National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AbbVie	Yes.	Thank you for your comment. No action needed.
	British Society of Gastroenterology	Yes. Crohn's disease continues to cause significant morbidity despite the current medications available. Crohn's is a serious and complex disease that can have a lifelong debilitating impact on patients if remission is not achieved. The BSG guidelines recommend that "Crohn's' disease patients refractory to immunomodulator therapy despite dose optimisation should be considered for biological therapy. Choice between anti-TNF therapy, ustekinumab and vedolizumab should be made on an individual basis, considering patient preference, cost, likely adherence, safety data and speed of response to the agent."(1) Despite well-defined pathways and updated British society of gastroenterology guidelines, existing therapies have significant drawbacks, highlighting a major unmet therapeutic need for people living with moderate to severe Crohn's disease. Specifically, primary failure of anti-TNF induction	Thank you for your comment. This technology has been referred to NICE as a Single Technology Appraisal. No action needed.

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		therapy occurs in 19–58% of patients in clinical trials (2). Among patients responsive to anti-TNF therapies, discontinuation due to secondary loss of response occurs in 17 to 22% of patients and approximately 40% required dose escalation to maintain treatment efficiency (3-4). Treatment failure is even higher among patients undergoing second line TNF inhibitor therapy. In a meta-analysis the proportion of patients have discontinued treatment due to loss of response was 68-77% at 12 months and 82 -90% by the end of year 2(3-4). Diminishing efficacy stems in part from immunogenicity and the formation of antibodies against biologics (4). Additional treatment options are urgently needed to help control disease and allow patients to return to their usual activities and potentially avoid surgery. As this disease often impact people during their early adulthood, poorly controlled disease has a dramatic impact on their education, careers and life opportunities. Our understanding is that this application is for EAMS use and is not a full application for NICE Technology Appraisal (similar to the ones previously published for Vedolizumab and Ustekinumab). So, our comments should be taken to be applicable only for EAMS use, until a full NICE Technology Appraisal for Risankizumab takes place. 1. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019. 2. Stidham R.W., Lee T.C., Higgins P.D., Deshpande A.R., Sussman D.A., Singal A.G., Elmunzer B.J., Saini S.D., Vijan S., Waljee A.K. Systematic review with network meta-analysis: The efficacy of anti-TNF agents for the	

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		treatment of Crohn's disease. Aliment. Pharmacol. Ther. 2014;39:1349–1362. 3. Gordon JP, McEwan PC, Maguire A, Sugrue DM, Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. Eur J Gastroenterol Hepatol. 2015;27(7):804-12. 4. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019;4(5):341-53	
Wording	British Society of Gastroenterology	The remit states 'Clinical management depends on disease activity, site, behaviour of disease, response to previous treatments, side-effect profiles of treatments and extra-intestinal manifestations, such as uveitis and arthritis'. As patients with Crohn's disease often need lifelong treatment and symptoms can be debilitating treatment considerations also include speed of action, long term safety, patient acceptability (e.g. frequency of dosage and mode of delivery of the drug) as well as impact on other co-morbidities e.g. cardiac or malignancy or psoriasis history. Extraintestinal manifestations should also include skin manifestations.	Thank you for your comment. The scope has been updated to reflect these additional considerations.
	Crohn's & Colitis UK	Yes. Currently, there are limited treatment options available in treating moderate to severe Crohn's disease. It is important that patients have the widest possible options available to them, particularly given what we are increasingly coming to understand in terms of the importance of personalised treatments.	Thank you for your comment. No changes to the scope needed.

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Timing Issues	AbbVie	The timing of this appraisal is appropriate.	Thank you for your comment. No changes to the scope needed.
	British Society of Gastroenterology	Given the high primary and secondary non-response rate of our current medications there is a large cohort of patients whose symptoms and disease are not controlled by current treatment options. This appraisal is a matter of urgency for these patients waiting for a new treatment option. Going forward to have a greater option available will greatly help clinicians trying to find the right option for the individual patient.	Thank you for your comment. No changes to the scope needed..
	Crohn's and Colitis UK	In light of Covid-19 and elective recovery, there is a benefit to an additional treatment option that can be administered at home to potentially reduce infection risk and pressure on the NHS (outpatient appointments, day cases and workforce).	Thank you for your comment. No changes to the scope needed.
	Tillotts Pharma UK Ltd	Low urgency. Existing therapies are well established and successful in managing symptoms except in a small proportion of patients with moderate to severe Crohn's disease, where symptoms remain uncontrolled.	Thank you for your comment. No changes to the scope needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Society of Gastroenterology	Background information is accurate. More information could be added on the proportion of patients who do not respond to current treatment.	Thank you for your comment. The background section of the scope is intended to provide a broad overview of the disease

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			and its expected management. It is anticipated that the proportion of people who do not respond to current treatment will be discussed during the appraisal. No changes to the scope needed.
	Crohn's & Colitis UK	1 in 133 children and adults are living with Inflammatory Bowel Disease. We would ask the Committee to revisit the description of the following sentences: "Less common symptoms include fever, nausea, vomiting, arthritis, inflammation and irritation of the eyes, mouth ulcers and areas of painful, red and swollen skin." - Remove less common - Refer to extra intestinal manifestations People with IBD are affected by more than just their bowel symptoms. Up to 50% will experience extraintestinal manifestations, involving different parts of their body, commonly joints, skin, bones, eyes, kidneys and liver. In addition to the symptoms listed in the "Background" section, we would like to see fatigue and anaemia included, as these are often overlooked, but have a significant impact (IBD UK report Crohn's and Colitis Care in the UK) We would also strongly advocate for recognition within this section of the debilitating impact of the condition on the daily lives and quality of life of those affected, including its impact on mental health and wellbeing, education, employment and relationships.	Thank you for your comment. The scope has been updated to reflect the comments made around the impact of the condition.

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		The symptoms of urgent diarrhoea, pain and fatigue, and associated stigma, can lead to people becoming depressed, anxious and isolated (Crohn's & Colitis UK Quality of Life Survey 2017 and 2018). Crohn's care has moved towards delivering personalised care and support, and not just remission, with a greater focus on the holistic needs of people with Crohn's disease (IBD Standards 2019). We would point out that the current guideline for Crohn's is not aligned with the IBD Standards or the most up-to-date British Society of Gastroenterology IBD guideline.	
The technology/ intervention	AbbVie	Yes, however, to clarify risankizumab is administered in induction by intravenous infusion followed by subcutaneous maintenance injection. It should also be noted that in addition to marketing authorization for moderate to severe plaque psoriasis, risankizumab also has marketing authorization for active psoriatic arthritis in the UK.	Thank you for your comment. The scope has been updated to clarify the administration method and include the marketing authorisation for active psoriatic arthritis.
	British Society of Gastroenterology	Aminosalicylates should be removed from comparators. Please remove all technologies related to irritable bowel syndrome (this is distinct from Crohn's disease /inflammatory bowel disease and not relevant whatsoever to this appraisal) I.e., 'Irritable bowel syndrome in adults: diagnosis and management' (2017). NICE guideline 61; 'irritable bowel syndrome in adults' (2016). NICE quality standard 114.	Thank you for your comment. The comparators are kept inclusive at this stage. Stakeholders can provide justification around the most appropriate comparators and the committee will consider

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			this during the appraisal. The scope has been updated to reflect comments around associated guidance.
Population	British Society of Gastroenterology	The published evidence for RZB from the ADVANCE, MOTIVATE and FORTIFY Programmes include patients with luminal Crohn's disease (ileal, ileocolonic and colonic), and does not include perianal fistulising Crohn's Disease. So, the EAMS use should be restricted to luminal Crohn's disease only	Thank you for your comment. The purpose of this scope is to set out the parameters for a technology evaluation which is a separate process to EAMs. The committee will consider the clinical evidence during this evaluation. However, the population has been kept broad at this stage to accommodate any potential change in marketing authorisation. No changes needed to the scope.
Comparators	AbbVie	We note that a comparison to conventional care is not required in the conventional care failure population.	Thank you for your comment. Conventional care has been removed as a comparator.

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	British Society of Gastroenterology	There is inadequate head-to-head data to determine at what point in a treatment pathway risankizumab should be used according to efficacy. Based on the published evidence, risankizumab should be approved for use after one or more biologic failure after discussion in a IBD MDT, and with all medical and surgical options for treatment of Crohn's disease discussed with the patient. The drug has not been compared with any other biologic in a head-to-head trial either for biologic responsive or non-responsive groups so no conclusions can be derived for its efficacy in these situations. Network meta-analysis suggests that its efficacy is best after anti TNF failure. Many factors are taken into account in current clinical practise when deciding which of these drugs in the best initial option for a patient E.g. a New diagnosis >65 yrs. may be directed toward ustekinumab or vedo due to the preferable side effect profile is this cohort when compared to anti-TNF b Patient with perianal fistulating disease will be given infliximab as the evidence base for its use in this cohort is greatest. As mentioned RZB has not been investigated in this population. c. Patient with psoriasis and Crohn's disease may be preferentially given ustekinumab as this drug is in both Flexibility in the pathway is important allowing patient and clinicians to come to shared decision re optimal care as per BSG guidelines. **Have all relevant comparators for risankizumab been included in the scope?** Yes **Which treatments are considered to be established clinical practice in the NHS for Crohn's disease?** Azathioprine/mercaptopurine	Thank you for your comment. Conventional care has been removed as a comparator because it is anticipated that rizankizumab will be indicated after at least 1 previous therapy. Best supportive care has been added as a comparator for people who may be taking risankizumab after all other biologic treatment options.

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		Infliximab/adalimumab/vedolizumab/and ustekinumab Steroids can be used for induction of remission To prevent post-operative recurrence metronidazole can be used Siddharth Singh, M Hassan Murad, Mathurin Fumery, Rocio Sedano, Vipul Jairath, Remo Panaccione, William J Sandborn, Christopher Ma, Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis, The Lancet Gastroenterology & Hepatology, Volume 6, Issue 12, 2021,	
	Crohn's & Coltiis UK	We would ask the Committee to remove steroids. Steroids are not recommended for maintenance of remission and are associated with a range of side effects (BSG IBD Guideline and IBD Standards 2019).	Thank you for your comment. Conventional therapy (steroids) has been removed from the scope.
Outcomes	British Society of Gastroenterology	Are the outcomes listed appropriate? 'The outcome measures listed are • disease activity (remission, response, relapse) • mucosal healing • surgery • adverse effects of treatment health-related quality of life.' Definitions of remission vary in studies: Important to include clinical as well as endoscopic remission. Response should include clinical, biochemical eg CRP and faecal calprotectin measures	Thank you for your comment. The list of outcomes is not intended to be exhaustive at this stage. Where relevant, the company is welcomed to provide the evidence on all outcomes that are important for people with the condition during the evaluation.

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		Should include steroid free remission as a surrogate marker of relapse.	
	Crohn's & Colitis UK	We would ask the Committee to consider additions of: • Avoidance of steroid therapy • Patient experience and outcomes. • Improved medicine adherence and self-management. • Hospitalisation, readmission and emergency admissions The ability to treat earlier with a personalised drug treatment regime judged to be more clinically effective has the potential to reduce the need for surgery. For women of childbearing age the chance to delay or potentially prevent surgery, which can reduce fecundity, is desirable.	Thank you for your comment. The list of outcomes is not intended to be exhaustive at this stage. Where relevant, the company is welcomed to provide the evidence on all outcomes that are important for people with the condition during the evaluation.
Equality and Diversity	AbbVie	None identified.	Thank you for your comment. No action required.
	British Society of Gastroenterology	No I do not think the proposed remit and scope exclude any people or population as described	Thank you for your comment. No changes to the scope needed.
	Crohn's & Colitis UK	The mode of administration is a benefit for those with disabilities and remote communities in terms of reducing the need for travel to hospital and could potentially improve adherence.	Thank you for your comment. No changes to the scope needed.
Other considerations	British Society of Gastroenterology	Yes Consider adding in patients who have not responded to vedolizumab or have contraindications to this	Thank you for your comment. Where relevant evidence allows, the committee will consider whether

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		Are there any other subgroups of people in whom risankizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Patients with concomitant psoriasis (cost effective)	further subgroups as such shall be considered during the appraisal. No changes to the scope needed.
	Tillotts Pharma UK Ltd	We do not believe consideration should be given to groups not covered by the terms of the marketing authorisation (as proposed) such as those who have not previously received a tumour necrosis factor alpha inhibitor	Thank you for your comment. The committee will only make recommendations within the marketing authorisation. Consideration of subgroups based on place in the treatment pathway has been removed from the scope.
Innovation	AbbVie	In terms of substantial health-related benefits not accounted for in the QALY calculation, it is expected that endoscopic outcomes and mucosal healing will not be reflected in the QALY calculation despite being a key treatment target in Crohn's disease. This is because whilst risankizumab included endoscopic outcomes as primary and secondary endpoints in its trials, the majority of comparators lack RCT data or variability in the definition of endoscopic outcomes makes it challenging to compare these outcomes robustly. Endoscopic and mucosal healing outcomes for risankizumab will be provided in the submission.	Thank you for your comment. No changes to the scope needed.

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	British Society of Gastroenterology	Currently approved/available Ustekinumab binds the p40 subunit of IL-12 and- 23, whereas risankizumab selectively blocks the IL-23 p19 subunit and therefore offers another treatment option to Crohn's disease patients who have not responded to other biologics. There are no head-to-head trials in Crohn's disease to suggest one is more effective or safer that the other. Both already approved for use in psoriasis (TA596 for risankizumab and TA340 for ustekinumab).	Thank you for your comment. No changes to the scope needed.
	Crohn's & Colitis UK	There is also an advantage to a further treatment option that can be administered at home, which avoids the need for patients to take time off work or education and during the current pandemic also avoids any potential risks associated with travel to hospital.	Thank you for your comment. No changes to the scope needed.
	Tillotts Pharma UK Ltd	Whilst this technology appears to provide a further option for management of patients with severe disease in whom existing treatments have been unsuccessful or unsuitable, it does not appear to offer a step change in the management of Crohn's disease.	Thank you for your comment. No changes to the scope needed.
Questions for consultation	AbbVie	**Q1) At what point in the treatment pathway would risankizumab be used? Would it be used as an alternative to:** • **Tumour necrosis factor-alpha inhibitors (infliximab and adalimumab); or** • **Vedolizumab and ustekinumab** **Or would risankizumab be used after these treatments already available in the NHS?** We would expect risankizumab to be used in line with its marketing authorisation. We also note that ustekinumab is a treatment option after	Thank you for your comment. No changes to the scope needed.

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		conventional care alongside the Tumour necrosis factor-alpha inhibitors (infliximab and adalimumab) in bullet point one. **Q2) Have all relevant comparators for risankizumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for Crohn's disease?** Our comments on comparators have been captured above. **Q3) Are the outcomes listed appropriate?** Yes. **Q4) Where do you consider risankizumab will fit into the existing NICE pathway, Crohn's disease?** Our comments on the population have been captured above. **Q5) 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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which risankizumab will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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.**	

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		Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. No issues identified. **Q6) Do you consider that the use of risankizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Our response on the health-related benefits excluded from the QALY calculation are captured above. **Q7) To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** None identified.	
	Tillotts Pharma UK Ltd	Should it be approved for use by NICE based on its safety, clinical and cost effectiveness, risankizumab, should be limited to the maintenance treatment of patients with moderate to severe Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. According to the information in Appendix B, clinical studies do not include the use of risankizumab in the induction of remission of active Crohn's disease and therefore maintenance therapy appears to be the limit of its utility.	Thank you for your comment. Where relevant and appropriate, risankizumab's positioning in the treatment pathway will be considered during the appraisal. The comparators in the scope have been updated to include best

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		It would therefore fit into the existing NICE pathway (NG129) after existing conventional (conventional steroids. budesonide, mercaptopurine, azathioprine, methotrexate) and biologic (infliximab, adalimumab) agents. Continued therapy beyond 8 weeks should be carefully reconsidered in a patient with no improvement within this time period.	supportive care if risankizumab is taken after all biologics currently in the treatment pathway.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Janssen

Bladder and Bowel Community (not taking part)