Single Technology Appraisal

Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]
Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]

Contents:

The following documents are made available to stakeholders:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

ID3986 Risankizumab for previously treated moderately to severely active Crohn's disease

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (patient/carer groups)	Crohn's & Colitis UK	We agree with the points raised in the British Society of Gastroenterology's submission.	Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
2	Consultee (patient/carer groups)	Crohn's & Colitis UK	We are concerned that the recommendation will disadvantage patients with Crohn's disease as there is an urgent need for more options for effective advanced therapies. Risankizumab is an innovative medicine with a novel mechanism of action. This has the potential to provide a lifeline for patients with Crohn's disease who have not responded to other treatments, or in whom other treatments have failed, and who have very limited other options. Patients with uncontrolled disease experience severe disabilities that affect their psychological, financial and social wellbeing. There is currently no medical or surgical cure for the condition and current available treatments are aimed at inducing and maintaining remission and improving quality of life. 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. This can have a profound effect on someone's work and education prospects as well as there being a significant cost for the health service in terms of the cost of emergency A&E visits and planned surgery. We urge the committee to reconsider their decision.	Thank you for your comments. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
3	Consultee (patient/carer groups)	Crohn's & Colitis UK	We are concerned with the draft guidance's over emphasis on the results of the network meta-analysis and the lack of direct comparison data with other biologics. In clinical practice, it is likely that this biologic will be given when most, if not all others have failed, offering a vital lifeline to patients who wish to delay surgery. The ADVANCE and MOTIVATE trials for example both had patients that had been categorised as having previous bio-failure with inadequate response or intolerance to one or more biologic. In the ADVANCE trial, 58% of participants	Thank you for your comments. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.

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			had failed previous biologic therapy and 30% had failed more than one biologic. In the MOTIVATE trial, all participants had failed previous biologic therapy and 53% had failed more than one biologic[i]. In the FORTIFI trial, 73% of participants had failed previous biologic therapy and 40% had failed more than one biologic[ii]. The results of the trials clearly showed that Risankizumab was effective in inducing remission in those who had previously failed other treatments, offering patients the opportunity to regain their health and their quality of life. We know that surgery would remain the only option for some patients in the absence of Risankizumab. This can have a significant physical and mental impact on patients as well as cause a considerable cost to the health service. For example, a cost analysis of more than 1,200 IBD patients revealed a total health care cost of €2,548 per patient-year for Crohn's Disease and €1,524 for ulcerative colitis, with over half of the health care costs arising from hospitalisation and surgery[iii]. For many people, surgery for Crohn's Disease results in a stoma, which has additional healthcare costs in terms of stoma supplies. Each year the UK spends approximately £364m on stoma products with the average clinical commissioning groups spend being £2.14m[iv]. There is also an economic impact due to time required off work both for the initial surgery and recovery – and, for some patients, ongoing time off as they adjust to life post-surgery. For many patients with Crohn's Disease, the prospect of surgery is one they face with considerable anxiety, and it can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. Clinical outcomes after pouch surgery remain variable and fertility in women can be significantly affected by any pelvic surgery.	
4	Consultee (patient/carer groups)	Crohn's & Colitis UK	We believe that the committee's concerns with the compliance of using an on-body device in the draft guidance are overstated. By the time most patients with Crohn's disease are prescribed Rizankizumab, they will have tried other medication that requires self-administration such as adalimumab, infliximab, ustekinumab. Self-administering maintenance doses of biologics supports condition self-	Thank you for your comments. Further discussion of the compliance of using an on-body device has been added to section 3.9 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the

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			management and enables patients to play an active role, empowering them to take more control of their condition[v]. 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[vi]. Furthermore, one of the key advantages of the on-body device is that it would give patients a treatment option to be taken at home. As well as being more convenient for patients, this has economic advantages as it reduces the need to take time off work to attend hospital for treatment and reduces travel and parking costs for the patient. It also reduces the time healthcare professionals need to spend on drug administration, freeing up capacity within busy IBD teams.	Final Draft guidance for more information.
5	Patient expert	N/A	As a patient with Crohn's disease, I agree with all the points made by the British Society of Gastroenterology and Crohn's and Colitis UK. I would like to add three additional points.	Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
6	Patient expert	N/A	Firstly, 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. However much decision-makers think they understand Crohn's disease, they often don't take full account of the impact that symptoms – especially extra-intestinal manifestations like extreme fatigue – have on a person's life.	Thank you for your comments. The need for further treatment options is discussed in section 3.2 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
7	Patient expert	N/A	Secondly, risankizumab does seem to offer an encouraging efficacy rate. The recently published meta-analysis highlighted by the British Society of Gastroenterology in its first point showed that risankizumab 600mg ranked as the most effective treatment in both biologic-naïve and biologic-exposed patients. It has been approved in the US and EU, with evidence from the US showing efficacy in patients whose disease has not responded to other advanced therapies. Without the approval of drugs like risankizumab, British patients will have their noses pressed against the window, denied the chance to regain the most valuable part of themselves: their health.	Thank you for your comments. Clinical effectiveness similarity is discussed in section 3.2 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
8	Patient expert	N/A	If NICE does decide to approve risankizumab, I urge you to approve it not just for patients with moderate and severe disease, but also those with mild disease who do not respond to any other treatment. Mild untreatable disease can still have a severe impact on your life – preventing a person leaving the house, having a career, or seeing friends. Without treatment with drugs like risankizumab, people with mild disease are left in limbo, counter-intuitively wishing their condition would become more severe in order to access treatment to enable them to recover.	Thank you for your comments. The marketing authorisation for risankizumab does not include mild disease, so a recommendation in mild disease cannot be made. Risankizumab is recommended for people who have had a previous biological treatment. Please see the

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				Final Draft guidance for more information.
9	Consultee (patient/carer groups)	British Society of Gastroenterology – IBD Section	We are concerned that the recommendation will disadvantage patients in the NHS access to a highly effective therapy for Crohn's disease. I understand these recommendations have been made due to economic modelling and differences in methodological views on appropriate network meta-analysis. We accept that comparative analysis of advanced therapies in IBD heavily rely on network meta-analysis in absence of head to head trial data. A recently published network meta-analysis by Alex Ford's group in Gut compared efficacy of advanced therapies for Crohns disease (*Barberio B, Gracie DJ, Black CJ, et al. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut 2023*). They showed that whilst infliximab 5mg/kg ranked first for induction of clinical remission in all patients with luminal CD, but **risankizumab 600mg was first in both biologic-naïve and biologic-exposed patients**. This comparative analysis included all approved advanced therapies (infliximab, adalimumab vedolizumab, ustekinumab) as well as novel drugs currently undergoing NICE appraisal in the same analysis similar to that recommended by the EAG.	Thank you for your comments. Clinical effectiveness similarity is discussed in section 3.8 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
10	Consultee (patient/carer groups)	British Society of Gastroenterology – IBD Section	In addition to its superior indirect comparative efficacy ranking, risankizumab has several advantages over some of the existing therapies. The burden on IBD services and infusion units have led to a significant shift in considering non-intravenous based maintenance therapies for treatment of Crohn's disease. 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. Risankizumab has also demonstrated a favourable safety profile in the clinical trial for Crohn's and data from long term studies reporting its use in patients with psoriasis. Moreover, as 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).	Thank you for your comments. The treatment options and their clinical effectiveness similarity is discussed in section 3.2 and 3.8 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
11	Consultee (patient/carer groups)	British Society of Gastroenterology – IBD Section	We believe that the EAGs assumption of 20-year maximum treatment duration is unreasonable and far from in-keeping with existing clinical practice. Although Crohn's is a lifelong condition, most advanced therapies we prescribe eventually lose effect or have to be discontinued due to other patient related factors.	Thank you for your comments. The company submitted a new cost-comparison model with 10 years horizon after consultation, please see section 3.12- 3.13 of Final Draft Guidance.

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			Treatment persistence with biologics has been reported in literature 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 we believe that modelling should be performed based on a maximum 1-year duration of use. • Blesl A, Binder L, Högenauer C, et al. Limited long-term treatment persistence of first anti-TNF therapy in 538 patients with inflammatory bowel diseases: a 20-year real-world study. Aliment Pharmacol Ther. 2021 Sep;54(5):667-677. doi: 10.1111/apt.16478. Epub 2021 Jun 20. • Hanrahan, T.P.; Chan, R.; Tassone, D.; et al. O. Persistence of Second and Third-Line Biologics in Inflammatory Bowel Disease: A Multi-Centre Cohort Study. *Future Pharmacol.* 2022, *2*, 669-680.	
12	Consultee (patient/carer groups)	British Society of Gastroenterology – IBD Section	Finally, risankizumab has been granted approval for its use in EU (European Commission and USA (FDA) last year. Very promising early real-world evidence from US has been reported in particularly in patients who are refractory to several lines of advanced therapies: • D Alsoud, D Franchimont, F D'Heygere, et al. Real-world effectiveness and safety of risankizumab in patients with moderate-to-severe multi-refractory Crohn's disease: a Belgian multi-centric cohort study, *Journal of Crohn's and Colitis*, Volume 16, Issue Supplement_1, January 2022, Pages i516–i517 • Fumery M, Defrance A, Roblin X, et al. Effectiveness and safety of risankizumab induction therapy for 100 patients with Crohn's disease: A GETAID multicentre cohort study. Aliment Pharmacol Ther. 2023 Feb;57(4):426-434. doi: 10.1111/apt.17358. Epub 2022 Dec 19. PMID: 36534763. There is a desperate need for effective advanced therapies for patients with Crohn's disease. Patients with active Crohn's have to endure a burden of disease	Thank you for your comments. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.

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			that goes beyond just uncontrolled gastrointestinal inflammation with disabilities that effect psychological, financial and social circumstances. Active Crohn's disease additionally has a significant economic burden on the National Health Service with unplanned emergency care, preventable hospitalisation and surgery and loss of work. Risankizumab provides an additional 'lifeline' for our patients. With patients in the European Union and USA now being treated for Crohns disease with risankizumab, we strongly feel that lack of access to risankizumab will significantly disadvantage our patients in the NHS. We feel, at the very least, risankizumab should be made available to patients who have failed first line advanced immunosuppressive therapy.	
13	Clinical expert	Consultant Gastroenterologist at Guy's & St Thomas' Hospital	**Comparative effectiveness** Whilst I'm sure that I don't have a full appreciation of the difference in opinion regarding network meta-analysis (NMA) methodology, I'd like to state my opinion as a clinician with experience in clinical trials. Looking at the phase III data, risankizumab appears to be an efficacious treatment, and very much comparable to ustekinumab (as per the NMA presented by Abbvie). With the knowledge that a recently published RCT (SEAVUE, Sands et al., Lancet 2022) showed ustekinumab and adalimumab have equivalent efficacy, it would appear unlikely that there is any clinically significant difference between these mechanisms. On a similar note, whilst I appreciate that the EAG quite rightly states that "connections in network meta-analyses should be based on comparator connections, not drug characteristics", the problem here is that the maintenance placebo, used as the connection, is not really a pure placebo; instead it's a drug withdrawal arm. Surely, within this context the offset of action of the drug (which is in part, but not entirely, related to half-life) should be taken into account. In this regard, ustekinumab is pharmacologically much more similar to risankizumab than other biological mechanisms. Finally, there is now published data (Fumery et al., AP&T, 2023) from the French IBD group (GETAID) that demonstrates real world effectiveness, amongst a cohort of 100 patients, that is very much in keeping with that previously published for ustekinumab. Importantly, almost all of these patients had been exposed to all biologic mechanisms and a significant proportion (78.5%) responded to risankizumab nonetheless. As yet unpublished data from my own centre combined with that of another (n=48) also demonstrate similar findings. Again, suggesting that these agents are likely to perform in a comparable manner when used in clinical practice.	Thank you for your comments. Clinical effectiveness similarity is discussed in section 3.8 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
14	Clinical expert	Consultant Gastroenterologist at Guy's & St Thomas' Hospital	**Treatment duration** The switch from a 1-year treatment duration assumption (as used in previous NICE technology appraisals) to a 20-year treatment duration assumption appears a sizeable departure and perhaps unfeasible to deliver. Whilst it is true that fewer patients than previously are discontinuing treatment at a year due to complete	Thank you for your comments. The company submitted a new cost-comparison model with 10 years horizon after consultation, please see section 3.12- 3.13 of Final Draft Guidance.

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			remission, it is also true that very few patients (if any) have been on the same biologic agent for 20 years. Biologic treatment withdrawal, in the setting of sustained deep remission, is clearly still of interest to patients and clinicians alike, and does still take place - just perhaps after something like 4 or 5 years, rather than the previously recommended 1. To try and model 20 years of treatment from a yearlong RCT, even with a long-term extension going out to 2 or 3 years, seems likely to be imprecise and prone to a variety of biases.		Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
15	Clinical expert	Consultant Gastroenterologist at Guy's & St Thomas' Hospital	**Sequencing** Similar to the above point, 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. There are also several other outcomes which would be missing from this type of analysis, including surgery (of various types, which may or may not mean a temporary/permanent discontinuation of treatment) or enrolment into a clinical trial.		Thank you for your comments. The company submitted a new cost-comparison model with 10 years horizon after consultation, please see section 3.12- 3.13 of Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
16	Clinical expert	Consultant Gastroenterologist at Guy's & St Thomas' Hospital	**On body injector (OBI)** There is now available, in abstract form, robustly collected, prospective data from a substudy (n=46) of the FORTIFY RCT, which is reassuring in terms of patient experience using the OBI. This also includes maintained disease control and safety (reference: Loftus et al. *The American Journal of Gastroenterology* 117():p S10, December 2022.)		Thank you for your comments. Further discussion of the compliance of using an on-body device has been added to section 3.9 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
17	Clinical expert	Consultant Gastroenterologist at Guy's & St Thomas' Hospital	Overall, I would like to take this opportunity to reiterate what an effective and important treatment risankizumab could become for people with Crohn's, many of whom have been failed by the range of treatments currently available to them. As someone who sees the massive detrimental impact Crohn's disease can have, it would seem greatly unfair if patients were to be denied the possibility of achieving remission and a normal quality of life due to lack of access to this novel option. Even if NICE were to position its use after failure of (or contraindication to) anti-TNF therapy, this would still represent a significant step forward in Crohn's treatment and present a valuable opportunity to patients.		Thank you for your comments. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
18	Web comment	Submission 1	Has all of the relevant evidence been taken into account?	Yes - but it has not always been appropriately interpreted. The benefit of Risankizumab in patients failing several biologics including ustekinumab is very important as are the stable deltas above placebo in both bio naive and experienced patients	Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
19	Web comment	Submission 1	Are the summaries of clinical and and cost effectiveness reasonable interpretations of	I cannot comments as I have not seen this analysis.	Thank you for your comment.

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			the evidence?		
20	Web comment	Submission 1	Are the recommendations sound and a suitable basis for guidance to the NHS?	NO. This is clearly an effective drug that offers a benefit to patients with a chronic illness refractory to other treatments. My personal experience of using it has been hugely positive. It would be a very negative decision if this were not available in teh NHS	Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
21	Web comment	Submission 1	**[Section 1.1 recommendations]** This does not to my mind fit the clinical evidence from the induction / maintenance trials which show excellent clinical efficacy. This is evidence in biologic naive patients, but it is most notable in patients previously exposed to biologics. There is a strong signal of efficacy even in patients who have failed several prior biologics and / or ustekinumab. Unlike many other biologics - the delta of benefit over placebo remains similar in bio exposed to bio naive patients. This drug has great potential to improve patients QoL and prevent teh need for surgery.		Thank you for your comments. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
22	Web comment	Submission 1	**[Section 1.2 recommendations]** We have at least 10 patients with Crohn's disease on Rizankizumab through this scheme. By definition they had not responded to or lost response to all available biologic agents and had a markedly impaired QoL. The drug has shown exceptional benefit. It would by hugely disappointing if we were not able to use it for such patients in teh future.		Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
23	Web comment	Submission 1	**[Section 1.2 recommendations] "**Standard treatments for moderately to severely active Crohn's disease when conventional treatments stop working are biological treatments (such as adalimumab, infliximab, ustekinumab and vedolizumab). Risankizumab is another biological treatment." It is the first available biologic in the anti p19 class.		Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
24	Web comment	Submission 1	**[Section 1.2 recommendations] "**This is because risankizumab has only been compared indirectly with them and the results are uncertain because of differences between the populations included in the trials and how the trials were carried out." Important to recognise the strong signal of benefit with significance compare to placebo in patients who had failed multiple biologics including ustekinumab. This new class of drugs shows benefit where others do not		Thank you for your comment. Current treatment options and clinical effectiveness similarity is discussed in sections 3.2 3.8 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
25	Web comment	Submission 1	**[Section 1.2 recommendations] "**s less effective and more expensive than other biological treatments for people having a first biological treatment." I am not familiar with the model used for this submission. But the results of other network met analyses strongly suggest that it is as least as effective as other biologics with positive SUCRAs		Thank you for your comment. Clinical effectiveness similarity is discussed in section 3.2 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the

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					Final Draft guidance for more information.
26	Web comment	Submission 1	**[Section 2.5 Price]** Clearly this is of critical importance.		Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
27	Web comment	Submission 1	**[Section 3.1 Crohns disease] "**ed for surgery which is of importance to patients. People with Crohn's disease fear the loss of remission and the arrival of flares because of the major impact these have on their life. The committee concluded that Crohn's disease can have a profound effect on people's quality of life and ability to do day-to-day activities" There is a clear unmet need for therapies that target novel pathways. Risankizumab has a new MOA and strong evidence of benefit. My own experience of using it has been very positive. It has a potential to make a significant impact on the burden of refractory disease that has been shown to increase the risk of surgery and both direct and indirect health costs		Thank you for your comments. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
28	Web comment	Submission 1	**[Section 3.2 treatment options] "**The clinical experts stated that tumour necrosis factor-alpha (TNF-alpha) inhibitors (infliximab or adalimumab, including biosimilars) are usually used firs" This reflects the lower acquisition costs of biosimilars		Thank you for your comment.
29	Web comment	Submission 1	**[Section 3.4 Primary outcomes]** This was the first clinical trial in Crohn's disease to include endoscopic response as a primary outcome. As such it has a much more robust outcome that its predecessors.		Thank you for your comment.
30	Web comment	Submission 1	**[Section 3.7 Network meta-analyses:] "**It also noted ustekinumab and vedolizumab, used in the different networks, have a similar half-life and are comparable treatment options." the pharmacokinetic half line 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 is manifest in teh high rates of ongoing benefit in patients receiving induction dosing and then being re randomised to placebo		Thank you for your comments. Clinical effectiveness similarity is discussed in section 3.8 of the Final Draft Guidance. Please see the Final Draft guidance for more information.
31	Web comment	Submission 2	Has all of the relevant evidence been taken into account?	Yes	Thank you for your comment.
32	Web comment	Submission 2	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	I'd dispute the interpretations - see below	Thank you for your comment. We have responded to each of your points separately.
33	Web comment	Submission 2	Are the recommendations sound and a suitable basis for guidance to the	No	Thank you for your comment. Risankizumab is recommended for people who have

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			NHS?		had a previous biological treatment. Please see the Final Draft guidance for more information.
34	Web comment	Submission 2	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	No - but there is a significant inconsistency in the position NICE are taking with regards to risankizumab vs vedolizumab (where the trials data are MUCH weaker - but it is NICE approved)	Thank you for your comment. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
35	Web comment	Submission 2	As it stands the position being adopted by NICE is substantially unhelpful with regards to managing patients with complex Crohn's disease. By all means position risankizumab so that it cannot be used as first line biologic (or maybe even as 2nd line); and by all means negotiate a better price - but anti-il23-specific therapies are a major step forwards for the management of Crohn's globally, the clinical trials data (and personal experience of having 'disease-refractory' patients in these trials in Cambridge) show that risankizumab works sometimes where no other treatments work - and we should absolutely have this as a NICE-approved option perhaps for 3rd line therapy in otherwise treatment-refractory Crohn's. Not to do so will make the UK a global out-lier in IBD management and significantly disadvantage our patients. As a note some level of consistency is required here. Risa is undoubtedly more effective than vedolizumab in Crohn's - both from trials data and experience. The cost is likely broadly equivalent. Vedo is NICE approved for Crohn's. Risa certainly should be also.		Thank you for your comments. Clinical effectiveness similarity is discussed in section 3.8 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
36	Consultee (company)	AbbVie	Maintenance NMA, including use of single network and adjustment for temporal changes in placebo response rates (ACD Section 3.7)	Only a brief list of the key topics was provided by the company as it submitted updated analyses. See committee papers to see the updated analyses.	Thank you for your comments. Clinical effectiveness similarity is discussed in section 3.8 of the Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
37	Consultee (company)	AbbVie	Cost-comparison analysis (ACD Section 3.14)		Thank you for your comments. Section 3.12- 3.13 of Final Draft Guidance discusses the new cost-comparison model. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.
38	Consultee (company)	AbbVie	On-body device (treatment discontinuation and wastage) (ACD Section 3.8)		Thank you for your comments. Further discussion of the compliance of using an on-body device has been added to section 3.9 of the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row		NICE Response Please respond to each comment
					Final Draft Guidance. Risankizumab is recommended for people who have had a previous biological treatment. Please see the Final Draft guidance for more information.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
[ID3986] risankizumab - CCUK DG stakeholder comments form RZ 140223.docx	Crohn's & Colitis UK	None	4	
[ID3986] risankizumab - DG stakeholder comments form - Kamila Kingstone RZ 150223.docx	N/A	N/A	4	
[ID3986] risankizumab - DG stakeholder comments form BSG 080223 RZ.docx	[British Society of Gastroenterology – IBD Section]	[None relevant to disclose]	4	
[ID3986] risankizumab - DG stakeholder comments form_Mark Samaan RZ 010223.docx	Invited clinical expert for initial committee meeting Consultant Gastroenterologist at Guy's & St Thomas' Hospital	Advisory fees: Janssen, Takeda, Sandoz, Samsung Bioepis, Galapagos, AbbVie, Bristol-Myers Squibb, Pfizer, Tillotts Lecture fees: Bristol-Myers Squibb, Janssen, Takeda, MSD, Falk, AbbVie, Galapagos	5	
Web comments	NA			Added manually
Company's comments	AbbVie			Added manually

[i] Haens et al, 2022, Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials, Lancet 2022; 399: 2015–30

[ii] Ferrente et al, 2022, Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial, Lancet 2022; 399: 2031–46

[iii] Odes S, Vardi H, Friger M , et al. ; European Collaborative Study on Inflammatory Bowel Disease. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology* 2006 ;131:719–28

[iv] Nursing Times online, 2022, Stoma savings: helping to reduce waste and spend in the NHS - Stoma savings: helping to reduce waste and spend in the NHS | Nursing Times

[v] IBD UK, IBD Standards, Self-management page

[vi] Wickman et al, 2016, Self-Care Among Patients With Inflammatory Bowel Disease, Gastroenterology Nursing 39(2):p 121-128

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Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AbbVie Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	As these are detailed technical responses that include tables and figures, full details are presented from Page 4 onwards. A brief list of the key topics covered is provided below.
1 (Page 4)	Maintenance NMA, including use of single network and adjustment for temporal changes in placebo response rates (ACD Section 3.7)
2 (Page 11)	Cost-comparison analysis (ACD Section 3.14)
3 (Page 20)	On-body device (treatment discontinuation and wastage) (ACD Section 3.8)

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Dear Appraisal Committee Members,

Thank you for the opportunity to comment on the appraisal consultation document (ACD) for risankizumab for previously treated moderately to severely active Crohn's disease (CD). We remain committed to resolving any remaining issues to enable patient access to risankizumab in this area of extremely high unmet need.

AbbVie acknowledge the comments outlined in the ACD around the maintenance network meta-analysis (NMA), cost-effectiveness model, and on-body device (OBD). However, we believe that the changes to the economic modelling approach outlined in the ACD diverge from clinical practice and from the precedents set in previous NICE CD technology appraisals (TAs), including TA456 (1) and TA352 (2).

Whilst we maintain that the maintenance NMA methodology applied in the company submission (CS) is clinically justified and robust, we have presented new maintenance NMAs that were conducted based on the committee's preferences. Key changes to the NMA methods include using a single maintenance network (previously a split network) and applying baseline adjustment for the temporal variation in placebo response rates. Consistent with the results of all previous NMAs presented during the different phases of this submission, the latest NMA results showed comparable efficacy between risankizumab and comparators for Crohn's Disease Activity Index (CDAI) clinical remission in the maintenance period. Therefore, as suggested by the committee, AbbVie developed a cost-comparison model to compare costs to the NHS of risankizumab versus comparators in the target population.

Healthcare professionals and patients have been in desperate need of additional effective therapies for CD, a highly debilitating and progressive disease with very limited advanced treatment options. AbbVie is committed to working with NICE to enable immediate access to risankizumab. At a price of [redacted] per unit for induction and maintenance treatments, cost-comparison analysis showed that risankizumab is cost saving versus all comparators.

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COMPANY RESPONSE

1. Network meta-analysis (NMA)

The committee disagreed with the company's approach to the maintenance NMAs, which split the evidence into two networks for (1) risankizumab and ustekinumab, and (2) the rest of the relevant comparators, for both the conventional care failure (CCF) and biologic failure (BF) populations. The committee preferred the use of a single network in combination with adjustment for temporal effect (this adjustment assumes that the variation observed in maintenance placebo response rates was the result of changes in rates over time). The committee also requested risk ratios (relative risks) rather than risk differences to describe the effects of the comparator treatments and suggested exploration of random effects (RE) models with informative priors (based on the work presented in Turner et al. 2014 (3)) as well as fixed effect (FE) models.

Throughout the risankizumab CD technology appraisal, AbbVie have conducted multiple NMAs for risankizumab versus comparators using several different methodologies, including a split network (in the CS) and single network (in clarification questions and technical engagement) for the maintenance period. The results have been consistent across the different NMA approaches, showing that risankizumab has broadly comparable efficacy to the rest of the comparators in CD, except for placebo where risankizumab always shows superiority (in line with the outcomes of the risankizumab CD clinical trials).

The company maintains that using a split network is the best approach for adjusting for the heterogeneity observed across the comparator trials. It is important to acknowledge that the heterogeneity in the trials included in the NMAs is not solely the result of the temporal effect (i.e., the years in which the relevant clinical trials were conducted) but is also related to other factors, including trial design (e.g., placebo withdrawal design) and duration of induction phase as well as drug mechanism of action, pharmacokinetics and pharmacodynamics. These factors were not acknowledged in the ACD, in which the focus was on the temporal effect. As described in the CS, when the split network was used, placebo heterogeneity was considerably reduced in the

interleukin (IL) inhibitor network and the direct comparability of risankizumab and ustekinumab greatly improved. There was also a clear differentiation in placebo efficacy in the maintenance trials, with risankizumab and ustekinumab demonstrating placebo remission rates that were sustained for notably longer than other comparators in the NMA; this was likely due to differences in the long-term effects of ustekinumab and risankizumab on pathological processes in CD versus other comparators.

Furthermore, the split network consistently produced results that reflect the comparator clinical trial data and clinical practice. In contrast, results obtained using alternative approaches lack face validity, as indicated by wide credible intervals (CrIs), reduced efficacy with biologic therapies versus placebo (e.g., risankizumab showed no marked difference from placebo in the NMAs, which contradicts data from the clinical trials), and inflation of absolute treatment efficacy (e.g., in the maintenance NMA with adjustment for temporal effect in the CCF population, adalimumab showed an 88% probability of response versus placebo [baseline regression year 2020; posterior probability of response 0.88; 95% CrI 0.71, 0.96]).

Nevertheless, the company has rerun the maintenance NMAs using the methodology proposed by the EAG and preferred by the committee (based on information provided during technical engagement) and the recommendations outlined in NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2 (4) and 5 (5). A summary of the changes made to the maintenance NMAs is provided in Table 1.

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Table 1: Summary of amendments to the maintenance NMA

Original maintenance NMA (as presented in CS)	Updated maintenance NMA based on EAG/NICE preferences	Additional information
Split network (1. RZB and UST; 2. rest of the comparators), applied to both CCF and BF populations	Single network, applied to both CCF and BF populations	Updated network diagrams for the single maintenance NMA networks are presented in Figure 1 (CCF) and Figure 2 (BF).
No baseline risk adjustment	Baseline adjustment for temporal effect in placebo response rates	The updated NMAs model the placebo clinical remission rates (expressed using the CDAI measure) to include a temporal association with the time at which the respective clinical trials were conducted (baseline years: 2000, 2010, or 2020). As all trials in the network use placebo as the reference treatment, the estimation of baseline risk based on the year of the respective trial is included in the NMA model directly. The placebo clinical remission rate in the maintenance trials served as the dependent variable and the year in which the trials were conducted was the independent variable. As the baseline risk is assumed to be based only on the year of the respective trial, the model converges for the 'baseline year' regression. Crucially, inherent in the single network with adjustment for temporal effect is the assumption that the heterogeneity results solely from a time difference (i.e., the years in which the relevant clinical trials were conducted). This methodology is an oversimplification of the issue of placebo heterogeneity and, although time may have an impact, other potential sources of heterogeneity, such as trial design, drug mechanism of action, pharmacokinetics and pharmacodynamics, have not been considered.
Efficacy outcomes described using the risk difference measure	Efficacy outcomes described using the risk ratio measure	As described in the CS, the risk difference measure was used because it addressed placebo rate variation observed in the biologic CD trials, yielded reasonable estimates, passed diagnostic tests based on model convergence and fit, has been used in prior NICE submissions, and has appeared in the published academic literature. However, following the committee's request, the risk ratio measure is used in the updated NMAs.
FE model (base case) and RE model (scenario)	RE model (base case) and FE model (scenario)	Given the general data sparsity, a FE framework was used in the base case analysis in the CS to avoid producing credible intervals that did not pass validity. In addition, given the similar DIC values between the FE and random effect (RE) models, the FE model was preferred since it is easier to interpret (as recommended

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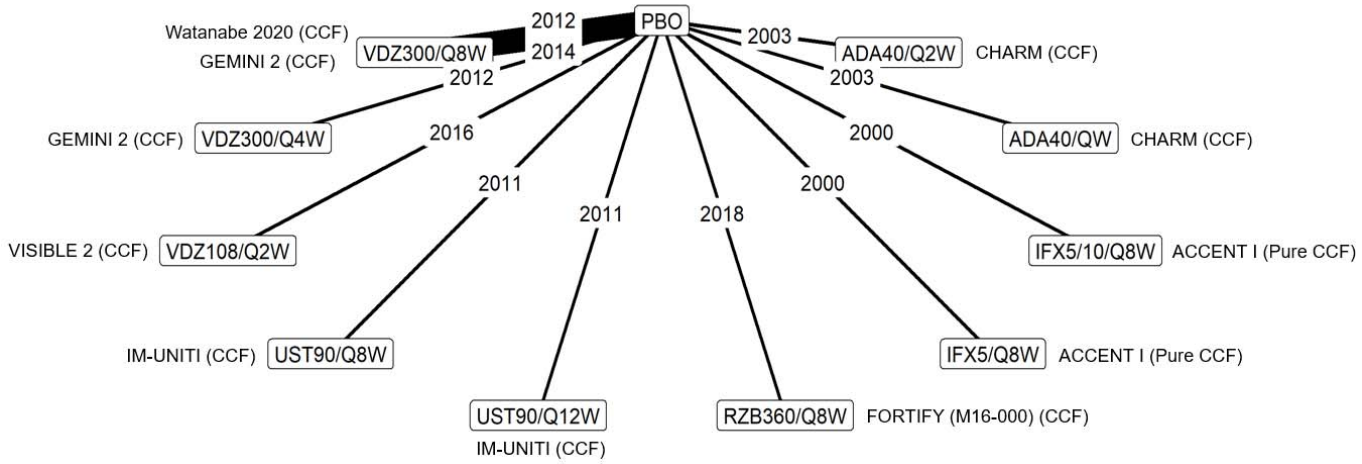
Original maintenance NMA (as presented in CS)	Updated maintenance NMA based on EAG/NICE preferences	Additional information
		by NICE DSU TSD 2 (4). However, following the committee's request, the RE frameworks is used in the base case of the updated NMAs.
No informative prior	Informative prior	A Turner et al. (2014) prior for general case was used on the heterogeneity parameter (i.e., baseline risk) in the RE model (3). Otherwise, vague priors were used. More precisely, the priors were derived as log-normal distributions for the between-study variance, applicable to meta-analyses of binary outcomes reported on the log odds-ratio scale.

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CS, company submission; DIC, deviance information criteria; DSU, Decision Support Unit; EAG, External Assessment Group; IFX, infliximab; FE, fixed effects; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RE, random effects; RZB, risankizumab; TSD, Technical Support Document; UST, ustekinumab; VDZ, vedolizumab.

Network diagrams for the maintenance NMAs with adjustment for the temporal effect in the CCF and BF populations are presented in Figure 1 and Figure 2, respectively.

Figure 1: Single network diagrams of included maintenance studies in CCF population



Abbreviations: ADA, adalimumab; CCF, conventional care failure; IFX, infliximab; PBO, placebo; QxW, every x weeks; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

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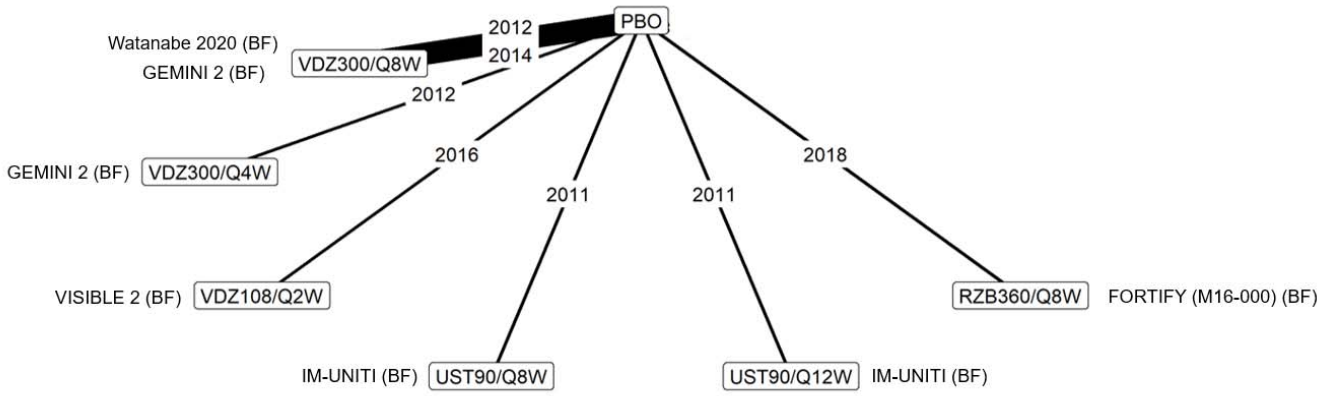
Figure 2: Single network diagram of included maintenance studies in BF population



Abbreviations: BF, biologic failure; PBO, placebo; QxW, every x weeks; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

Results

The results of the updated NMAs for the CCF and BF populations are presented in Table 2 and Table 3, respectively. As requested by the committee, data presented are posterior risk ratios (95% CrI) for CDAI clinical remission with risankizumab versus comparators using RE models (with informative priors). The risk ratio results of FE models (Table 9 and Table 10) are presented in the Appendix. Overall, the outcomes of the updated maintenance NMAs show that risankizumab has comparable efficacy with the other biologic therapies for CD.

In the RE model for the CCF population, the risk ratios for risankizumab versus active comparators ranged from [redacted] to [redacted] with baseline regression year 2000 and from [redacted] to [redacted] with baseline regression year 2010 (Table 2). With 2020 as the baseline regression year, the range narrowed to [redacted] to [redacted]. No statistically significant differences were observed, indicating equivalent efficacy between all treatments regardless of the baseline regression year. Consistent findings were observed in the FE model (Table 9).

In the RE model for the BF population, the risk ratios ranged from [redacted] to [redacted] with 2000 as the baseline regression year, from [redacted] to [redacted] with 2010 as the baseline regression year, and from [redacted] to [redacted] with 2020 as the baseline regression year. These narrow ranges were consistent across the RE (Table 3) and FE (Table 10) models. Similar to the CCF population, for the BF population, no statistically significant differences were observed, showing comparable efficacy between the treatments regardless of the baseline regression year.

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. The clinical comparability of risankizumab and other active treatments was also supported by clinical expert opinion after presenting the results of these and all previously submitted NMAs. However, it is important to note that the results of the updated single-network maintenance NMAs lack face validity and the minimal difference between risankizumab and placebo does not align with the results of the risankizumab clinical trials, in which risankizumab demonstrated greater efficacy versus placebo.

Given that these biologic therapies have been shown to have similar efficacy regardless of the NMA methodology that has been used, the company followed the suggestion of the committee and conducted a cost-comparison analysis (see Section 2).

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Table 2: Results of the single-network maintenance NMA, with adjustment for the temporal effect, for CDAI clinical remission in CCF population (RE model)

Posterior risk ratio (95% CrI), RZB vs comparators	Baseline year regression (2000)	Baseline year regression (2010)	Baseline year regression (2020)
PBO	[redacted]	[redacted]	[redacted]
ADA Q2W	[redacted]	[redacted]	[redacted]
ADA QW	[redacted]	[redacted]	[redacted]
IFX5/10 Q8W	[redacted]	[redacted]	[redacted]
IFX5 Q8W	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[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.

Table 3: Results of the single-network maintenance NMA, with adjustment for the temporal effect, for CDAI clinical remission in BF population (RE model)

Posterior risk ratio (95% CrI), RZB vs comparators	Baseline year regression (2000)	Baseline year regression (2010)	Baseline year regression (2020)
PBO	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[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.

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2. Cost-comparison model

The updated NMAs presented above indicate comparable clinical efficacy (CDAI clinical remission) between risankizumab and the relevant comparators for the treatment of previously treated moderately to severely active CD. As mentioned in the previous Section, this conclusion on clinical comparability has been validated with clinical experts. Accordingly, in line with the committee's recommendation, the company performed a cost-comparison analysis for risankizumab versus all relevant comparator biologic therapies.

Methods

Overview

A cost-comparison analysis was conducted to evaluate the cost to the NHS of using risankizumab versus adalimumab, infliximab, ustekinumab and vedolizumab for previously treated moderately to severely active CD. The cost-comparison model was developed in Microsoft Excel.

Model features

Comparators

In the model, risankizumab is compared against tumour necrosis factor (TNF)-alpha inhibitors (adalimumab, infliximab, and their biosimilars), ustekinumab and vedolizumab, as these are both aligned with the committee's recommendation of relevant comparators, and are treatments approved by NICE for the treatment of moderately to severely active CD and would be displaced by the introduction of risankizumab.

Time horizon

The base-case time horizon (biologic treatment duration) in the model is 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.

Discounting

Costs were not discounted in the analysis in line with the NICE user guide for cost-comparison appraisals (6).

Model inputs

Intervention and comparator acquisition costs

Unit costs for comparators were sourced from the British National Formulary (7-10) and are presented in Table 6.

Ustekinumab intravenous (IV) dosing is weight-based. An average dose of 390 mg, equating to three 130 mg vials, was calculated based on trial population data presented in the ustekinumab Summary of Product Characteristics (SmPC) (11). The weight characteristics of the model population reflects the weight distribution of patients from the post-hoc analysis of the risankizumab CD clinical trials, as shown in Table 4.

Table 4: Weight distribution characteristics and corresponding UST induction dose

Parameter	Value	UST induction dose	Source
Proportion ≤55kg*	[redacted]	260 mg	Distribution: Post-hoc analysis of MOTIVATE and ADVANCE ITT1A population (12); dosing: UST SmPC (11)
Proportion >55kg and ≤85kg*	[redacted]	390 mg	
Proportion >85kg*	[redacted]	520 mg	

Abbreviations: ITT, intention to treat; SmPC, Summary of Product Characteristics; UST, ustekinumab.
*Weight distribution for a mean weight of 71.1 kg.

Adalimumab, infliximab, ustekinumab and vedolizumab are all available as either standard-dose or high-dose maintenance therapy. The proportion of patients on the standard and high doses of the comparator interventions is based on UK clinical expert input (13) and presented in Table 5 (the same values were used in the CS, Table 74). Risankizumab is administered as a fixed dose and therefore has no high-dose maintenance therapy option.

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Table 5: Proportion of patients on standard- and high-dose maintenance therapy in the cost-comparison model

Intervention	Proportion of patients on standard-dose maintenance therapy	Proportion of patients on high-dose maintenance therapy
RZB	100%	N/A
ADA 160/80	50.0%	50.0%
ADA 80/40	50.0%	50.0%
ADA biosimilar	50.0%	50.0%
IFX IV	60.0%	40.0%
IFX IV biosimilar	60.0%	40.0%
IFX SC	100%	N/A
UST	7.5%	92.5%
VDZ IV	70.0%	30.0%
VDZ SC	100%	N/A

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; N/A, not applicable; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

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Table 6: Acquisition costs of RZB and comparators

Treatment	Pharmaceutical formulation	Anticipated care setting	Acquisition cost per unit	Acquisition cost (excluding VAT): Year 1	Acquisition cost (excluding VAT): Year 2+	Method of administration	Recommended dose (standard)	Dosing frequency (standard)	Dose escalation (maintenance)
RZB (PAS price)	600 mg solution for infusion 360 mg solution for injection	Secondary care	IV: [redacted] SC: [redacted]	Induction: [redacted] Maintenance: [redacted] **Total:** [redacted]	[redacted]	Induction: IV Maintenance: SC	Induction: 600 mg Maintenance: 360 mg	Induction: weeks 0, 4 and 8 Maintenance: Q8W from week 12	N/A
ADA 160/80 (Humira®)	80 mg/0.8 mL solution for injection in pre-filled pen/syringe	Secondary care	SC: £704.28	Induction: £2,112.84 Maintenance: £12,677.04 **Total: £14,789.88**	£13,733.46	Induction: SC Maintenance: SC	Induction: 160/80 mg Maintenance: 40 mg	Induction: 160 mg at week 0; 80 mg SC at week 2 Maintenance Q2W from week 4	40 mg SC QW
ADA 80/40 (Humira®)	40 mg/0.4 mL solution for injection in pre-filled pen/syringe	Secondary care	SC: £352.14	Induction: £1,056.42 Maintenance: £12,677.04 **Total: £13,733.46**	£13,733.46	Induction: SC Maintenance: SC	Induction: 80/40 mg Maintenance: 40 mg	Induction: 80 mg SC at week 0; 40 mg SC at week 2 Maintenance: Q2W from week 4	40 mg SC QW
ADA (cheapest biosimilar available)	40 mg/0.4 mL solution for injection in pre-filled pen	Secondary care	SC: £316.80	Induction: £1,900.80 Maintenance: £11,404.80 **Total: £13,305.60**	£12,355.20	Induction: SC Maintenance: SC	Induction: 160/80 mg Maintenance: 40 mg	Induction: 160 mg at week 0; 80 mg SC at week 2 Maintenance: Q2W from week 4	40 mg SC QW

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Treatment	Pharmaceutical formulation	Anticipated care setting	Acquisition cost per unit	Acquisition cost (excluding VAT): Year 1	Acquisition cost (excluding VAT): Year 2+	Method of administration	Recommended dose (standard)	Dosing frequency (standard)	Dose escalation (maintenance)
IFX IV (Remicade®)	100 mg powder for concentrate for solution for infusion	Secondary care	IV: £419.62	***Blended IV/SC*** Induction: £3,356.96 Maintenance: £11,392.71 **Total: £14,749.67** ***Blended IV biosimilar/SC*** Induction: £3,016.00 Maintenance: £10,676.69 **Total: £13,692.69**	***Blended IV/SC*** £12,546.66 ***Blended IV biosimilar/SC*** £11,770.98	Induction: IV Maintenance: IV	Induction: 5 mg/kg Maintenance: 5 mg/kg	Induction: weeks 0 and 2 Maintenance: Q8W from week 6	10 mg/kg Q8W
IFX IV (cheapest biosimilar available)	100 mg powder for concentrate for solution for infusion	Secondary care	IV: £377.00			Induction: IV Maintenance: IV	Induction: 5 mg/kg Maintenance: 5 mg/kg	Induction: weeks 0 and 2 Maintenance: Q8W from week 6	10 mg/kg Q8W
IFX SC (Remsima® SC)	120 mg solution for injection in pre-filled pen	Secondary care	IV: £377.00 SC: £377.66			Induction: IV Maintenance: SC	Induction: 5 mg/kg Maintenance: 120 mg	Induction: weeks 0 and 2 Maintenance: Q2W from week 6	N/A
UST (Stelara®) (list price)	130 mg/26 mL concentration for solution for infusion vial 90 mg/1 mL solution for injection in pre-filled syringe	Secondary care	IV: £2,147.00 SC: £2,147.00	Induction: £6,436.71 Maintenance: £12,559.95 **Total: £18,996.66**	£13,606.61	Induction: IV Maintenance: SC	Induction: 6 mg/kg Maintenance: 90 mg	Induction: week 0 Maintenance: Q12W from Week 8	Q8W

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Treatment	Pharmaceutical formulation	Anticipated care setting	Acquisition cost per unit	Acquisition cost (excluding VAT): Year 1	Acquisition cost (excluding VAT): Year 2+	Method of administration	Recommended dose (standard)	Dosing frequency (standard)	Dose escalation (maintenance)
VDZ IV (300 mg) (Entyvio®)	300 mg powder for concentrate for solution for infusion vials	Secondary care	IV: £2,050.00	***Blended IV/SC*** Induction: £6,150.00 Maintenance: 11,838.75 **Total: £17,988.75**	***Blended IV/SC*** £15,323.75	Induction: IV Maintenance: IV	Induction: 300 mg Maintenance: 300 mg	Induction: weeks 0, 2 and 6 Maintenance: Q8W from week 14	Q4W
VDZ SC (108 mg) (Entyvio®)	300 mg powder for concentrate for solution for infusion vials 108 mg/0.68 mL solution for injection in pre-filled pen/syringe	Secondary care	IV: £2,050.00 SC: £512.50			Induction: IV Maintenance: SC	Induction: 300 mg Maintenance: 108 mg	Induction: weeks 0, 2 and 6 Maintenance: Q2W from week 14	N/A

Abbreviations: ADA, adalimumab; BNF, British National Formulary; IFX, infliximab; IV, intravenous; N/A, not applicable; PAS, Patient Access Scheme; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; TA, technology appraisal; UST, ustekinumab; VAT, value-added tax; VDZ, vedolizumab.

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Intervention and comparator healthcare resource use and associated costs

Risankizumab is administered IV in the induction period and by OBD in the maintenance period. Adalimumab is administered subcutaneously (SC) in the induction and maintenance periods. Ustekinumab is administered IV in the induction period and SC in the maintenance period. Infliximab and vedolizumab are administered IV in the induction period and either IV or SC in the maintenance period. The decision to use the IV or SC regimens of infliximab and vedolizumab depends on many factors, including clinical judgement, patient preference and resource availability (14, 15). Therefore, in the cost-comparison analysis, a blended approach to the IV and SC maintenance regimens of infliximab and vedolizumab was used. The analysis assumed a 50/50 split between patients receiving the IV or SC maintenance regimens, meaning that risankizumab was compared against:

- Adalimumab 160/80
- Adalimumab 80/40
- Adalimumab biosimilar
- Infliximab IV/SC (50% IV/50% SC)
- Infliximab IV biosimilar/SC (50% IV/50% SC)
- Ustekinumab
- Vedolizumab IV/SC (50% IV/50% SC)

Infusions (IV) were administered in a hospital setting (for first and subsequent doses), and therefore all doses were costed at £245.00. SC administrations assumed a cost for the first dose only (training by a nurse) at £41.00 and no additional cost to the NHS for subsequent doses (as these are typically self-administered). Details of the number of units and associated administration costs for risankizumab and comparators are presented in Table 7.

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Table 7: Resource costs of the intervention and comparator technologies (Year 1 and Year 2+)

Intervention		Year 1			Year 2+	Reference
		Induction	Maintenance	Total		
RZB	Number of units	3.00	5.00	**8.00**	6.50	**IV costs:** NHS Payment by Results tariff 2020/21 (16) – Inflammatory Bowel Disease without Interventions, with CC Score 0 (item code: FD02H) accessed in June 2022, consistent with TA352 (2). **SC costs:** PSSRU 2021 (17) Cost per working hour of band 5 Nurse, accessed in June 2022.
	Costs	£735.00	£41.00	**£776.00**	£0.00	
ADA 160/80	Number of units	2.00	36.00	**38.00**	39.00	
	Costs	£41.00	£0.00	**£41.00**	£0.00	
ADA 80/40	Number of units	2.00	36.00	**38.00**	39.00	
	Costs	£41.00	£0.00	**£41.00**	£0.00	
ADA biosimilar	Number of units	2.00	36.00	**38.00**	39.00	
	Costs	£41.00	£0.00	**£41.00**	£0.00	
IFX IV/SC	Number of units	2.00	14.50	**16.50**	16.25	
	Costs	£490.00	£755.50	**£1,245.50**	£796.25	
IFX IV biosimilar/SC	Number of units	2.00	14.50	**16.50**	16.25	
	Costs	£490.00	£755.50	**£1,245.50**	£796.25	
UST	Number of units	1.00	5.85	**6.85**	6.34	
	Costs	£245.00	£41.00	**£286.00**	£0.00	
VDZ IV/SC	Number of units	3.00	12.90	**15.90**	17.23	
	Costs	£735.00	£853.50	**£1,588.50**	£1,035.13	

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; N/A, not applicable; NHS, National Health Service; PAS, Patient Access Scheme; PSSRU, Personal Social Services Research Unit; RZB, risankizumab; SC, subcutaneous; TA, technology appraisal; UST, ustekinumab; VDZ, vedolizumab.

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Results

In the analysis presented below, the risankizumab PAS price is compared to the list price of the comparators. As PAS prices are confidential, it was not feasible to perform cost-comparison analyses using PAS prices for the comparator biologic therapies.

Base-case results

Results of the base-case analysis are presented in Table 8. The total costs with risankizumab were [redacted]. Risankizumab was associated with lower costs than all other treatments.

Table 8: Base-case results – 10-year treatment duration

Technology	Total costs
RZB ([redacted] unit price)	[redacted]
ADA 160/80 (list price)	£138,432
ADA 80/40 (list price)	£137,376
ADA biosimilar	£124,543
IFX IV/SC (list price)	£136,081
IFX IV biosimilar/SC (list price)	£128,043
UST (list price)	£141,742
VDZ IV/SC (list price)	£166,807

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

The savings associated with risankizumab are derived from the lower acquisition and administration costs for risankizumab versus comparators. The unit cost of [redacted] for risankizumab CD for the induction and maintenance treatments also offers acquisition cost savings. The OBD reduces the requirement for healthcare professional support with maintenance treatment and therefore reduces administration costs compared with comparator IV formulations.

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3. On-body device

As discussed in the CS, maintenance risankizumab therapy was administered as four SC injections in FORTIFY but will be administered using an OBD in clinical practice. The committee was satisfied with results from other clinical trials which showed bioequivalence for risankizumab CD administered using the OBD or via SC injection, and also concluded that people with CD are likely to welcome the OBD as an alternative drug delivery mechanism (ACD Section 3.8). However, the committee noted that the OBD may affect treatment adherence compared with clinical trial data because of lack of experience with the device. Therefore, the committee requested additional exploratory analyses around the effects of the OBD on treatment discontinuation and wastage (ACD Section 3.14).

As reported in Appendix E of the technical engagement response form, M16-000 sub-study 4 was an open-label OBD administration and long-term extension study (18). The study evaluated participants' ability to self-administer risankizumab using an OBD and found that all patients were able to successfully self-administer risankizumab. Patients rated their experience and device acceptability, with scores indicating positive feelings about the OBD.

The extent of drug wastage with risankizumab CD is unlikely to differ from that of comparators. Adalimumab, infliximab, ustekinumab and vedolizumab are all single-use formulations (whether IV or SC). Therefore, any wastage with risankizumab would equally apply to all biologic therapies, negating any impact on economic outcomes.

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APPENDIX

Temporal NMA – risk ratios (FE model)

Table 9: Results of the single-network maintenance NMA, with adjustment for the temporal effect, for CDAI clinical remission in CCF population (FE model)

Posterior risk ratio (95% CrI), RZB vs comparators	Baseline year regression (2000)	Baseline year regression (2010)	Baseline year regression (2020)
PBO	[redacted]	[redacted]	[redacted]
ADA Q2W	[redacted]	[redacted]	[redacted]
ADA QW	[redacted]	[redacted]	[redacted]
IFX5/10 Q8W	[redacted]	[redacted]	[redacted]
IFX5 Q8W	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]

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

Table 10: Results of the single-network maintenance NMA, with adjustment for the temporal effect, for CDAI clinical remission in BF population (FE model)

Posterior risk ratio (95% CrI), RZB vs comparators	Baseline year regression (2000)	Baseline year regression (2010)	Baseline year regression (2020)
PBO	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[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; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Crohn's & Colitis UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We agree with the points raised in the British Society of Gastroenterology's submission.
2	We are concerned that the recommendation will disadvantage patients with Crohn's disease as there is an urgent need for more options for effective advanced therapies. Risankizumab is an innovative medicine with a novel mechanism of action. This has the potential to provide a lifeline for patients with Crohn's disease who have not responded to other treatments, or in whom other treatments have failed, and who have very limited other options. Patients with uncontrolled disease experience severe disabilities that affect their psychological, financial and social wellbeing. There is currently no medical or surgical cure for the condition and current available treatments are aimed at inducing and maintaining remission and improving quality of life. 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. This can have a profound effect on someone's work and education prospects as well as there being a significant cost for the health service in terms of the cost of emergency A&E visits and planned surgery. We urge the committee to reconsider their decision.
3	We are concerned with the draft guidance's over emphasis on the results of the network meta-analysis and the lack of direct comparison data with other biologics. In clinical practice, it is likely that this biologic will be given when most, if not all others have failed, offering a vital lifeline to patients who wish to delay surgery. The ADVANCE and MOTIVATE trials for example both had patients that had been categorised as having previous bio-failure with inadequate response or intolerance to one or more biologic. In the ADVANCE trial, 58% of participants had failed previous biologic therapy and 30% had failed more than one biologic. In the MOTIVATE trial, all participants had failed previous biologic therapy and 53% had failed more than one biologic[i]. In the FORTIFI trial, 73% of participants had failed previous biologic therapy and 40% had failed more than one biologic[ii]. The results of the trials clearly showed that Risankizumab was effective in inducing remission in those who had previously failed other treatments, offering patients the opportunity to regain their health and their quality of life. We know that surgery would remain the only option for some patients in the absence of Risankizumab. This can have a significant physical and mental impact on patients as well as cause a considerable cost to the health service. For example, a cost analysis of more than 1,200

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	IBD patients revealed a total health care cost of €2,548 per patient-year for Crohn's Disease and €1,524 for ulcerative colitis, with over half of the health care costs arising from hospitalisation and surgery[iii]. For many people, surgery for Crohn's Disease results in a stoma, which has additional healthcare costs in terms of stoma supplies. Each year the UK spends approximately £364m on stoma products with the average clinical commissioning groups spend being £2.14m[iv]. There is also an economic impact due to time required off work both for the initial surgery and recovery – and, for some patients, ongoing time off as they adjust to life post-surgery. For many patients with Crohn's Disease, the prospect of surgery is one they face with considerable anxiety, and it can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. Clinical outcomes after pouch surgery remain variable and fertility in women can be significantly affected by any pelvic surgery.
4	We believe that the committee's concerns with the compliance of using an on-body device in the draft guidance are overstated. By the time most patients with Crohn's disease are prescribed Rizankizumab, they will have tried other medication that requires self-administration such as adalimumab, infliximab, ustekinumab. 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[v]. 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[vi]. Furthermore, one of the key advantages of the on-body device is that it would give patients a treatment option to be taken at home. As well as being more convenient for patients, this has economic advantages as it reduces the need to take time off work to attend hospital for treatment and reduces travel and parking costs for the patient. It also reduces the time healthcare professionals need to spend on drug administration, freeing up capacity within busy IBD teams.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

[i] Haens et al, 2022, Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials, Lancet 2022; 399: 2015–30

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[iv] Nursing Times online, 2022, Stoma savings: helping to reduce waste and spend in the NHS - Stoma savings: helping to reduce waste and spend in the NHS | Nursing Times

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Society of Gastroenterology – IBD Section**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None relevant to disclose**]

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the recommendation will disadvantage patients in the NHS access to a highly effective therapy for Crohn's disease. I understand these recommendations have been made due to economic modelling and differences in methodological views on appropriate network meta-analysis. We accept that comparative analysis of advanced therapies in IBD heavily rely on network meta-analysis in absence of head to head trial data. A recently published network meta-analysis by Alex Ford's group in Gut compared efficacy of advanced therapies for Crohns disease (*Barberio B, Gracie DJ, Black CJ, et al. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut 2023*). They showed that whilst infliximab 5mg/kg ranked first for induction of clinical remission in all patients with luminal CD, but **risankizumab 600mg was first in both biologic-naïve and biologic-exposed patients**. This comparative analysis included all approved advanced therapies (infliximab, adalimumab vedolizumab, ustekinumab) as well as novel drugs currently undergoing NICE appraisal in the same analysis similar to that recommended by the EAG.
2	In addition to its superior indirect comparative efficacy ranking, risankizumab has several advantages over some of the existing therapies. The burden on IBD services and infusion units have led to a significant shift in considering non-intravenous based maintenance therapies for treatment of Crohn's disease. 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. Risankizumab has also demonstrated a favourable safety profile in the clinical trial for Crohn's and data from long term studies reporting its use in patients with psoriasis. Moreover, as 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).
3	We believe that the EAGs assumption of 20-year maximum treatment duration is unreasonable and far from in-keeping with existing clinical practice. Although Crohn's is a lifelong condition, most advanced therapies we prescribe eventually lose effect or have to be discontinued due to other patient related factors. Treatment persistence with biologics has been reported in literature with median durations of 2 to 3 years; this itself is an argument for the ongoing need of effective

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	advanced therapies. Consistent with previous NICE TAs we believe that modelling should be performed based on a maximum 1-year duration of use. • Blesl A, Binder L, Högenauer C, et al. Limited long-term treatment persistence of first anti-TNF therapy in 538 patients with inflammatory bowel diseases: a 20-year real-world study. Aliment Pharmacol Ther. 2021 Sep;54(5):667-677. doi: 10.1111/apt.16478. Epub 2021 Jun 20. • Hanrahan, T.P.; Chan, R.; Tassone, D.; et al. O. Persistence of Second and Third-Line Biologics in Inflammatory Bowel Disease: A Multi-Centre Cohort Study. *Future Pharmacol.* 2022, *2*, 669-680.
4	Finally, risankizumab has been granted approval for its use in EU (European Commission and USA (FDA) last year. Very promising early real-world evidence from US has been reported in particularly in patients who are refractory to several lines of advanced therapies: • D Alsoud, D Franchimont, F D'Heygere, et al. Real-world effectiveness and safety of risankizumab in patients with moderate-to-severe multi-refractory Crohn's disease: a Belgian multi-centric cohort study, *Journal of Crohn's and Colitis*, Volume 16, Issue Supplement_1, January 2022, Pages i516–i517 • Fumery M, Defrance A, Roblin X, et al. Effectiveness and safety of risankizumab induction therapy for 100 patients with Crohn's disease: A GETAID multicentre cohort study. Aliment Pharmacol Ther. 2023 Feb;57(4):426-434. doi: 10.1111/apt.17358. Epub 2022 Dec 19. PMID: 36534763. There is a desperate need for effective advanced therapies for patients with Crohn's disease. Patients with active Crohn's have to endure a burden of disease that goes beyond just uncontrolled gastrointestinal inflammation with disabilities that effect psychological, financial and social circumstances. Active Crohn's disease additionally has a significant economic burden on the National Health Service with unplanned emergency care, preventable hospitalisation and surgery and loss of work. Risankizumab provides an additional 'lifeline' for our patients. With patients in the European Union and USA now being treated for Crohns disease with risankizumab, we strongly feel that lack of access to risankizumab will significantly disadvantage our patients in the NHS. We feel, at the very least, risankizumab should be made available to patients who have failed first line advanced immunosuppressive therapy.
4	
5	
6	

Insert extra rows as needed

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Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Invited clinical expert for initial committee meeting Consultant Gastroenterologist at Guy's & St Thomas' Hospital
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	• Advisory fees: Janssen, Takeda, Sandoz, Samsung Bioepis, Galapagos, AbbVie, Bristol-Myers Squibb, Pfizer, Tillotts • Lecture fees: Bristol-Myers Squibb, Janssen, Takeda, MSD, Falk, AbbVie, Galapagos

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Name of commentator person completing form:	Mark Samaan
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Comparative effectiveness** Whilst I'm sure that I don't have a full appreciation of the difference in opinion regarding network meta-analysis (NMA) methodology, I'd like to state my opinion as a clinician with experience in clinical trials. Looking at the phase III data, risankizumab appears to be an efficacious treatment, and very much comparable to ustekinumab (as per the NMA presented by Abbvie). With the knowledge that a recently published RCT (SEAVUE, Sands et al., Lancet 2022) showed ustekinumab and adalimumab have equivalent efficacy, it would appear unlikely that there is any clinically significant difference between these mechanisms. On a similar note, whilst I appreciate that the EAG quite rightly states that "connections in network meta-analyses should be based on comparator connections, not drug characteristics", the problem here is that the maintenance placebo, used as the connection, is not really a pure placebo; instead it's a drug withdrawal arm. Surely, within this context the offset of action of the drug (which is in part, but not entirely, related to half-life) should be taken into account. In this regard, ustekinumab is pharmacologically much more similar to risankizumab than other biological mechanisms. Finally, there is now published data (Fumery et al., AP&T, 2023) from the French IBD group (GETAID) that demonstrates real world effectiveness, amongst a cohort of 100 patients, that is very much in keeping with that previously published for ustekinumab. Importantly, almost all of these patients had been exposed to all biologic mechanisms and a significant proportion (78.5%) responded to risankizumab nonetheless. As yet unpublished data from my own centre combined with that of another (n=48) also demonstrate similar findings. Again, suggesting that these agents are likely to perform in a comparable manner when used in clinical practice.
2	**Treatment duration** The switch from a 1-year treatment duration assumption (as used in previous NICE technology appraisals) to a 20-year treatment duration assumption appears a sizeable departure and perhaps unfeasible to deliver. Whilst it is true that fewer patients than previously are discontinuing treatment at a year due to complete remission, it is also true that very few patients (if any) have been on the same biologic agent for 20 years. Biologic treatment withdrawal, in the setting of sustained deep remission, is clearly still of interest to patients and clinicians alike, and does still take place - just perhaps after something like 4 or 5 years, rather than the previously recommended 1. To try and model 20 years of treatment from a yearlong RCT, even with a long-term extension going out to 2 or 3 years, seems likely to be imprecise and prone to a variety of biases.
3	**Sequencing** Similar to the above point, 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. There are also several other outcomes which would be missing from this type of analysis, including surgery

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	(of various types, which may or may not mean a temporary/permanent discontinuation of treatment) or enrolment into a clinical trial.
4	**On body injector (OBI)** There is now available, in abstract form, robustly collected, prospective data from a substudy (n=46) of the FORTIFY RCT, which is reassuring in terms of patient experience using the OBI. This also includes maintained disease control and safety (reference: Loftus et al. *The American Journal of Gastroenterology* 117():p S10, December 2022.)
5	Overall, I would like to take this opportunity to reiterate what an effective and important treatment risankizumab could become for people with Crohn's, many of whom have been failed by the range of treatments currently available to them. As someone who sees the massive detrimental impact Crohn's disease can have, it would seem greatly unfair if patients were to be denied the possibility of achieving remission and a normal quality of life due to lack of access to this novel option. Even if NICE were to position its use after failure of (or contraindication to) anti-TNF therapy, this would still represent a significant step forward in Crohn's treatment and present a valuable opportunity to patients.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	N/A
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Name of commentator person completing form:	Kamila Kingstone
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	As a patient with Crohn's disease, I agree with all the points made by the British Society of Gastroenterology and Crohn's and Colitis UK. I would like to add three additional points.
2	Firstly, 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. However much decision-makers think they understand Crohn's disease, they often don't take full account of the impact that symptoms – especially extra-intestinal manifestations like extreme fatigue – have on a person's life.
3	Secondly, risankizumab does seem to offer an encouraging efficacy rate. The recently published meta-analysis highlighted by the British Society of Gastroenterology in its first point showed that risankizumab 600mg ranked as the most effective treatment in both biologic-naïve and biologic-exposed patients. It has been approved in the US and EU, with evidence from the US showing efficacy in patients whose disease has not responded to other advanced therapies. Without the approval of drugs like risankizumab, British patients will have their noses pressed against the window, denied the chance to regain the most valuable part of themselves: their health.
4	If NICE does decide to approve risankizumab, I urge you to approve it not just for patients with moderate and severe disease, but also those with mild disease who do not respond to any other treatment. Mild untreatable disease can still have a severe impact on your life – preventing a person leaving the house, having a career, or seeing friends. Without treatment with drugs like risankizumab, people with mild disease are left in limbo, counter-intuitively wishing their condition would become more severe in order to access treatment to enable them to recover.

Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

Yes - but it has not always been appropriately interpreted. The benefit of Risankizumab in patients failing several biologics including ustekinumab is very important as are the stable deltas above placebo in both bio naive and experienced patients

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I cannot comments as I have not seen this analysis.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

NO. This is clearly an effective drug that offers a benefit to patients with a chronic illness refractory to other treatments. My personal experience of using it has been hugely positive. It would be a very negative decision if this were not available in the NHS.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- 1.1 Recommendations

This does not to my mind fit the clinical evidence from the induction / maintenance trials which show excellent clinical efficacy. This is evidence in biologic naive patients, but it is most notable in patients previously exposed to biologics. There is a strong signal of efficacy even in patients who have failed several prior biologics and / or ustekinumab. Unlike many other biologics - the delta of benefit over placebo remains similar in bio exposed to bio naive patients. This drug has great potential to improve patients QoL and prevent the need for surgery.

- 1.2 Recommendations

We have at least 10 patients with Crohn's disease on Rizankizumab through this scheme. By definition they had not responded to or lost response to all available biologic agents and had a markedly impaired QoL. The drug has shown exceptional benefit. It would by hugely disappointing if we were not able to use it for such patients in the future.

- 1.2 Recommendations: “Standard treatments for moderately to severely active Crohn's disease when conventional treatments stop working are biological treatments (such as adalimumab, infliximab, ustekinumab and vedolizumab). Risankizumab is another biological treatment.”

It is the first available biologic in the anti p19 class.

- 1.2 Recommendations: “This is because risankizumab has only been compared indirectly with them and the results are uncertain because of differences between the populations included in the trials and how the trials were carried out.”

Important to recognise the strong signal of benefit with significance compare to placebo in patients who had failed multiple biologics including ustekinumab. This new class of drugs shows benefit where others do not.

- 1.2 Recommendations: “s less effective and more expensive than other biological treatments for people having a first biological treatment.”

I am not familiar with the model used for this submission. But the results of other network met analyses strongly suggest that it is as least as effective as other biologics with positive SUCRAs

- 2.5 Price

Clearly this is of critical importance.

- 3.1 Crohns disesase: “ed for surgery which is of importance to patients. People with Crohn's disease fear the loss of remission and the arrival of flares because of the major impact these have on their life. The committee concluded that Crohn's disease can have a profound effect on people's quality of life and ability to do day-to-day activities”

There is a clear unmet need for therapies that target novel pathways. Risankizumab has a new MOA and strong evidence of benefit. My own experience of using it has been very positive. It has a potential to make a

significant impact on the burden of refractory disease that has been shown to increase the risk of surgery and both direct and indirect health costs.

- 3.2 Treatment Options: “The clinical experts stated that tumour necrosis factor-alpha (TNF-alpha) inhibitors (infliximab or adalimumab, including biosimilars) are usually used first”

This reflects the lower acquisition costs of biosimilar.

- 3.4 Primary outcomes

This was the first clinical trial in Crohn's disease to include endoscopic response as a primary outcome. As such it has a much more robust outcome that its predecessors.

- 3.7 Network meta-analyses: “It also noted ustekinumab and vedolizumab, used in the different networks, have a similar half-life and are comparable treatment options.”

the pharmacokinetic half line 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 is manifest in the high rates of ongoing benefit in patients receiving induction dosing and then being re randomised to placebo

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I'd dispute the interpretations - see below

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No

- "Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?"

No - but there is a significant inconsistency in the position NICE are taking with regards to risankizumab vs vedolizumab (where the trials data are MUCH weaker - but it is NICE approved)

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

"As it stands the position being adopted by NICE is substantially unhelpful with regards to managing patients with complex Crohn's disease. By all means position risankizumab so that it cannot be used as first line biologic (or maybe even as 2nd line); and by all means negotiate a better price - but anti-il23-specific therapies are a major step forwards for the management of Crohn's globally, the clinical trials data (and personal experience of having 'disease-refractory' patients in these trials in Cambridge) show that risankizumab works sometimes where no other treatments work - and we should absolutely have this as a NICE-approved option perhaps for 3rd line therapy in otherwise treatment-refractory Crohn's. Not to do so will make the UK a global out-lier in IBD management and significantly disadvantage our patients.

As a note some level of consistency is required here. Risa is undoubtedly more effective than vedolizumab in Crohn's - both from trials data and experience. The cost is likely broadly equivalent. Vedo is NICE approved for Crohn's. Risa certainly should be also."

Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]

A Single Technology Appraisal

Addendum #2

ERG review of company ACD response

February, 2023

Produced by

Peninsula Technology Assessment Group (PenTAG)
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Declared competing interests of the authors

None.

Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This addendum is linked to ERG report

Barnish MS, Naik J, Sullivan W, Brand A, Hook E, Matthews J, Edmondson-Jones M, Robinson S, Digby-Bell J, Melendez-Torres GJ. Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]. Peninsula Technology Assessment Group (PenTAG), 2023.

1. SUMMARY

The purpose of this addendum is to describe and critique the extent to which the company's response to draft guidance documentation addresses the committee's documented concerns and requests.

In response to draft guidance, the company have provided some new network meta-analysis (NMA) results, but have not incorporated these results into the latest cost-effectiveness model. Nor have the company addressed any of the committee's other requests for the cost-effectiveness model, as stated in section 3.14 of the draft guidance document:

"..if the company chooses to present updated results using cost-utility analyses, a new model that explores the sequence of biological treatments is needed. The committee asks the company to apply its preference in regard to model structure (see section 3.9), treatment duration (see section 3.10), transition matrices in the maintenance model (see section 3.11) and other assumptions (see section 3.12). It would also welcome exploratory analyses around the effects of the on-body device on treatment discontinuation and wastage (see section 3.8)."

Instead, the company have provided a cost-comparison analysis (using a model not previously seen by the EAG), which the company justify based on a perception of comparable effectiveness across biologic treatments in the company's updated NMA results. The committee noted elsewhere in 3.14 that a cost comparison may be appropriate given NMA uncertainty and potential similarity across biologic treatments. The company state that their cost-comparison analysis "*showed that risankizumab is cost saving versus all comparators*", but these results and are contingent on strict and contentious assumptions and do not reflect confidential price agreements for comparators.

Overall, the EAG advise caution in interpreting updated NMA results as evidence for efficacy equivalence between risankizumab and its comparators and are mindful to highlight the assumptions and limitations inherent to the company's cost-comparison analysis. In the next two sections of this addendum document, the updated NMA and cost-comparison analysis are explored in turn, before the document closes with assessment of the company's latest commentary on the on-body device.

2. COMPANY'S UPDATED NMA

In their response to ACD, the company reiterates their preference for a fixed-effects NMA with a split maintenance network, but acknowledge committee and EAG preferences for random-effects NMAs including informative priors based on previously published norms and including a joined-up network for maintenance phase and temporal adjustment for placebo effects.

The arguments presented by the company for their preferred NMA are not new and the EAG do not propose to reiterate previously expressed views in respect of each party's preferred scenarios, except to acknowledge it is equally plausible that instead of a random-effects NMA generating unduly wide credible intervals, that a fixed-effects NMA generated unduly narrow credible intervals given manifest heterogeneity in the included trials.

The 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. However, it considers in the following paragraphs the assertion that risankizumab has demonstrated equivalent efficacy so as to merit a cost-comparison analysis.

On the whole, the EAG regard that the case for equivalent efficacy is lacking. This is particularly striking with respect to the company's fixed-effects NMAs in the CCF population (Tables 9 and 10 in the ACD response), which suggest that adalimumab QW and infliximab 5/10 Q8W are superior in maintenance phase to risankizumab.

However, taking up the committee and EAG preferred NMAs, the EAG observe that there is an important distinction between non-inferiority and equivalence. For equivalence to be established, credible intervals arising from NMA estimates should be completely contained within a pre-specified equivalence margin either side of parity. This is clearly not the case in these meta-analyses, and indeed (as cited by the company in their argument against this NMA scenario) the width of credible intervals suggests the possibility in some cases of either significant benefit or significant loss from choosing a comparator instead of risankizumab. The EAG also notes that in a true equivalence context, risankizumab would be expected to generate point estimates against comparators reflecting benefit of risankizumab about 50% of the time. This is also clearly not the case in any of the presented NMAs.

3. COMPANY'S COST-COMPARISON ANALYSIS

Given the limited evidence for effectiveness equivalence across treatments discussed in the previous section, the EAG question the usefulness of cost-comparison. Nevertheless, if effectiveness equivalence is assumed to hold, the limitations and assumptions of the company's cost-comparison analysis (CCA) are then important to consider, for any inference from its results to be drawn. This section sets out the key characteristics and limitations of the company's CCA, including how it differs in scope from the cost side of the cost-effectiveness analysis (CEA), and presents some exploratory analyses around the company's headline cost-comparison results.

The company's CCA is far simpler than the CEA, primarily in that it only considers costs associated with treatment acquisition or administration. However, even within this restricted scope, the CCA differs markedly from the CEA.

Firstly, the CEA assumed patients could discontinue treatment before being subsequently treated with conventional care over a lifetime (60-year) horizon. The CCA assumes no discontinuation and adopts a 10-year time horizon. This difference, combined with the different data-driven treatment discontinuation assumptions across treatment arms in the EAG-preferred CEA, to a large extent explain the difference in cost results across the CEA and CCA. In truth, neither approach reflects clinical practice, where patients do discontinue, and next move onto the most suitable of the available remaining biologic therapy options. In Section 3.1, the impact of imposing different treatment discontinuation assumptions upon CCA results is explored.

Secondly, while the CEA analysed the decision problem for the biological failure (BF) population and conventional care failure (CCF) population separately, the CCA does not make this distinction.

Thirdly, while the CEA treated vedolizumab administered subcutaneously (SC) as a distinct treatment option to vedolizumab administered intravenously (IV), the CCA considers vedolizumab as one treatment option, with a proportion assumed to be administered IV as opposed to SC. The same is true for other in-scope treatments that can be administered IV or SC: infliximab and its biosimilar. The company assume a 50:50 split between IV and SC for vedolizumab, infliximab and infliximab biosimilar in the CCA, though provide no justification for the assumed 50:50 split. This is important for CCA results, as illustrated in EAG exploratory analyses in Section 3.2, in which the assumed split between IV and SC is varied.

Fourthly, while in the CEA expert-elicited annual estimates of the probability of dose escalation for applicable comparators were converted to 2-week probability estimates and applied per-cycle, in the CCA, dose escalation is assumed to occur at time zero, for all patients affected. In this, the CCA approach deviates from the company's CEA approach in a manner that clearly biases results in favour of risankizumab (and other treatments not associated with dose escalation). Exploratory EAG scenarios in Section 3.3 illustrate the impact of varying the proportion of standard- versus high-dose maintenance assumptions on the company's CCA results.

Aside from these differences and other more minor simplifications by which the CCA deviates from the CEA in its analysis of treatment and administration costs, the relative importance of treatment and administration assumptions is clearly greater when the focus of the analysis is so reduced. Most notably, in the CEA and in the CCA, each IV administration is assumed to cost the NHS £245, while SC administration is assumed to cost £41 in the first instance, and to cost nothing thereafter. Importantly, these SC administration assumptions are assumed to apply to risankizumab SC administration using the on-body device (OBD). Exploratory EAG analyses in Section 3.4 illustrate the impact of different OBD administration costs upon the company's CCA results. As discussed in Section 4, the implications of the OBD device, for treatment discontinuation and wastage, remain highly uncertain.

3.1. EAG treatment discontinuation scenario analyses

To investigate the impact of treatment discontinuation on the cost-comparison results, the EAG have implemented an exploratory scenario whereby annual evidence-based discontinuation rates across treatments are implemented each year. The scenario applies the company literature-sourced annual treatment discontinuation rates reported in CS Doc B, Table 75, replicated here in Table 1. The EAG notes that while this scenario provides an insight into the impact of treatment discontinuation upon the company's CCA results, the subsequent treatment pathway remains unrepresented by the modelling approach.

Table 1: Annual treatment discontinuation probability

Treatment arm	Annual discontinuation probability
Risankizumab	4.26%
Ustekinumab	8.00%
Vedolizumab IV/SC	41.39%

Treatment arm	Annual discontinuation probability
Adalimumab 160/80	8.05%
Adalimumab 80/40	8.05%
Adalimumab biosimilar	8.05%
Infliximab IV biosimilar/SC	8.05%
Infliximab IV/SC	8.05%

Abbreviations: IV, intravenous; SC, subcutaneous.

Note: Annual discontinuation probabilities are sourced from the company submission, Doc B, Table 75

The scenario allows patients to experience treatment discontinuation over the entire 10-year time horizon, using the annual discontinuation rates sourced from the literature (Table 1). Following discontinuation, patients are assumed to incur no further costs, per the company's CCA assumptions.

Table 2 presents the total costs over the 10-year time horizon for each treatment, with Table 3 presenting the incremental cost difference, risankizumab versus each comparator, using comparator list prices. The results of the treatment discontinuation scenario suggest that risankizumab would only be cost-saving versus ustekinumab (-[redacted]). Results using cPAS prices are presented in the cPAS appendix.

Table 2: Total 10-year costs - Treatment discontinuation scenario (comparator list prices)

Treatment arm	Company	EAG Scenario
Risankizumab	[redacted]	[redacted]
Ustekinumab	£141,742	£101,877
Vedolizumab IV/SC	£166,807	£42,554
Adalimumab 160/80	£138,432	£97,986
Adalimumab 80/40	£137,376	£96,929
Adalimumab biosimilar	£124,543	£88,156
Infliximab IV biosimilar/SC	£128,043	£91,032
Infliximab IV/SC	£136,081	£96,785

Abbreviations: EAG, external assessment group, IV, intravenous; SC, subcutaneous.

Table 3: Total 10-year incremental cost-difference versus risankizumab - Treatment discontinuation scenario (comparator list prices)

Treatment arm	Company	EAG Scenario
Ustekinumab	[redacted]	[redacted]
Vedolizumab IV/SC	[redacted]	[redacted]
Adalimumab 160/80	[redacted]	[redacted]
Adalimumab 80/40	[redacted]	[redacted]
Adalimumab biosimilar	[redacted]	[redacted]
Infliximab IV biosimilar/SC	[redacted]	[redacted]
Infliximab IV/SC	[redacted]	[redacted]

Abbreviations: EAG, external assessment group, IV, intravenous; SC, subcutaneous.

Note: Negative incremental cost-difference represent cost-savings for risankizumab.

3.2. EAG IV versus SC scenario analyses

Figure 1 illustrates the relationship between (i) the proportion of vedolizumab patients assumed to receive vedolizumab IV (as opposed to SC) and (ii) the estimated difference in 10-year total costs across risankizumab and vedolizumab arms of the company's CCA, using comparator list prices.

Figure 2 presents the same relationship when the treatment discontinuation assumptions described in Section 3.1 are also applied.

Figure 1: Relationship between headline CCA results versus vedolizumab, and IV vs SC administration assumptions for vedolizumab

Abbreviations: IV, intravenous; SC, subcutaneous.

Note: Negative incremental cost-difference represent cost-savings for risankizumab.

Figure 2: Figure 1, with Section 3.1 treatment discontinuation assumptions applied

Abbreviations: IV, intravenous; SC, subcutaneous.

Note: Negative incremental cost-difference represent cost-savings for risankizumab.

3.3. EAG standard-dose versus high-dose maintenance scenario analyses

The company's expert-elicited annual estimates of dose-escalation were presented in Table 5 of the Company's response to ACD, and are reproduced below in Table 4.

Table 4: Proportion of patients on standard- and high-dose maintenance

Treatment arm	Proportion on standard-dose maintenance	Proportion on high-dose maintenance
Risankizumab	100%	0%
Ustekinumab	7.5%	92.5%
Vedolizumab IV	70%	30%
Vedolizumab SC	100%	0%

Treatment arm	Proportion on standard-dose maintenance	Proportion on high-dose maintenance
Adalimumab 160/80	50%	50%
Adalimumab 80/40	50%	50%
Adalimumab biosimilar	50%	50%
Infliximab IV	60%	40%
Infliximab IV biosimilar	60%	40%
Infliximab SC	100%	0%

Abbreviations: IV, intravenous; SC, subcutaneous.

The company's CCA results are sensitive to the proportion of patients assumed to receive standard- versus a high-dose maintenance, as is seen in Figure 3. At comparator list prices, vedolizumab is the only treatment that remains more expensive than risankizumab when varying the proportion of patients assumed to receive standard-dose treatment from 0% to 100%.

Figure 4 presents the results of the same analysis when the treatment discontinuation assumptions described in Section 3.1 are also applied. When treatment discontinuation is considered, vedolizumab becomes less expensive than risankizumab irrespective of dose escalation assumptions, with the contrast between the two figures demonstrating the sensitivity of the model to treatment discontinuation assumptions.

Figure 3: Relationship between incremental projected 10-year costs, risankizumab versus comparators, and the proportion of standard- versus high-dose maintenance (comparator list prices) – no treatment discontinuation

Abbreviations: IV, intravenous; SC, subcutaneous.

Note: Negative cost-difference represent cost-savings for risankizumab.

Note: The model assumes risankizumab, vedolizumab SC and infliximab SC treatments cannot be dose escalated. As such, vedolizumab, infliximab and infliximab biosimilar regimens in this figure are comprised of a 50:50 IV to SC split.

Figure 4: Relationship between incremental projected 10-year costs, risankizumab versus comparators, and the proportion of standard- versus high-dose maintenance (comparator list prices) – treatment discontinuation enabled

Abbreviations: IV, intravenous; SC, subcutaneous.

Note: Negative cost-difference represent cost-savings for risankizumab.

Note: The model assumes risankizumab, vedolizumab SC and infliximab SC treatments cannot be dose escalated. As such, vedolizumab, infliximab and infliximab biosimilar regimens in this figure are comprised of a 50:50 IV to SC split.

3.4. EAG OBD administration cost scenario analyses

To investigate the impact of OBD administration costs exceeding those assumed for SC treatments in the company's CCA upon CCA results, the EAG have implemented three exploratory scenarios:

1. Scenario 1: Assume first-time SC administration cost (£41) to apply for all OBD treatments in the first year
2. Scenario 2: Assume first-time SC administration cost (£41) to apply for the first three OBD treatments
3. Scenario 3: Assume the IV administration cost (£245) applies for the first OBD treatment, with the first-time SC administration cost (£41) to apply for the remaining OBD treatments in year 1

These scenarios are not informed by specific clinical rationale. Rather, they are designed to illustrate how the CCA results change if the company's minimal OBD administration cost assumptions are relaxed. Results are presented in Table 5 (total 10-year costs) and Table 6 (total 10-year incremental cost, risankizumab versus comparators), at comparator list prices. Table 7 and Table 8 present the results of the same scenarios when the treatment discontinuation assumptions described in Section 3.1 are applied. The isolated impact of these changes to OBD administration assumptions for CCA results is small (<£400).

As noted above, the implications of the OBD device for treatment discontinuation and wastage, remain highly uncertain, and have not been explored. This is discussed in greater detail in Section 4.

Table 5: Total 10-year cost – OBD administration cost scenarios (comparator list prices) – no treatment discontinuation

Treatment arm	Company	EAG Scenario 1	EAG Scenario 2	EAG Scenario 3
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	£141,742	£141,742	£141,742	£141,742
Vedolizumab IV/SC	£166,807	£166,807	£166,807	£166,807
Adalimumab 160/80	£138,432	£138,432	£138,432	£138,432
Adalimumab 80/40	£137,376	£137,376	£137,376	£137,376
Adalimumab biosimilar	£124,543	£124,543	£124,543	£124,543

Treatment arm	Company	EAG Scenario 1	EAG Scenario 2	EAG Scenario 3
Infliximab IV biosimilar/SC	£128,043	£128,043	£128,043	£128,043
Infliximab IV/SC	£136,081	£136,081	£136,081	£136,081

Abbreviations: EAG, external assessment group; IV, intravenous; OBD, on-body device; SC, subcutaneous.

Table 6: Total 10-year risankizumab cost-difference – OBD administration cost scenarios (comparator list prices) – no treatment discontinuation

Treatment arm	Company	EAG Scenario 1	EAG Scenario 2	EAG Scenario 3
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab IV/SC	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 160/80	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 80/40	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab IV biosimilar/SC	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab IV/SC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; IV, intravenous; OBD, on-body device; SC, subcutaneous.

Note: Negative cost-difference represent cost-savings for risankizumab.

Table 7: Total 10-year cost – OBD administration cost scenarios (comparator list prices) – Treatment discontinuation enabled

Treatment arm	Company	EAG Scenario 1	EAG Scenario 2	EAG Scenario 3
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	£101,877	£101,877	£101,877	£101,877
Vedolizumab IV/SC	£42,554	£42,554	£42,554	£42,554
Adalimumab 160/80	£97,986	£97,986	£97,986	£97,986
Adalimumab 80/40	£96,929	£96,929	£96,929	£96,929
Adalimumab biosimilar	£88,156	£88,156	£88,156	£88,156
Infliximab IV biosimilar/SC	£91,032	£91,032	£91,032	£91,032
Infliximab IV/SC	£96,785	£96,785	£96,785	£96,785

Abbreviations: EAG, external assessment group; IV, intravenous; OBD, on-body device; SC, subcutaneous.

Table 8: Total 10-year risankizumab cost-difference – OBD administration cost scenarios (comparator list prices) – Treatment discontinuation enabled

Treatment arm	Company	EAG Scenario 1	EAG Scenario 2	EAG Scenario 3
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab IV/SC	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 160/80	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 80/40	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab IV biosimilar/SC	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab IV/SC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; IV, intravenous; OBD, on-body device; SC, subcutaneous.

Note: Negative cost-difference represent cost-savings for risankizumab.

4. COMPANY'S ON-BODY DEVICE COMMENTARY

In section 3.8 of the draft guidance document, the committee acknowledge the evidence for bioequivalence between risankizumab delivered SC by 4 injections (as in the FORTIFY trial) and delivered SC by the on-body device (as will be the case in clinical practice), and note the patient expert insight that the new device is likely to be welcomed, subject to the volume and comfort of the delivery. However, the committee share the EAG's concern that potential differences in adherence and wastage across the two delivery approaches are both unknown and potentially consequential for patient outcomes and NHS costs. Given this, the committee requested further exploratory analysis.

In response, the company have acknowledged the committee's position and request, but provided no further evidence or exploratory analysis. Instead, the company refer again to the short-term (16 week) and small sample (n=[redacted]) M16-000 sub-study 4 data the company presented at technical engagement. Now, as then, the EAG are concerned that these limited data may not reflect clinical practice at all well, in particular owing to the entry criteria for this study (which included actively receiving SC maintenance therapy in sub-study 3) and the direct office supervision environment for on-body device administration in the study.

The EAG again refer to the UK Clinical Pharmacy Association (UKCPA) response to technical engagement, which noted some key reasons to anticipate issues with the on-body device in practice:

"*Poor tolerability due to injection site reactions/adverse effects may impact drug persistence which will not have been captured in the trial.*"

"*There is a risk of the OBD failing. This can be before inserting the drug vial or during the injection phase. If it fails pre-insertion of the vial, it will need to be ascertained if the device itself can be replaced and thereby saving wastage of the drug vial and cost; OR if the OBD is only supplied as package with the drug vial. This should not incur extra cost to the NHS as device failure with pre-filled pens is common too and usually credited*".

Now, as at technical engagement, the EAG are concerned that the M16-000 sub-study 4 results may do little to address the tolerability concerns raised by the UKCPA. Given the office supervision administration environment of the study, the ability of M16-000 sub-study 4 results to address concerns of the on-body device failing in routine practice is clearly limited.