Risankizumab for previously treated moderately to severely active Crohn's disease

For public – AIC and CIC information was redacted

Technology appraisal committee A – 7th March 2023

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Company: AbbVie

Process: STA 2022

NICE

Key issues

In response to draft guidance, the company has submitted cost-comparison analysis

Clinical effectiveness

- Is the company's maintenance NMA appropriate for decision-making?
- Is the committee satisfied that risankizumab and its comparators in the CCF (ustekinumab, adalimumab and infliximab), and BF populations (ustekinumab and vedolizumab) have similar clinical effectiveness?

If cost-comparison is appropriate

- What time horizon would be the most appropriate?
- Is the proportion of patients starting on high doses appropriate?
- Is the company's IV/SC blended approach for comparators appropriate?
- Should treatment discontinuation or follow-up treatments be included?
- Are any further OBD exploratory analyses needed?

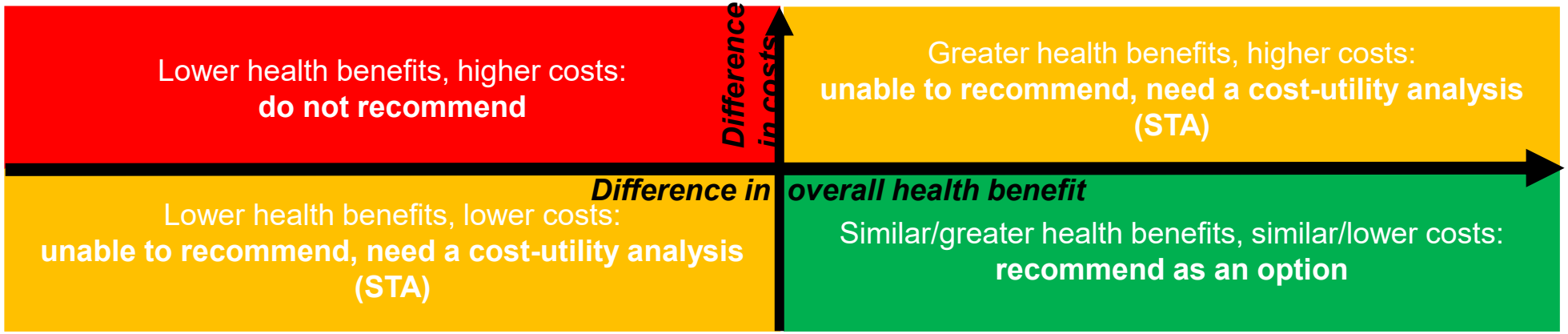
Cost-comparison analyses

6.4.3 For technologies evaluated using cost-comparison analysis, the committee usually recommends a technology when it considers that:

- there is enough certainty that the technology has at **least equivalent** clinical or health and social care system benefits compared with current management, and **overall uses less** resources or
- there is enough certainty that the technology has **significantly greater** clinical or health and social care system benefits compared with established practice in the NHS, and **overall uses similar** resources.

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

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



Draft recommendation

Risankizumab is not recommended, within its marketing authorisation, for treating moderately to severely active Crohn's disease in people 16 years and over that has not responded well enough or lost response to conventional treatment or a biological treatment, or when these treatments are not tolerated or suitable.

Committee stated new analyses were needed:

- Model structure not suitable for decision-making → did not model follow on treatments or use of risankizumab for longer than a year.
- Estimated incremental QALY estimates were minimal → cost comparison may be relevant if it is demonstrated that risankizumab has the same clinical effectiveness as its comparators.
    - Stated its preferences for network meta-analysis model.

Abbreviations: QALY, quality-adjusted life year

RECAP: Crohn's disease

CD is a debilitating chronic relapsing systemic inflammatory bowel disease

It causes inflammation and mucosal ulceration anywhere in digestive system, but most commonly in the last section of the small intestine (35%), sometimes also affecting the beginning of the colon (40%). It often relapses and has acute exacerbations 'flares' in remission or less active disease.

Patient perspectives

- Current treatments are not enough, many are leading painful, miserable lives.
- Risankizumab offers a novel and effective treatment option and increases choice for both clinicians and patients.
- Risankizumab may delay or prevent surgery in patients with CD.
- Risankizumab could be the difference between a person struggling to get through a daily fog of pain, exhaustion, and uncontrollable diarrhoea, and a person living their life happily and healthily to the full.

"I have so much I could, and want, to contribute to the world. I want to be part of society, to work, to meet a partner, to … – but I can't do it without drugs like Risankizumab. I therefore ask you to consider patients like me when you are assessing its approvability."

Risankizumab (Skyrizi, AbbVie)

MHRA Marketing authorisation (MA)	• For the treatment of patients 16 years and older with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable.
Mechanism of action	• Humanised IgG1 monoclonal antibody. Binds with high affinity to the p19 subunit of IL-23 cytokine. This blocks the binding of IL-23 to IL-23Rα without binding to IL-12.
Administration	• Induction: 3 doses – 600mg IV every 4 weeks (week 0, 4 & 8). • Maintenance: 360mg SC on body device (OBD) every 8 weeks from week 12 (risankizumab was delivered using SC injections in the key trial, it will be delivered using OBD). No stopping or review rule in SPC.
Price	• Price is commercial in confidence. • Patient Access Scheme (PAS) applicable.

NICE **Note**: the CE mark is pending for the OBD. Risankizumab administered using the OBD for Crohn's disease will not be available in the UK until the CE mark is granted. [redacted]

Treatment pathway

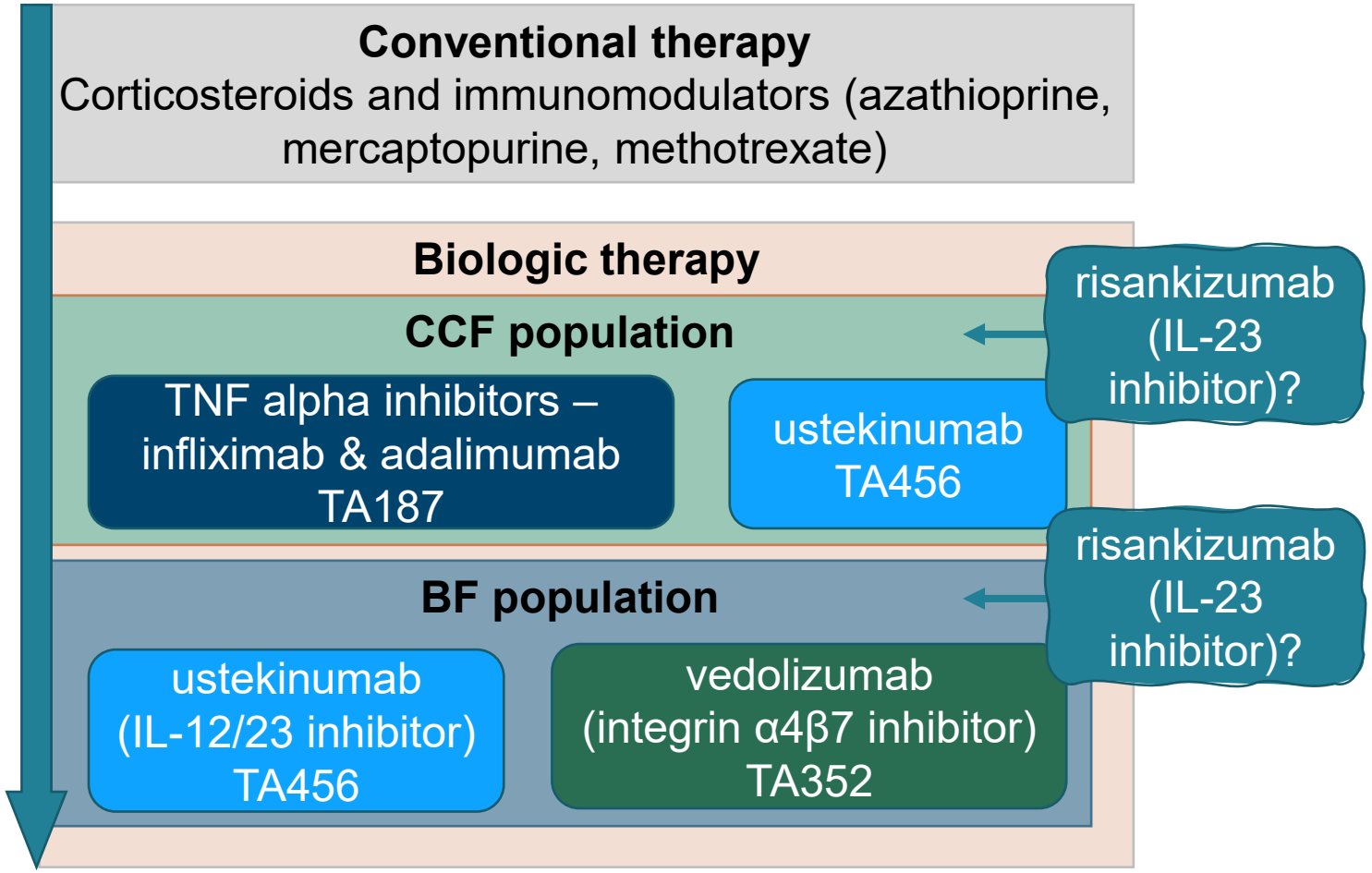
2 populations:

- **Conventional care failure (CCF) population** ~ non-Bio-IR population (non-biologic inadequate response/intolerance).
- **Biologic failure (BF) population** ~ Bio-IR (biologic inadequate response/intolerance).

Note:

- biosimilars are available for infliximab and adalimumab.
- TA456 & TA187 states, if > 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

Figure: Moderately to severely active Crohn's disease



Network meta analysis (NMA): ACM1 company approach

Company and EAG suggested different approaches to NMA

- Risankizumab assessed in placebo controlled trials (ADVANCE and MOTIVATE (induction), and FORTIFY (maintenance).
- No trial data directly comparing risankizumab with comparators so company carried out Bayesian NMAs for induction and maintenance treatment for CCF and BF populations.
- Noted differences between trials included: time of follow up, patient populations – differences in baseline risks + stratification by CCF/BF, temporal effect (remission in placebo groups greater in later trials).
- For maintenance NMA company split the network into 2 groups ‘based on biologic half-life, induction duration and study heterogeneity such as differences in study designs or populations’
  - A) *risankizumab* + *ustekinumab*
  - *B) adalimumab* + *infliximab* + *vedolizumab*.
- Company preferred fixed effect model (FE) because random effects (RE) model gave wide credible intervals which included values which favoured placebo over biologics which is implausible.
- Results were presented as absolute rates of the outcome for each comparator.

ACM1 NMA: EAG approach + committee preferences

	Company	EAG	Committee preference
Network	Split into 2 networks - Company stated single network gives implausible results. Estimated rates of remission higher in placebo arm	Single. Networks should be based on comparator connections not drug characteristics	Single
Fixed effect or random model	Fixed effect	Random effect because of heterogeneity	Random effect model should be explored
Adjustments	No further adjustments- Company used split network because of trial heterogeneity. Noted methodological challenges in accounting for heterogeneity	Adjusted for temporal effect	Agreed with adjustment for temporal effect
Treatment effect	Risk difference	n/a used company model	modelling risk ratios may be more informative and allow further exploration of data to improve the precision of estimates

RECAP: cost effectiveness model used at ACM1

Committee's key concerns were assumption of maximum 12 month risankizumab duration and no modelled biological treatments after the first treatment

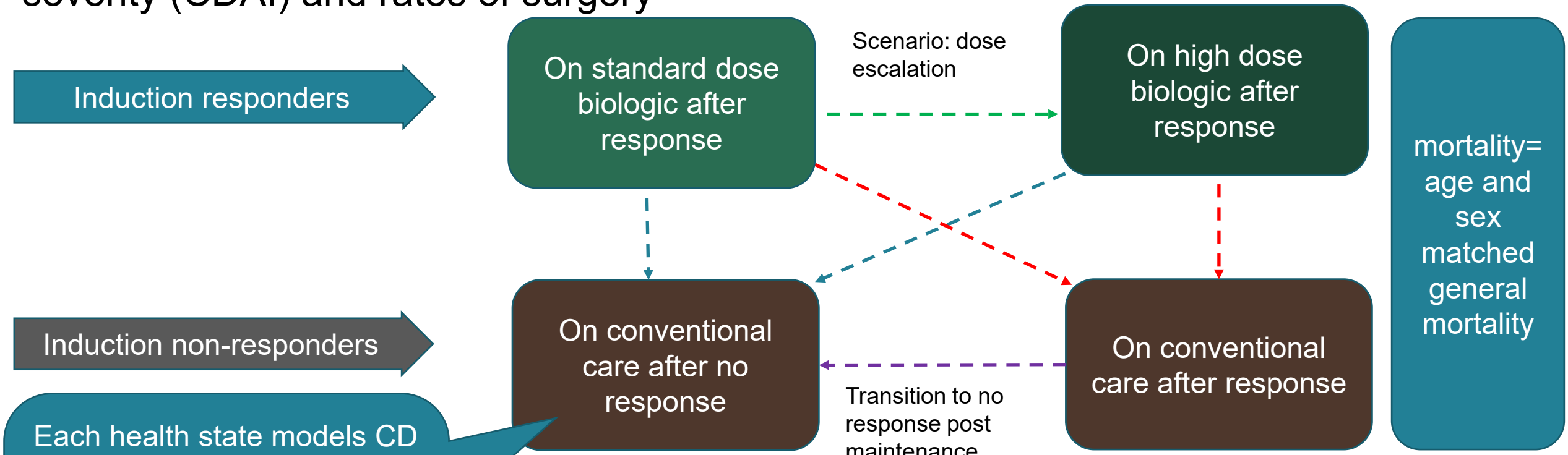
Model type: decision tree for induction, Markov for maintenance treatment.

Maintenance model:

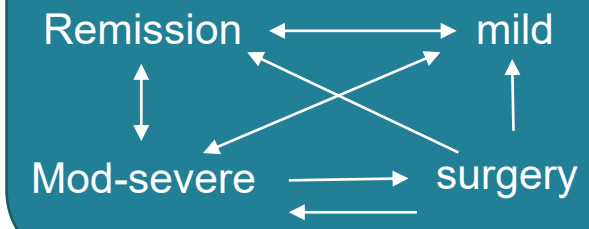
- All people had conventional care after stopping a biological treatment. Stopping biological treatment was modelled to be either:
    - Loss of efficacy.
    - Maximum treatment duration of 12 months (maximum duration in risankizumab and comparator treatments). EAG exploratory analyses allowed 20 year duration.
- Company stated that model consistent with previous NICE appraisals of treatments for Crohn's disease
- In the maintenance model, disease severity as measured by CDAI was modelled over time based on risankizumab trial data (using data from end of induction and at 1 year of maintenance). For comparators, this was further calibrated to results from the NMA.
- Committee concluded that model was not suitable for decision-making because it did not reflect the treatment pathway in which people may have further biological treatments after their initial one and people may stay on a biological treatment for longer than a year.

ACM1 Long-term model structure: maintenance + post maintenance Markov

Health states by treatment and response. Each health state models change in CD severity (CDAI) and rates of surgery



Each health state models CD severity (CDAI) and surgery



Severity definition:

- Remission: CDAI <150
- Mild CD: 150 ≤ CDAI <220
- Moderate to severe CD: 220 ≤ CDAI <600

Key:

- Discontinuation loss of efficacy
- Discontinuation max treatment duration (company assumes 52 weeks)

Overview: recap of committee conclusions from ACM1

Issue	Committee conclusion	DG section
Need for additional treatment option	The availability of a further treatment option to improve symptoms and bring the disease into remission would be highly valued by people with CD.	3.2
Comparators	• for the conventional care failure population are adalimumab, infliximab and ustekinumab. • for the biological treatment failure population are vedolizumab and ustekinumab.	3.3
OBD	OBD is likely to be welcomed by people with CD, but agreed that further exploratory analyses are needed – analyses around treatment discontinuation and wastage are welcome.	3.8, 3.14
Model structure	Although a CDAI-based model may be appropriate, the model is not suitable for decision-making because it did not reflect the treatment pathway in which people can have more than 1 biological treatment.	3.9
New analyses	• updated NMAs to explore the similarity of the biological treatments and, if appropriate, cost-comparison analyses. • if the company chooses cost-utility analyses, a new model that explores the sequence of biological treatments is needed.	3.14

Abbreviations: CD, Crohn's disease; DG, draft guidance; OBD, on body device.

Consultation responses to draft guidance

Comments received from:

- Clinical expert (company nominated)
- Crohn's & Colitis UK
- British Society of Gastroenterology – IBD Section (also endorsed in Crohn's & Colitis UK and patients expert submissions)
- Patient expert
- Web comments (2 submissions)
- Company

Abbreviations: IBD, Inflammatory Bowel Disease

Consultation themes: unmet need for further treatment options and a case for risankizumab 1/2

Crohn's & Colitis UK:

The range of options available for treating Crohn's Disease remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies.

British Society of Gastroenterology:

- Risankizumab has several advantages over some of the existing therapies... As risankizumab is delivered subcutaneously after the initial intravenous induction, this itself will have significant benefits in reducing the pressures on already overstretched IBD services and improve patient compliance.
- Psoriasis can often co-exist with Crohn's disease, this is an effective single treatment option for patients needing escalation to an advanced therapy for patients with these co-morbidities (in contrast to anti-TNF agents which often result in a significant flare of psoriasis).

Consultation themes: unmet need for further treatment options and a case for risankizumab 2/2

Patient expert:

there is a serious lack of treatments for patients with Crohn's disease, with each currently available drug offering limited probabilities of remission which, if reached, might only last a few weeks, months, or years. This leaves thousands of people languishing in limbo for years, living secluded, painful, half-lives while the rest of the world continues on around them**.**

Web comment 2:

anti-il23-specific therapies are a major step forwards clinical trials and personal experience show that risankizumab works sometimes where no other treatments work.

Consultation themes: expected similarity in clinical effectiveness between risankizumab and comparators

Clinical expert:

- Risankizumab appears to be efficacious treatment, and very much comparable to ustekinumab. Sands et al. 2022 showed that ustekinumab and adalimumab have equivalent efficacy in biologic-naive patients with moderately to severely active CD: it would appear unlikely that there is any clinically significant difference between these mechanisms. French real word data from 100 people (Fumery et al. 2023) and unpublished data from UK (n=48) suggest that these agents are likely to perform in a comparable manner when used in clinical practice. Importantly, almost all of these patients had been exposed to all biologic mechanisms and a significant proportion (78.5%) responded to risankizumab nonetheless.

Web comment 1:

- *In response to "[the EAG] also noted ustekinumab and vedolizumab, used in the different networks, have a similar half-life and are comparable treatment options."* The pharmacokinetic half [life] may be similar, but the pharmacodynamic impact is very different both ustekinumab and risankizumab suppress IL-22 (a biomarker of efficacy) for 22-24 weeks which is far longer that the impact of vedolizumab. This manifests in the high rates of ongoing benefit in patients receiving induction dosing and then being re-randomised to placebo.
- Consistency is needed [Risankizumab] is undoubtedly more effective than vedolizumab in Crohn's - both from trials data and experience... [Vedolizumab] is NICE approved for Crohn's. [Risankizumab] certainly should be also.

Consultation themes: feasibility and fairness of updating cost effectiveness model

British Society of Gastroenterology:

- **Maximum treatment duration:** 20-year maximum treatment duration is unreasonable and far from clinical practice. Although CD is a lifelong condition, most advanced therapies eventually lose effect or have to be discontinued due to other patient related factors. Treatment persistence with biologics has been reported with median durations of 2 to 3 years; this itself is an argument for the ongoing need of effective advanced therapies. Consistent with previous NICE TAs, 1-year duration is appropriate.

Clinical expert:

- **Maximum treatment duration**: fewer patients than previously are discontinuing treatment at 1 year due to complete remission, but very few patients (if any) have been on the same biologic agent for 20 years. Biologic treatment withdrawal, in sustained deep remission, is still of interest to patients and clinicians, and happens - just perhaps after 4 or 5 years.
- **Modelling treatment sequencing**: Sequencing is clearly a really important area and a topic of great interest in IBD medicine at the moment. However, to model all of the various biologic permutations from the basis of this placebo-controlled trial of a single agent would appear a big ask.

Consultation themes: on body device

Crohn's & Colitis UK:

- compliance concerns [using OBD] are overstated, patients have experience with self-administration;
- Self-administration is more convenient and free capacity within IBD teams.
- Self-administering maintenance doses of biologics supports condition self-management and enables patients to play an active role, empowering them to take more control of their condition.
- Research suggests that the use of medical treatment is an act of self-care that supports patients to feel like they are a step ahead of their condition and is an important coping mechanism.

Clinical expert:

- Prospective OBD data are now available from FORTIFY substudy (n=46) which is reassuring in terms of patient experience using the OBD (Loftus et al. 2022)

Company response overview

Issue	Committee conclusion	Company draft guidance response
Network meta-analyses (NMAs) for maintenance	• Single network with an adjustment for temporal effect, • risk ratios rather than risk difference and presenting the credible intervals around the estimates, and • explore random effects as well as fixed-effect models.	• Supplied NMAs as per committee's preferences.
On body device (OBD)	Exploratory analyses around on treatment discontinuation and wastage.	• Evidence indicates patients have positive feelings about the OBD. • No exploratory analyses provided: wastage with risankizumab would also apply to comparators, negating impact on economic outcomes.
Model	• Cost-comparison if supported by evidence, or • new cost-utility model exploring the sequence of biological treatments and following committee's preferences as stated in the draft guidance.	• Provided a new cost-comparison model because 'overall, the results of the updated single-network maintenance NMAs (with adjustment for the temporal effect) showed broadly comparable efficacy for risankizumab and comparator biologic therapies'.

New maintenance NMAs: CDAI clinical remission

CCF population

Table: Results of the single-network maintenance NMA, with adjustment for the temporal effect (baseline year regression 2020), for CDAI clinical remission

Posterior risk ratio (95% CrI) RZB vs comparators	Baseline year regression (2020) Random effects model	Baseline year regression (2020) Fixed effects model
PBO	[redacted]	[redacted]
ADA Q2W	[redacted]	[redacted]
ADA QW	[redacted]	[redacted]
IFX5/10 Q8W	[redacted]	[redacted]
IFX5 Q8W	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CrI, credible interval; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; RE, random effects; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

New maintenance NMAs: CDAI clinical remission

BF population

Table: Results of the single-network maintenance NMA, with adjustment for the temporal effect (baseline year regression 2020), for CDAI clinical remission

Posterior risk ratio (95% CrI) RZB vs comparators	Baseline year regression 2020 Random effects model	Baseline year regression 2020 Fixed effects model
PBO	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; CrI, credible interval; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; RE, random effects; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

EAG critique of company's updated NMA

Company:

- Provided updated NMA analyses as per committee preference, although maintains that the original analyses were clinically justified and robust.
- Stated that consistent with the results of all previous NMAs, the latest NMA results showed comparable efficacy between risankizumab and comparators for Crohn's Disease Activity Index (CDAI) clinical remission in the maintenance period. "No statistically significant differences were observed, indicating equivalent efficacy between all treatments"
- Noted updated NMA may lack face validity because showed less benefit for risankizumab vs. placebo than trials

EAG:

- Were unable to scrutinise the company's implementation of the updated NMAs given both the availability of data and code, neither of which were provided, and the time to prepare this response.
- Insufficient evidence supporting effectiveness equivalence across treatments was submitted
- The updated NMA does not support effectiveness equivalence across treatments.

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Are the company's updated networks suitable for decision-making?
Is the committee satisfied that risankizumab and its comparators

- in the CCF (ustekinumab, adalimumab and infliximab), and
- BF populations (ustekinumab and vedolizumab) have similar clinical effectiveness?

Company's new cost-comparison model: key features

Cost comparison model has new assumptions to original cost utility model – key issues for discussion **highlighted**

Time horizon	10 years, which reflects a time horizon in which a patient is expected to experience disease stabilisation and is long enough to ensure differences in costs are adequately captured.
Ustekinumab IV dosing	Dosing is weight-based: based on MOTIVATE and ADVANCE post hoc data average dose of 390 mg is assumed = >55kg and ≤85kg dose (3 x 130 mg vials).
High-dose maintenance	Some comparators can be used at standard or high doses: assumption that in maintenance 50% of people taking adalimumab, 40% taking infliximab, 92.5% taking ustekinumab and 30% taking vedolizumab IV start on the high dose.
IV vs SC maintenance	(Infliximab and vedolizumab) IV or SC use depends on many factors → assumption: blended approach assuming 50/50 split of patients receiving these IV or SC
Administration cost	Infusions (IV) costed at £245.00 each. SC administrations assumed a cost for the first dose only (training by a nurse) at £41.00 and no additional cost to for subsequent doses.
Comparators	• CCF population: ustekinumab, adalimumab 160/80, adalimumab 80/40, adalimumab biosimilar, **only blended infliximab IV/SC** and infliximab IV biosimilar/SC • BF population: ustekinumab and **only blended vedolizumab IV/SC**
Other	• **Treatment discontinuation not included** • **Follow-up treatments not included**

EAG critique of company's cost comparison model - summary

Company:

- Based on NMAs supporting comparable clinical efficacy a cost comparison was conducted.

EAG:

Summarises the key new differences from the previous analyses:

- assumes no treatment discontinuation
- assumes a 10-year time horizon (and follow-up treatments are still not considered)
- only a blended approach is used for IV/SC vedolizumab and infliximab – this has a big effect on the cost
- results are presented for the whole population, rather than for CCF and BF population
- dose escalation starts at baseline.

Provided scenario analyses:

- around OBD as none were included in the company's response to the draft guidance
- around treatment discontinuation, IV/SC and dose escalation (including combining assumptions).

Still concerned with OBD: limited data from the small substudy collected in a controlled environment may not reflect clinical practice. Implications of OBD for treatment discontinuation & wastage, remain highly uncertain.

EAG scenarios: treatment discontinuation

- The scenario allows patients to experience treatment discontinuation over the entire 10-year time horizon, using the annual discontinuation rates sourced from the literature (see Table).
- Following discontinuation, patients are assumed to incur no further costs.

Table: Annual treatment discontinuation probability due to lack of efficacy

Treatment arm	Annual discontinuation probability	Source (table 75 in CS)
Risankizumab	4.26%	FORTIFY
Ustekinumab	8.00%	Feagan et al. (2016)
Vedolizumab IV/SC	41.39%	NICE TA456 (GEMINI II)
Adalimumab 160/80	8.05%	NICE TA456 (assumed equal to infliximab)
Adalimumab 80/40	8.05%	
Adalimumab biosimilar	8.05%	
Infliximab IV biosimilar/SC	8.05%	NICE TA456 (ACCENT I)
Infliximab IV/SC	8.05%	

- As a result treatments with higher discontinuation probability become cheaper.
- Vedolizumab cost decreases the most markedly.

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Are the annual discontinuation rates (and their range) clinically plausible?

EAG scenarios: IV versus SC scenario analyses

- blended approach assuming 50/50 split of people having IV or SC is assumed by the company.
- EAG scenario, varies the proportion of people having IV or SC formulation for vedolizumab.

- As SC is cheaper than IV, the more SC formulation is used, the cheaper the total vedolizumab treatment is.

EAG scenarios: standard-dose versus high-dose maintenance scenario analyses

- 50% of people taking adalimumab, 40% taking infliximab, 92.5% taking ustekinumab and 30% taking vedolizumab IV start on the high dose in the company model.
- EAG scenario increases the proportion of people starting on standard dose.

- As the standard dose is cheaper, increasing % of people starting on the standard dose decreases the total cost of treatments.

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Do the proportions starting on higher doses of comparators align with clinical experience? Does 50:50 IV/SC for infliximab and vedolizumab align with clinical experience?

EAG scenarios: OBD administration cost

- SC administrations assumed a cost for the first dose only (training by a nurse) at £41.00 and no additional cost for subsequent doses is used in the company model.
- EAG scenarios assume higher cost (assuming SC administration cost for the whole first year; first three treatments; or using IV cost for first treatment with SC cost for all first-year treatments).

- This results in a small total increased total cost for risankizumab.

Is the committee satisfied that no further OBD analyses are needed?

Key issues

Clinical effectiveness

- Is the company's maintenance NMA appropriate for decision-making?
- Is the committee satisfied that risankizumab and its comparators in the CCF (ustekinumab, adalimumab and infliximab), and BF populations (ustekinumab and vedolizumab) have similar clinical effectiveness?

If cost-comparison is appropriate

- What time horizon would be the most appropriate?
- Is the proportion of patients starting on high doses appropriate?
- Is the company's IV/SC blended approach for comparators appropriate?
- Should treatment discontinuation or follow-up treatments be included?
- Are any further OBD exploratory analyses needed?

Cost-effectiveness results

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

Cost-comparison: summary results with comparator PAS

Company did not present cost-comparison results by BF and CCF population

- Risankizumab is not cost-saving compared with all comparators in the company base case.

Comparator	population	Company's results for risankizumab vs comparator	EAG's scenarios results for risankizumab vs comparator
Ustekinumab	BF, CCF	Cost-saving	Cost-saving in some scenarios not in others
Vedolizumab IV/SC	BF	Cost-saving	Cost-saving in some scenarios not in others
Adalimumab 160/80	CCF	Not cost-saving	Not cost-saving
Adalimumab 80/40	CCF	Not cost-saving	Not cost-saving
Adalimumab biosimilar	CCF	Not cost-saving	Not cost-saving
Infliximab IV biosimilar/SC	CCF	Not cost-saving	Not cost-saving
Infliximab IV/SC	CCF	Not cost-saving	Not cost-saving

Other considerations

Equality considerations

- No potential equality issues were raised.

Innovation

Company:

- Risankizumab is a new class of biologic with a novel mode of action that selectively targets IL-23 that has the potential to address an unmet clinical need.
- Promising Innovative Medicine (PIM) designation (10/2021).
- Early Access to Medicines Scheme (EAMS) positive final scientific opinion (4/2022).