater percentage of patients achieved clinical remission at week 40 with mirikizumab group versus placebo

- **Clinical remission at week 40** is defined as achieving a MMS subscore for rectal bleeding=0, stool frequency=0 or 1 with ≥ 1 point decrease from baseline, and endoscopy=0 or 1 (excluding friability)
- **mITT** is defined as all randomized participants who received at least one dose of study drug and who had the MMS measured correctly at baseline. Participants were analysed per their assigned treatment arm regardless of the actual treatment received

Abbreviations: MMS: modified Mayo score; mITT: modified intention-to-treat; RCT: Randomised controlled trial

Comparative effectiveness – company's NMA

- In the absence of direct efficacy evidence, company conducted a NMA comparing the efficacy and safety of mirikizumab versus relevant comparators
- Analyses were conducted for induction and maintenance phases for both the biologic-naïve and biologic-failed populations
- The outcomes of main interest in the NMA were clinical response and remission
- Fixed effects and random effects models with and without adjustment for baseline risk conducted
  - Model choice for each outcome and population subgroup made using goodness-of-fit statistics, in particular the deviance information criteria (DIC), and also covariate coefficient statistics
  - Adjustment for baseline risk made using exploratory analysis utilising meta-regression

Abbreviations: NMA: Network meta-analysis

Base case NMA results – induction phase

Outcome	versus placebo [OR (95% CI)]	versus vedolizumab [OR (95% CI)]	versus ustekinumab [OR (95% CI)]
Biologic naïve population			
Clinical response[a]	[redacted]	[redacted]	[redacted]
Clinical remission[a]	[redacted]	[redacted]	[redacted]
Biologic failed population			
Clinical response[b]	[redacted]	[redacted]	[redacted]
Clinical remission[b]	[redacted]	[redacted]	[redacted]
Overall population			
All cause discontinuation[a]	[redacted]	[redacted]	[redacted]
SAEs[b]	[redacted]	[redacted]	[redacted]

[a] Random effects model
[b] Fixed effects model
Abbreviations: CI: Confidence interval; NMA: Network meta-analysis; OR: Odds ratio; SAEs: Serious adverse events

Source: EAG report, table 4

Base case NMA results – maintenance phase

Outcome	versus placebo [OR (95% CI)]	versus vedolizumab [OR (95% CI)] (108mg Q2W; 300mg Q4W; 300mg Q8W)	versus ustekinumab [OR (95% CI)] (90mg Q8W; 90mg Q12W)
Biologic naïve population			
Clinical response[b,c]	[redacted]	[redacted]	[redacted]
Clinical remission[b,c]	[redacted]	[redacted]	[redacted]
Biologic failed population			
Clinical response[b]	[redacted]	[redacted]	[redacted]
Clinical remission[b]	[redacted]	[redacted]	[redacted]

[a] Random effects model
[b] Fixed effects model
[b] Includes baseline risk adjustment NMAs, using an exploratory analysis utilising meta-regression to adjust for baseline risk
Abbreviations: CI: Confidence interval; NMA: Network meta-analysis; OR: Odds ratio Q2W; Every two weeks; Q4W: Every four weeks; Q8W; Every eight weeks; Q12W: Every twelve weeks

EAG critique of company's NMA

- **Overall, no major concerns with the company's NMA**
  - Mirikizumab appears to have [redacted] treatment effects in the induction and maintenance treatment phases than, and a similar safety profile to, vedolizumab and ustekinumab
- The statistical models chosen for the different outcomes were appropriate, and addressed limitations noted in previous technology appraisals in this topic
- Some concerns with the NMA:
  i. Systematic literature searches (SLRs) were performed over six months ago ➔ There is risk that there may have been recent relevant studies that will not have been included in the NMA
  ii. The biologic-naïve subgroup (people who had not received any prior biologic, including a Janus kinas inhibitor) analyses do not fully reflect the NICE scope population
    - SLR eligibility criteria was not limited to only adults who were intolerant of, or whose disease has had an inadequate response, or loss of response to previous biologic therapy or conventional therapy, as per the NICE scope
    - However, biologic naïve participants included in the NMA were not necessarily intolerant of, or had had an inadequate response to or loss of response to conventional therapy
  iii. Baseline effects were modelled using placebo-arm data from included RCTs rather than using representative UK-specific data inline NICE TSD 5 ➔ The impact of this on the results is unclear

Abbreviations: NMA: Network meta-analysis; RCTs: Randomised controlled trials; TSD: Technical support document

EAG critique of company's NMA

- Some concerns with the NMA (continued):
  iv. Considerable clinical and statistical heterogeneity in the broad NMA network that includes a wide range of approved targeted therapies and emerging therapies for ulcerative colitis
    - A narrower NMA may have resulted in more precise estimates of comparative clinical efficacy
  v. Non-inferiority and equivalence of treatment effect and safety not statistically assessed using relevant equivalence or non-inferiority trials ➔ Findings based on statistical significance in the NMA
  vi. Some inconsistency observed in justification of whether a fixed effects or random effects model is the most appropriate
    - For induction of clinical response and remission in a biologic-naïve population, the DIC was lowest for the fixed effects model (indicating a better fitting model), however a random effects model was preferred by the company due to the heterogeneity observed across the network
    - Given limitations of a sparse network, the degree of heterogeneity observed and the small differences in DIC, the EAG considers the company's approach is reasonable
    - Overall conclusions across the outcomes and populations do not change depending on the model selected

Abbreviations: DIC: Deviance information criteria; NMA: Network meta-analysis

Cost-comparison results – company's base case

Results include **list prices** for mirikizumab, ustekinumab and vedolizumab

Company's base case assumptions:

1. 10 years time horizon
2. 0% discount rate
3. **Increased dose or administration frequency for 30% of patients for relevant comparators and [redacted] of patients on treatment re-induction per cycle for mirikizumab, reflecting clinical data from the LUCENT trials**
4. No intended induction period
5. Incorporation of vial sharing, so no drug wastage assumed

Population	Incremental costs for mirikizumab vs comparators		
	Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC/IV)
Biologic naïve	[redacted]	[redacted]	[redacted]
Biologic failed	[redacted]	[redacted]	[redacted]

Abbreviations: IV: Intravenous; PAS: Patient access scheme; SC: Subcutaneous

Cost-comparison results – scenario analysis

Biologic naïve population

Results include **list prices** for mirikizumab, ustekinumab and vedolizumab

Scenario		Incremental costs for mirikizumab vs comparators		
		Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC/IV)
Company base case		[redacted]	[redacted]	[redacted]
1. No dose escalation for comparators and no re-induction for mirikizumab		[redacted]	[redacted]	[redacted]
2. 30% of patients on treatment re-induction per cycle for mirikizumab		[redacted]	[redacted]	[redacted]
3. Extended induction period**		[redacted]	[redacted]	[redacted]
4. Mirikizumab re-induction rate*	10%*	[redacted]	[redacted]	[redacted]
	15%*	[redacted]	[redacted]	[redacted]
5. Include EAG adverse event costs of £3,898*		[redacted]	[redacted]	[redacted]
6. Time horizon	5 years	[redacted]	[redacted]	[redacted]
	15 years*	[redacted]	[redacted]	[redacted]
7. Drug wastage		[redacted]	[redacted]	[redacted]
8. Discount rate	3.5%	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]

* EAG did not provide it's base case results but conducted additional scenario analysis to the company base case

** EAG corrected company's error by applying the correct treatment duration of 24 weeks for mirikizumab

Abbreviations: IV: Intravenous; SC: Subcutaneous

Cost-comparison results – scenario analysis

Biologic failed population

Results include **list prices** for mirikizumab, ustekinumab and vedolizumab

Scenario		Incremental costs for mirikizumab vs comparators		
		Ustekinumab	Vedolizumab (IV)	Vedolizumab (SC/IV)
Company base case		[redacted]	[redacted]	[redacted]
1. No dose escalation for comparators and no re-induction for mirikizumab		[redacted]	[redacted]	[redacted]
2. 30% dose escalation for comparators and 30% re-induction per cycle for mirikizumab		[redacted]	[redacted]	[redacted]
3. Extended induction period**		[redacted]	[redacted]	[redacted]
4. Mirikizumab re-induction rate*	10%*	[redacted]	[redacted]	[redacted]
	15%*	[redacted]	[redacted]	[redacted]
5. Include EAG adverse event costs of £3,898*		[redacted]	[redacted]	[redacted]
6. Time horizon	5 years	[redacted]	[redacted]	[redacted]
	15 years*	[redacted]	[redacted]	[redacted]
7. Drug wastage		[redacted]	[redacted]	[redacted]
8. Discount rate	3.5%	[redacted]	[redacted]	[redacted]
	5%	[redacted]	[redacted]	[redacted]

* EAG did not provide it's base case results but conducted additional scenario analysis to the company base case

** EAG corrected company's error by applying the correct treatment duration of 24 weeks for mirikizumab

Abbreviations: IV: Intravenous; SC: Subcutaneous

Other uncertainties

Uncertainity	Description	EAG considerations
Partly positioning mirikizumab in biologic-naïve patients	The population specified in the company decision problem differs from the NICE scope in that among people who cannot tolerate conventional treatment or in whom conventional treatment has not worked well enough, the company is positioning mirikizumab treatment only in the subgroup for whom other biologic treatments are not suitable. This population is referred to as “biologic-naïve” and considered a sub-population of the proposed marketing authorisation	• Unclear what the company means when stating they are partly positioning mirikizumab for managing moderately to severely active ulcerative colitis in biologic-naïve patients (that is, people for whom conventional treatment cannot be tolerated or is not working well enough) in whom “other biologic treatment is not suitable” • None of the comparator drugs specified in the NICE scope, for which recommendations have been published have the same restriction as proposed by the company for mirikizumab.

Potential recommendations

Recommendations for ustekinumab and vedolizumab for treating moderately to severely active ulcerative colitis

TA633 (ustekinumab):

Recommended as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if:

- a tumour necrosis factor-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) or
- a tumour necrosis factor-alpha inhibitor cannot be tolerated or is not suitable, and
- the company provides ustekinumab at the same price or lower than that agreed with the Commercial Medicines Unit

TA342 (vedolizumab):

Recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults

Abbreviations: TA: Technology appraisal

Potential recommendations

Other previous guidance's for treating moderately to severely active ulcerative colitis

TA856 (upadacitinib), TA792 (filgotinib):

Recommended as an option for treating moderately to severely active ulcerative colitis in adults, only:

- when conventional or biological treatment cannot be tolerated, or
- if the disease has not responded well enough or has stopped responding to these treatments, and
- if the company provides it according to the commercial arrangement

TA828 (ozanimod):

Mirikizumab is recommended as an option for treating moderately to severely active ulcerative colitis in adults, only:

- 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, and
- if the company provides it according to the commercial arrangement

TA547 (tofacitinib):

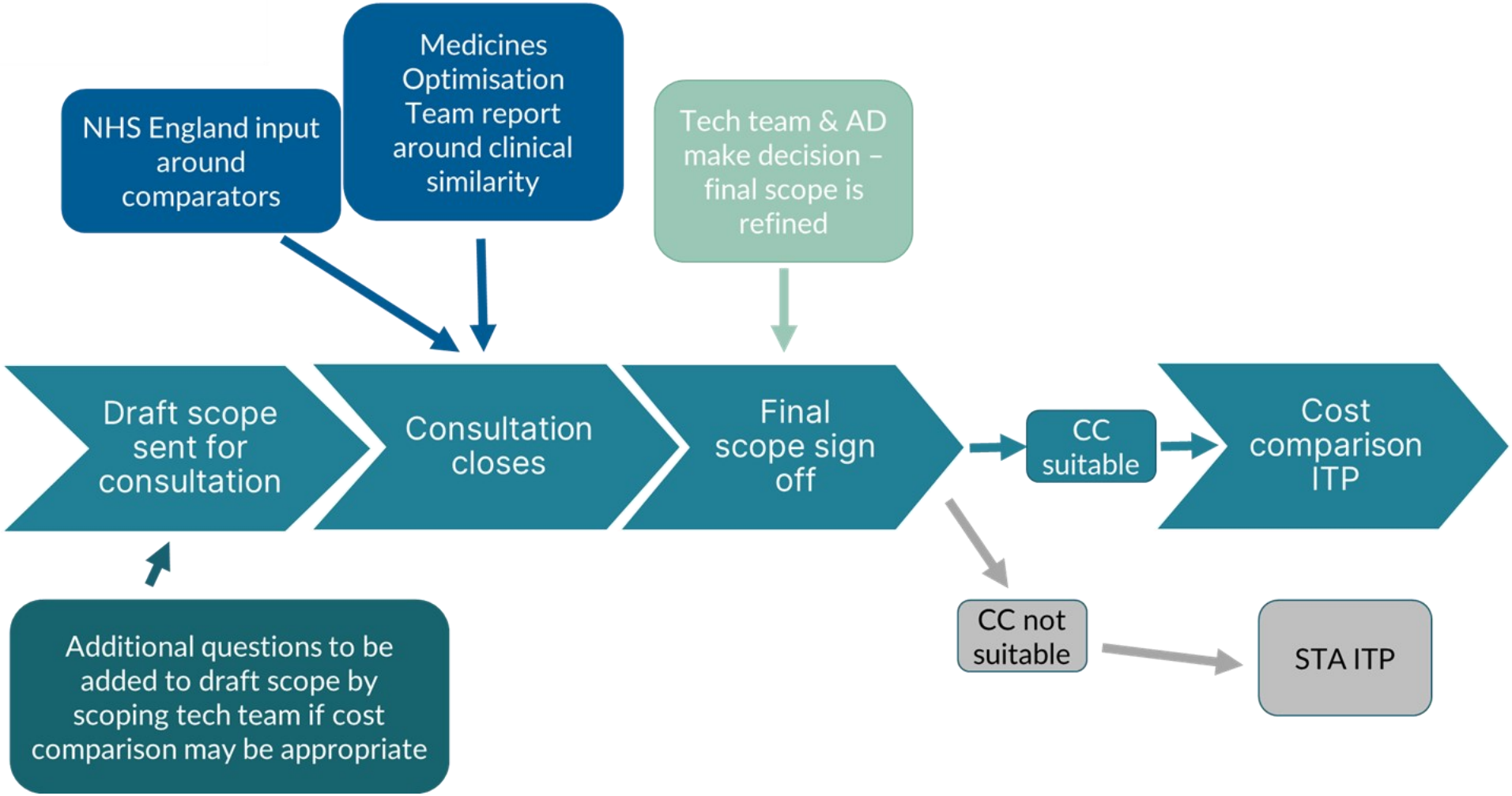
Recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment

Abbreviations: TA: Technology appraisal

NICE National Institute for Health and Care Excellence

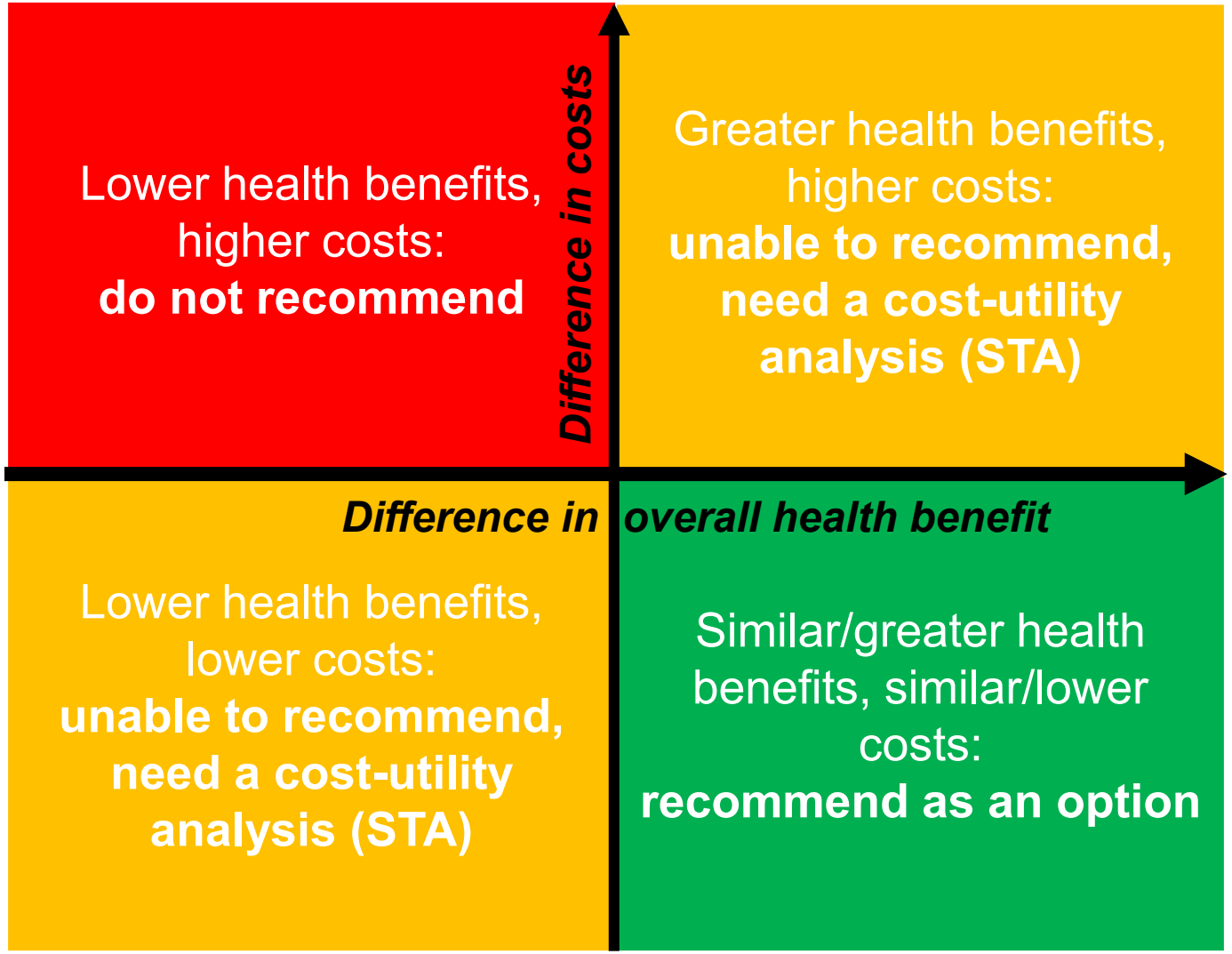
Thank you.

Process – Streamlined cost comparison



Abbreviations: CC: cost comparison; ITP: Invitation to participate; STA: Single technology appraisal; AD: Associate director

Potential recommendations: cost comparison



Abbreviations: STA: Single technology appraisal