NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Risankizumab for previously treated moderately to severely active ulcerative colitis in people aged 16 and over [ID6209]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Risankizumab for previously treated moderately to severely active ulcerative colitis in people aged 16 and over [ID6209]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from AbbVie:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Crohns and Colitis

4. **Expert personal perspectives** from:
   Professor Peter Irving- Consultant Gastroenterologist, clinical expert nominated by AbbVie

5. **External Assessment Report** prepared by Bristol Technology Assessment Group

6. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Risankizumab for treating moderately to severely active ulcerative colitis [ID6209]

Document B

Company evidence submission

November 2023

File name	Version	Contains confidential information	Date
ID6209_Risankizumab in UC_NICE Document B_Redacted	Final	No	3rd November 2023

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This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

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Tables and figures

Abbreviations

Acronym	Definition
AE	Adverse event
AMS	Adapted Mayo score
ANCOVA	Analysis of covariance
AO	As observed
AZA	Azathioprine
BNF	British National Formulary
BSG	British Society of Gastroenterologists
CA	Clinical assessment
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CSR	Clinical study report
CT	Conventional therapy
DMARDs	Disease-modifying antirheumatic drugs
DSU	Decision Support Unit
EAIR	Exposure adjusted incidence rate

Acronym	Definition
EIM	Extra-intestinal manifestations
EMA	European Medicines Agency
eMIT	Electronic market information tool
EMS	Endoscopic Mayo subscore
EQ-5D-5L	European Quality of Life 5 Dimensions
FACIT-F	Functional assessment of chronic illness therapy-fatigue
FCP	Faecal calprotectin
FMS	Full Mayo score
GB	Great Britain
GLM	Generalised linear model
GP	Geopolitical conflict
HEMI	Histologic endoscopic mucosal improvement
HEMR	Histologic endoscopic mucosal remission
HIR	Higher induction dosing regimen
hs-CRP	High-sensitivity C-reactive protein
HSUV	Health statue utility values
IBD	Irritable bowel disease
IBDQ	Inflammatory bowel disease questionnaire
ICER	Incremental cost-effectiveness analysis
IgG1	Immunoglobulin G1
IL	Interleukins
IPD	Individual patient-level data
IR	Inadequate responder
IRT	Interactive response technology
ITT	Intention-to-treat
IV	Intravenous
JAK	Janus kinase
LS	Least squares
MACE	Major adverse cardiovascular events
MAR	Missing-at-random
MCMC	Markov Chain Monte Carlo
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Multiple imputation
MIMS	Monthly index of medical specialties
MMRM	Mixed-effect model repeat measurement
MTX	Methotrexate
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NRI	Non-responder imputation
NRI-MI	Non-responder imputation while incorporating multiple imputation
OC	Observed cases
OL	Open label
PAS	Patient access scheme

Acronym	Definition
PBO	Placebo
PD	Prematurely discontinued
PGA	Physician's global assessment
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSRF	Potential scale reduction factor
PSS	Personal social services
Q8W	Once every 8 weeks
Q12W	Once every 12 weeks
R	Response
RR	Re-randomised responder
RBS	Rectal bleeding subscore
RBT	Return-to-Baseline
RCT	Randomised control trial
RTB	Multiple Imputation Incorporating Return-To-Baseline
RZB	Risankizumab
S1P	Sphingosine 1-phosphate
SAE	Serious adverse event
SC	Subcutaneously
SD	Standard deviation
SF-36	Short form 36
SFS	Stool frequency subscore
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
SUCRA	Surface under the cumulative ranking curve
TA	Technology appraisal
TDM	Therapeutic drug monitoring
TEAE	Treatment-emergent adverse event
Th	T-helper
TNF	Tumor necrosis factor
TSD	Technical Support Document
TT	Treat-through
UC	Ulcerative colitis
UC-SQ	UC-symptom questionnaire
UCEIS	Ulcerative colitis endoscopic index of severity
VAT	Value-added tax
VBA	Visual basic for applications
WPAI-UC	Work productivity and impairment questionnaire – ulcerative colitis
6-MP	Mercaptopurine

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission assesses the cost-effectiveness of risankizumab, a humanised immunoglobulin G1 (IgG1) monoclonal antibody inhibitor of interleukin-23 (IL-23), in patients with previously treated moderately to severely active ulcerative colitis (UC).

Risankizumab currently holds a UK marketing authorisation for the treatment of:[1]

- Plaque psoriasis: moderate to severe plaque psoriasis, in adults who are candidates for systemic therapy
- Psoriatic arthritis: alone or in combination with methotrexate (MTX), for active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs)
- Crohn's disease: patients 16 years and older[a] with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable

[a] In Northern Ireland, the marketing authorisation for risankizumab in Crohn's disease is restricted to adults.

In all of the above indications risankizumab has been appraised and recommended for use by NICE via the cost-comparison pathway.[2-4]

In UC, risankizumab is anticipated to be indicated [redacted].[5]

In this submission, risankizumab is positioned as a treatment for patients with moderately to severely active UC in whom tumour necrosis factor (TNF)-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

This positioning represents a subpopulation of the anticipated licensed indication and the population specified in the NICE final scope for this evaluation. This is in line with the population recommended by NICE for ustekinumab (TA633),[6] which is considered the most relevant comparator to risankizumab in this submission.

The NICE user guide states that a cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in published technology appraisal guidance for the same indication.[7]

As such, a cost-comparison analysis has been conducted for this submission between risankizumab and ustekinumab for the reasons stated below:

- Ustekinumab represents established UK clinical practice in the proposed target population. Additionally, feedback from UK clinical experts is that risankizumab would be considered as an alternative treatment to ustekinumab in the proposed target population.

- Both treatments have a related mechanism of action of targeting interleukins (IL) and both treatments inhibit IL-23. They also have a similar route of administration; intravenously (IV) in the induction phase and subcutaneously (SC) in the maintenance phase.
- Evidence from a series of network meta-analyses (NMAs), conducted in an overall population of patients with moderately to severely active UC regardless of prior biologic therapy exposure and in the subgroups of patients both with/without prior exposure to biologic therapies, showed comparable efficacy and safety in terms of clinical remission, clinical response, endoscopic improvement, serious infections and serious adverse events (SAEs) between risankizumab and ustekinumab.

The decision problem addressed within this submission is outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or one or more biologic therapies.	Adults with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.	The target population for risankizumab in this submission is in line with the anticipated use of risankizumab in UK clinical practice and with the patient population in which ustekinumab is recommended by NICE in TA633.[6] This positioning represents a subpopulation of the anticipated licensed indication and the population specified in the NICE final scope for this evaluation.
Intervention	Risankizumab	Risankizumab	In line with the NICE final scope.
Comparator(s)	At least one of the following treatments, according to NICE guidance: • TNF-α inhibitors (such as infliximab, adalimumab or golimumab) • JAK inhibitors (such as tofacitinib, filgotinib or upadacitinib) • ustekinumab • vedolizumab • ozanimod • etrasimod (subject to ongoing NICE evaluation) • mirikizumab	• Ustekinumab	The target population for risankizumab is adults with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough. In this position, it is anticipated that risankizumab will represent an alternative treatment option to ustekinumab only. Ustekinumab is considered the most relevant comparator to risankizumab for the following reasons: • Ustekinumab represents established UK clinical practice in the proposed target population. Additionally, feedback from UK clinical experts is that risankizumab would be considered as an alternative treatment to ustekinumab in the proposed target population. • Both treatments have a related mechanism of action of targeting ILs and both treatments inhibit IL-23. They also

			have a similar route of administration; IV in the induction phase and SC in the maintenance phase. • Evidence from a series of NMAs, conducted in an overall population of patients with moderately to severely active UC regardless of prior biologic therapy exposure and in the subgroups of patients both with/without prior exposure to biologic therapies, showed comparable efficacy and safety in terms of clinical remission, clinical response, endoscopic improvement, serious infections and serious AEs between risankizumab and ustekinumab. TNF-α inhibitors, JAK inhibitors, vedolizumab and ozanimod are not considered relevant comparators to risankizumab in this indication as they have a different mechanism of action to risankizumab and it is not anticipated that risankizumab would be considered an alternative treatment to these therapies. Whilst mirikizumab has a similar mechanism of action to risankizumab, it is not established UK clinical practice and therefore is not considered a relevant comparator. Finally, etrasimod is not a relevant comparator as it has not yet been appraised by NICE in this indication.
Outcomes	The outcome measures to be considered include: • rate of and duration of response, relapse and remission	All outcomes specified in the NICE final scope are included in this submission as follows: • proportion of patients with clinical response and remission	In line with NICE final scope.

	• corticosteroid-free remission • rate of endoscopic improvement • rate of hospitalisation • rate of surgical intervention • mortality • adverse effects of treatment • health-related quality of life	(assessed by the Adapted Mayo score) at Week 12 and Week 52 • proportion of patients with corticosteroid-free remission through Week 52 • proportion of patients with endoscopic improvement (assessed by the endoscopy subscore) at Week 12 and Week 52 • proportion of patients with UC-related hospitalisation through Week 12 and Week 52 • occurrence of UC-related surgeries through Week 12 and Week 52 • mortality • adverse effects of treatment • health-related quality of life (assessed using EQ-5D-5L, WPAI-UC, SF-36, FACIT-Fatigue, PGIS and IBDQ)	In addition, further outcomes of clinical importance are also included in this submission, including but not limited to: • proportion of patients with no bowel urgency at Week 12 and Week 52 • proportion of patients with no abdominal pain at Week 12 and Week 52 • proportion of patients with no nocturnal bowel movements at Week 12 and Week 52 • proportion of patients with no tenesmus at Week 12 and Week 52 • change from baseline in number of faecal incontinence episodes at Week 12 and Week 52 • change from baseline in number of days per week with sleep interrupted due to UC at Week 12 and Week 52
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out • The reference case stipulates that	• A cost-comparison analysis has been conducted to estimate the incremental costs of risankizumab versus ustekinumab, in line with the NICE reference case • A 10-year time horizon was adopted within the analysis to sufficiently reflect any differences in costs between the technologies being compared • Costs were considered from an NHS and Personal and Social Services perspective (PSS) • A patient access scheme (PAS)	Evidence from a series of NMAs, conducted in an overall population of patients with moderately to severely active UC regardless of prior biologic therapy exposure and in the subgroups of patients both with/without prior exposure to biologic therapies, showed comparable efficacy and safety in terms of clinical remission, clinical response, endoscopic improvement, serious infections and serious AEs between risankizumab and ustekinumab. A cost-comparison analysis between the two treatments has therefore been conducted for this submission.

	the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account • The availability and cost of biosimilar and generic products should be taken into account	for risankizumab was included in the analysis	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: 1. people who have been previously treated with 1 or more biologic therapies 2. people who have been previously treated with a JAK inhibitor 3. people who have not received a prior biologic therapy or a JAK inhibitor	Clinical efficacy data for risankizumab from the pivotal INSPIRE and COMMAND trials have been presented within this submission for the following subgroups: • Advanced therapy-inadequate responder (IR), defined as patients who have had an intolerance or inadequate response to advanced therapy – see Section B.3.7 • Non-advanced therapy-IR, defined as patients who have had an inadequate response or intolerance to conventional therapy. This population also included patients who had previously received biologic therapy or tofacitinib but had stopped therapy based on	In line with the NICE final scope. The advanced therapy-IR subgroup data includes patients in subgroups 1 and 2 specified in the NICE final scope. The non-advanced therapy-IR subgroup data includes patients in subgroup 3 specified in the NICE final scope.

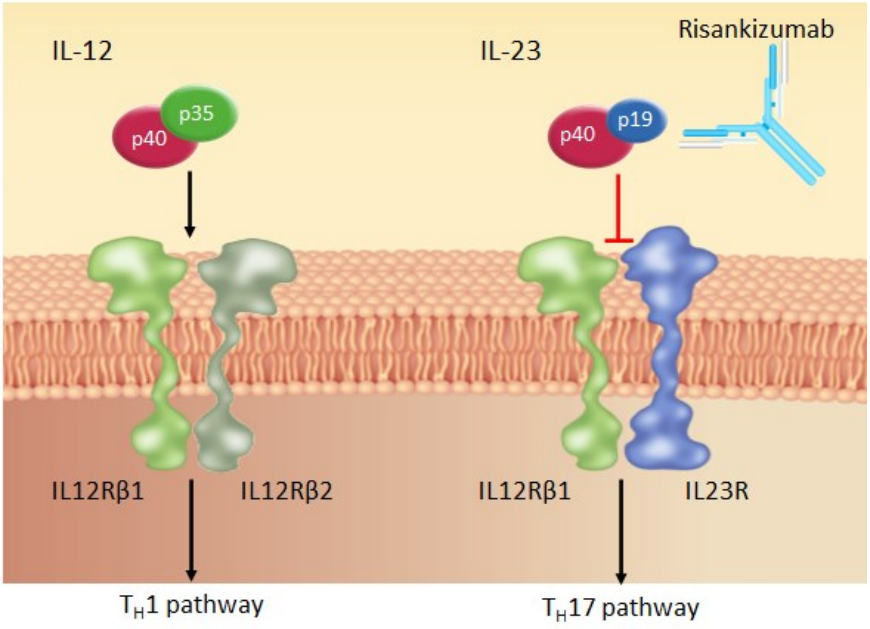
		reasons other than inadequate response or intolerance – see Section B.3.3.1	

Abbreviations: EQ-5D-5L: European Quality of Life 5 Dimensions; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ: Inflammatory Bowel disease Questionnaire; IR: inadequate responder; JAK: Janus kinase; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; PAS: patient access scheme; PGIS: Patient Global Impression of Severity; SF-36: Short Form 36; TNF-α: tumour necrosis factor-α; UC: ulcerative colitis; WPAI-UC: Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis.

B.1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with risankizumab for the treatment of patients with previously treated moderately to severely active UC is presented in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Risankizumab (Skyrizi®)
Mechanism of action	Risankizumab is a humanised IgG1 monoclonal antibody that selectively binds with high affinity to the p19 subunit of human IL-23 (without binding to IL-12) and inhibits its interaction with the IL-23 receptor complex.[1] IL-23 is a cytokine that is involved in inflammatory and immune responses; it is sometimes referred to as a 'master cytokine' because it regulates cells which themselves further promote inflammation.[8] For example, IL-23 binds to T-helper (Th)-17 cells and macrophages which in turn promote the release of other cytokines, such as IL-17, IL-6, IL-1, IL-22 and tumour necrosis factor (TNF).[8] This IL-23-Th17-IL17 pathway is believed to be crucial in the development of gastrointestinal symptoms and associated bowel damage in UC.[9] By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and the release of proinflammatory cytokines (Figure 1).[1] In turn, this leads to a reduction in inflammation and therefore a reduction in the symptoms and associated bowel damage experienced for patients with UC.[9] Finally, risankizumab exhibits linear pharmacokinetics when administered intravenously or subcutaneously, with a long terminal half-life of approximately 28 days and peak plasma concentrations occurring approximately 3–14 days after dosing.[10] **Figure 1: Inhibition of IL-23p19 by risankizumab**  **Abbreviations:** IL: interleukin; Th: T-helper.

Marketing authorisation/CE mark status	A marketing authorisation extension application for risankizumab was submitted to the EMA (via the centralised procedure including Northern Ireland)/MHRA in September 2023 for [redacted] EMA Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in [redacted]. A marketing authorisation submission to the MHRA for a license in Great Britain is to be made via the EU recognition procedure after the CHMP opinion is received.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	A link to the MHRA Summary of Product Characteristics (SmPC) for risankizumab is provided in Appendix C. A draft version of the EU SmPC that includes risankizumab as a treatment for UC has been included as part of the reference pack. Risankizumab is anticipated to be indicated for the treatment of:[5] • [redacted] Contraindications to risankizumab include:[1] • Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC • Clinically important active infections (e.g. active tuberculosis) - see section 4.4 of the SmPC
Method of administration and dosage	Risankizumab is intended for use under the guidance and supervision of a clinician experienced in the diagnosis and treatment of UC. The recommended dose for risankizumab in patients with UC is:[1] • **Induction:** 1200 mg (2 x 600 mg) administered IV at Week 0, Week 4, and Week 8 • **Maintenance:** 180 mg or 360 mg administered SC via an on-body device Q8W from Week 12
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	**Induction**: The list price of one dose of risankizumab 1200 mg (2 x 600 mg) IV is 2 x £3,326.09 = £6,652.18.[11] The cost of induction treatment with risankizumab for one patient with UC at list price is £19,956.54. **Maintenance:** The list price of one dose of risankizumab 180 mg SC is [redacted] and one dose of risankizumab 360 mg SC is £3,326.09. The cost of one year of maintenance treatment with risankizumab for one patient with UC at list price is [redacted] for the 180 mg SC dose and £21,619.59 for the 360 mg SC dose.
Patient access scheme/commercial arrangement (if applicable)	A confidential PAS discount is available that offers risankizumab at a reduced price as follows: **Induction**: The PAS price of one dose of risankizumab 1200 mg (2 x 600 mg) IV is [redacted]. **Maintenance:** The PAS price of one dose of risankizumab 180 mg SC is [redacted] and one dose of risankizumab 360 mg SC is [redacted].

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; IgG1: immunoglobulin G1; IL: interleukin; MHRA: Medicines and Healthcare products Regulatory Agency; MMA: marketing authorisation application; PAS: patient access scheme; Q8W: once every 8 weeks; SC: subcutaneous; SmPC: Summary of Product Characteristics; Th: T-helper; UC: ulcerative colitis.

B.1.3 Health condition and position of the technology in the treatment pathway

Summary of the health condition

- UC is a chronic systemic inflammatory bowel disease (IBD) that is characterised by alternating periods of remission and relapse, resulting from inflammation in the inner lining of the colon.[12, 13]
- Patients with UC can develop several debilitating symptoms including abdominal cramps, severe pain, rectal bleeding, bloody stools, persistent diarrhoea, and fatigue.[12-15]
- UC is a heterogenous disease, with patients presenting with substantial differences in disease location, disease activity, disease presentation and disease course.[16]
- The symptoms of UC can have a debilitating impact on patients' functioning, wellbeing, and HRQoL,[17, 18] and on daily activities including their ability to work, attend school/places of education, and carry out parenting tasks.[19]
- UC is the most common form of IBD in the UK; in England, the incidence of UC in adults is approximately 10 per 100,000 and the prevalence is approximately 570 per 100,000.[20, 21]
- Although there are several treatment options for UC, none of these are curative. The goals of current treatment are to induce remission of active disease and maintain durable remission over the long term, whilst preserving a good health-related quality of life (HRQoL) and reducing the need for surgery.[22] In addition, mucosal healing (which can be captured by endoscopic improvement +/- histologic remission) is a clinically important and meaningful goal in UC as it is associated with reduced relapse and colectomy rates, as well as improved HRQoL.[23]
- The direct medical costs of treating UC and the indirect costs associated with lost work productivity for people with UC represent a significant economic burden to society. If hospitalisation is needed to control a UC relapse, this leads to a greater than 20-fold increase in costs compared with the quiescent cases of the disease,[24] reinforcing the need for new therapies that are able to induce and maintain both remission and mucosal healing and reduce long-term complications.

UK treatment pathway for UC and the positioning of risankizumab

- The most recent clinical guidelines for UC are available from NICE (NG130 [2019]), the British Society of Gastroenterologists [2019] and the European Crohn's and Colitis Organisation [2021].[21, 25, 26]
- The first line of treatment for UC comprises conventional therapy, which is typically used to manage patients with mild to moderate disease. Conventional therapy includes a range of therapies including aminosalicylates, corticosteroids and immunomodulators.[21, 27]
- The management of moderately to severely active UC is more challenging and may require the use of advanced therapies, if treatment with conventional therapy is associated with a poor response, is not tolerated, or is contraindicated.[6, 21, 28-33]
- In the UK, the majority of patients with moderately to severely active UC receive TNF-α inhibitors as first-line advanced therapy, due to the wealth of experience and familiarity

with their use in UK clinical practice, as well as the availability and affordability of biosimilar products for both infliximab and adalimumab.[6, 21, 27, 30, 34, 35] However, primary failure of induction therapy with TNF-α inhibitors has been reported in 19–58% of patients in clinical trials.[36]

- Patients in whom TNF-α inhibitors are deemed unsuitable, or where patients have had an inadequate response to, lost response to, or were intolerant to a TNF-α inhibitor, are typically prescribed other advanced therapies with different mechanisms of action, including interleukin inhibitors (ustekinumab or mirikizumab), anti-integrins (vedolizumab), S1P receptor modulators (ozanimod) or JAK inhibitors (tofacitinib, filgotinib or upadacitinib).
- However, as for all advanced therapy options, patients with moderately to severely active UC will face a risk of relapse and non-response; many patients will need to cycle through multiple therapeutic options in order to achieve clinical remission and mucosal healing following relapse on previous treatments. Clinician and patient choice of treatment is likely to depend on factors including failure to respond or loss of response, contradiction or unsuitability and type of prior treatment received.
- Risankizumab is positioned as a treatment for patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough. In this position, it is anticipated that risankizumab will represent an alternative treatment option to ustekinumab, which has received a positive recommendation for reimbursement by NICE in patients with previously treated moderately to severely active UC and has a related mechanism of action to risankizumab through the inhibition of interleukins.
- A NICE recommendation for risankizumab in the proposed target patient population would fulfil a considerable unmet need in this group of patients and provide both patients and clinicians a further option for the treatment of moderately to severely active UC.

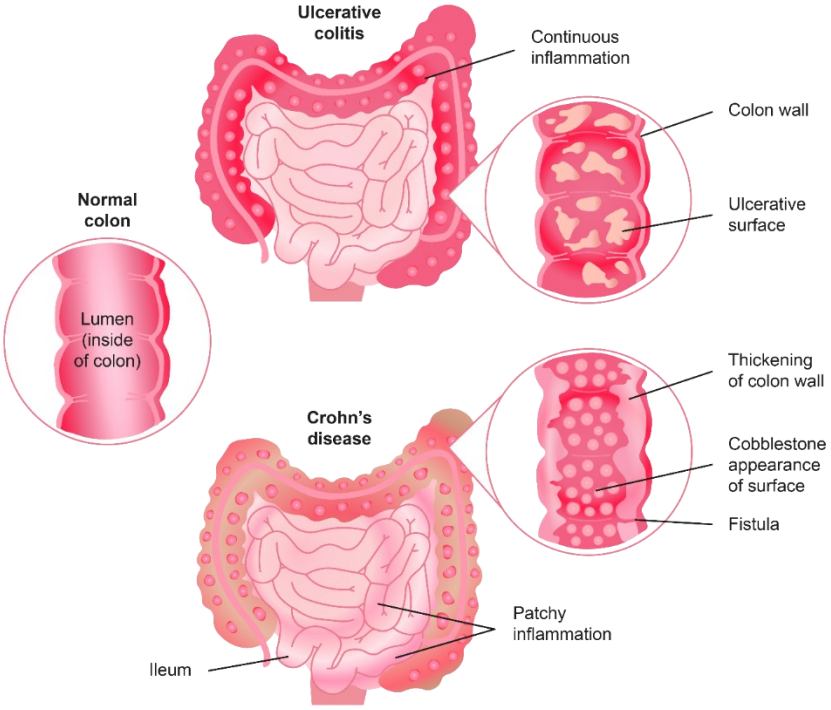
B.1.3.1 Health condition

Disease overview

UC is a chronic, systemic form of IBD that is characterised by alternating periods of remission and relapse, resulting from inflammation in the mucosal surface (inner lining) of the colon.[12, 13] The inflammation typically presents in the rectum and extends proximally (up the length of the colon) in a continuous manner throughout the entire colon.[14] As a result, patients with UC develop a number of debilitating symptoms including abdominal cramps and severe pain, rectal bleeding, bloody stools, persistent diarrhoea, and fatigue that significantly impacts their HRQoL.[12-15] Persistent uncontrolled UC leads to an increased risk for colorectal cancer, risk of surgery and can lead to the development of fibrotic colon (an excessive accumulation of scar tissue in the intestinal wall).[37, 38, 39]

In UC, there is continuous inflammation of the colon, and the mucosal lining is specifically affected. UC is therefore distinct to Crohn's disease, another form of IBD which can affect all four layers of the intestinal wall in any part of the gastrointestinal tract and can present with patches of healthy tissue between inflamed areas (Figure 2).[40]

Figure 2: Inflammation of the large bowel in ulcerative colitis versus Crohn's disease



Source: Adapted from patient.gastro.org.

The location of inflammation in UC can involve varying lengths of the colon, which can be used to classify the disease into four categories. The least extensive category is ulcerative proctitis, where only the region closer to the rectum is affected. In cases of proctosigmoiditis, the rectum and sigmoid colon are affected; in left-sided colitis, the rectum as well as the sigmoid and descending colon are affected. The most extensive category is pancolitis, where the entire colon is inflamed.[41]

Epidemiology

UC is the most common form of IBD. In England, the incidence of UC in adults is approximately 10 per 100,000 and the prevalence is approximately 570 per 100,000.[20, 21] Based on the latest England population estimates, this equates to approximately ~250,000 adults currently living with UC in England, and a further ~4,500 adults newly diagnosed with UC each year.[42]

While UC most commonly presents in adolescence and early adulthood, it may occur at any age.[43] Most patients are diagnosed between 17–40 years of age,[44] thus the burden of disease and associated disability impacts patients from a young age during critical stages of their education and throughout their most productive years.

Diagnosis and severity

The diagnosis of UC is based on clinical symptoms confirmed by objective findings from endoscopic examinations (imaging of the inside of the colon) and histological examinations (the study of microscopic tissue structures).[12, 14, 27] The aim of these examinations is to rule out infectious (e.g. bacterial, parasitic, viral, and fungal) and non-infectious (e.g. microscopic colitis, malabsorption of bile acid, bacterial overgrowth, malignant causes, and diarrhoea induced by drugs) causes of diarrhoea prior to diagnosis.[14, 27] A diagnosis of UC, as well as the extent and

severity of disease, is confirmed by a full ileocolonoscopy (a diagnostic imaging test of the inside of the ileum and colon), typically within the first year of a patient presenting with symptoms.[27] Alongside histological examination of the biopsy, a full ileocolonoscopy allows for a definitive confirmation of UC versus Crohn's disease to help guide initial treatment choices.[27]

The severity of UC is typically evaluated based on the results of endoscopic examinations and/or patient symptoms.[45] Several classifications and grades of disease exist which are predominantly based on scoring systems.[45] One of the most commonly used scoring systems in UK clinical practice is the Mayo Scoring System.[6, 29, 33]

The 4-component Full Mayo score (Table 3) ranges from 0–12 points and consists of the sum of four sub-scores: stool frequency, rectal bleeding, endoscopic findings, and Physician's global assessment (PGA). The PGA is a scoring system which acknowledges other criteria including the patient's daily abdominal discomfort, general sense of well-being, performance status, and physical findings.[46]

Two modifications of the Full Mayo score can be used: the adapted Mayo score and the partial adapted Mayo score. With the Adapted Mayo scoring system, the PGA sub-score is excluded as this component is a subjective measure and therefore can be considered a limitation in the assessment of UC disease severity.[47] In the partial Adapted Mayo scoring system, the score comprises a composite of the rectal bleeding and stool frequency sub-scores.[48] This can be used in instances where an endoscopy has not yet been performed or cannot be performed.

Table 3: Full Mayo scoring system (4-component)

	Normal (0)	Mild (1)	Moderate (2)	Severe (3)
Number of bowel movements per day	Normal	1–2 stools more than normal for the patient	3–4 stools more than normal for the patient	≥5 stools more than normal for the patient
Rectal bleeding	None	Steaks of blood in stool occurs less than half the time	Obvious blood with stool most of the time	Blood alone passes
Findings on endoscopy	Normal	Erythema, decreases vascular pattern, mild friability	Marked erythema, lack of vascular pattern, friability, erosions	Spontaneous bleeding, ulceration
PGA	Normal	Mild	Moderate	Severe

Abbreviations: PGA: Physician's Global Assessment.
Source: Lewis *et al*. (2008).[48]

B.1.3.2 Disease burden

Symptom burden

The symptoms of UC, which derive from the inflammation of the colon, are diverse and commonly include the development of abdominal cramps and severe pain, rectal bleeding, bloody stools, bowel urgency, persistent diarrhoea, and fatigue.[13-15] In a UK-based survey of patients with IBD aged ≤29 years (N=1,081; 36.3% of patients had UC) extreme fatigue was the most frequently reported symptom (75.9%) followed by pain (49.4%) and diarrhoea (44.0%).[49] The survey also found that 78% of patients with UC had experienced a relapse (the return of

active symptoms) that year with almost half being hospitalised in the same period.[49] Relapses (also referred to as flare-ups) can often last for several weeks in some patients; more frequent or prolonged flare-ups are indicative of a more difficult to control disease and these patients may experience a greater negative impact on their HRQoL.[50]

UC is a chronic, lifelong disease with no cure that is associated with significant morbidity. Whilst there are treatments available which can help induce remission, an estimated 50% of people with UC will have at least one relapse per year.[51] When a patient with UC relapses, they are at a heightened risk of developing severe complications such as toxic megacolon (when the colon stops contracting and relaxing, and dilates due to inflammation), severe bleeding and dehydration, which requires emergency medical attention.[52] In some cases, life-saving surgery is needed for patients who are admitted to hospital with a severe relapse of UC if they do not respond to intensive medical treatment.[14, 15] Approximately 25% of people with UC have one or more episodes of acute severe UC in their lifetime.[51]

A particularly debilitating aspect of UC is that around 30% of people with UC will also experience symptoms that affect other areas of the body beyond the colon. These are termed extra-intestinal manifestations (EIM) and can include pauci-articular arthritis (arthritis involving fewer than five joints), aphthous mouth ulcers (recurrent sores inside the mouth) and metabolic bone disease.[53] These EIM are often difficult to treat and can affect both morbidity as well as mortality (e.g. in the case of the EIM lung parenchymal disease).[54] They also have a hugely debilitating impact on patients' HRQoL.[55] The prevalence of untreated EIM in patients with UC has been shown to prolong the UC disease course and prevent mucosal healing.[55]

Long-term complications associated with UC include the development of colorectal cancer, disease extension (mucosal inflammation extending proximally to involve more of the colon) and the development of a fibrotic colon which leads to loss of normal function and/or narrowing in the intestine as a result of scar tissue formation.[56-58] Patients with UC are twice as likely to develop colorectal cancer compared with the general population.[6, 59] The risk of developing colorectal cancer increases with disease extent and duration as well as disease activity and therefore it is thought that the presence of chronic inflammation promotes carcinogenesis.[59, 60]

Quality of life impact and psychosocial burden

In addition to the debilitating physical burden of UC, the disease can have a considerable impact on patients' HRQoL and poses a significant psychosocial burden. Bowel urgency, fatigue, abdominal pain, diarrhoea, the need to use the toilet soon after eating, and rectal bleeding have all been identified in patient-reported and physician-reported surveys as common symptoms and symptoms that have the greatest impact on HRQoL.[61] As a result, these symptoms can have a substantial impact on patients' wellbeing,[17, 18] as well as their daily activities including their ability to work, attend school/places of education, and carry out parenting tasks.[19] UC is most commonly diagnosed before the age of 30,[12] meaning that patients with UC can live with these negative impacts on HRQoL for a significant proportion of their life. Furthermore, patients' constant fear of losing control of bowel movements can mean they struggle to attend social events, leading to an increased risk of self-isolation.[62] A large international survey (N=4670; 33% of patients had UC) found that 35% of patients with IBD felt their disease prohibited them from pursuing an intimate relationship and 26% felt it prevented them from making or keeping friends.[63]

Finally, increased disease activity is associated with increased symptoms, and reduced patient

HRQoL.[64] A cross-sectional UK study reporting outcomes for the Inflammatory Bowel Disease Questionnaire (IBDQ), which reports on four domains (bowel symptoms, systematic symptoms, emotional function and social function), found that the baseline score for patients with moderate to severe disease was significantly ($p<0.001$) reduced compared to patients with mild disease (116.41 versus 148.81, respectively), signifying worsening symptoms and reduced HRQoL.[65]

Economic burden

The medical needs for patients with UC place a significant burden on healthcare resources.[66] The average annual cost of care for treating patients with UC in the UK in 2015 was £1,693 for a patient with UC in remission, £2,903 for a patient in relapse with mild to moderate UC, and £10,760 for a patient in relapse with severe UC in 2015.[66]

In addition, owing to the early age of onset, UC negatively impacts patients' work life during the most productive years of work (18–64).[63, 67] Patients with UC may be forced to take significant periods of absence from work, as well as reduced working hours, due to the symptoms of the disease.[63, 68] Findings from a large international survey (N=4670; 33% of patients had UC) showed that approximately 3 out of 4 patients with IBD missed work due to their illness and one-third of patients lost or quit a job. In particular, work productivity was found to be seriously impaired in patients with moderately to severely active UC, with productivity impairment increasing with disease severity.[63, 67]

Collectively, the direct medical costs and indirect costs associated with lost work productivity associated with UC represent a significant economic burden to society. Importantly, disease relapses have been found to lead to a 2–3-fold increase in healthcare costs for patients compared to those with stable disease. If hospitalisation is needed to control a relapse, this leads to a greater than 20-fold increase in costs compared with UC patients whose disease is currently inactive (no inflammation seen on colonoscopy); indeed, hospitalisation costs have been found to account for 41–55% of direct medical costs for UC in Western countries.[24] This reinforces the need for new therapies that are able to induce and maintain remission, thus limiting the costs associated with disease relapse and subsequent hospitalisation.

B.1.3.3 Current treatment pathway and proposed positioning of risankizumab

Treatment aims

Whilst there are a number of therapeutic options available for patients with UC, no treatments are curative. The goals of current treatment include inducing remission of active disease and maintaining durable remission over the long term, whilst maintaining HRQoL and reducing the need for surgery.[22] Further to this, current guidance by the British Society of Gastroenterologists (BSG) recognises the importance of endoscopic outcomes such as mucosal healing in addition to controlling clinical symptoms.[27] Mucosal healing typically refers to the absence of macroscopic mucosal inflammation of ulceration, which can be captured by endoscopic outcomes such as endoscopic improvement +/- histologic remission.[27] Mucosal healing represents an important therapeutic goal in clinical practice as it is associated with reduced relapses, reduced colectomy rates, improved patients' HRQoL and the achievement of long-term corticosteroid-free remission.[23, 69] Inducing mucosal healing therefore leads to improved long-term outcomes for patients which in turn can be linked to a reduced burden on healthcare resources.[70]

An additional treatment aim in UC includes reducing corticosteroid exposure and the achievement of corticosteroid-free remission. Although corticosteroids can be effective in controlling relapses, they are not considered effective in controlling the condition in the long-term.[71] Additionally, long-term use of corticosteroids is associated with a multitude of significant AEs and comorbidities including osteoporosis, pre-disposition to diabetes, weight gain, hypertension, risk of infection, cataracts and psychological effects.[71] Indeed, long-term corticosteroid-free remission is associated with improved HRQoL in UC patients and a decreased risk of surgery.[72, 73] Steroid burden continues to be a significant issue in IBD patients; in a 2019 study of UK IBD outpatients, 14.8% of patients were observed to have steroid excess or dependency relative to the recommended ECCO guidelines on steroid exposure.[74] Together, the AEs associated with long-term use of corticosteroids and their current excess use in the UK highlight the importance of achieving corticosteroid-free remission as a treatment goal in UC.

Current treatment options

The most recent clinical guidelines for UC in the UK are available from NICE (NG130 [2019]), the BSG (2019) and the European Crohn's and Colitis Organisation [2021].[21, 25, 26] The typical UK treatment pathway for UC is presented in Figure 3 and summarised below, based on NG130 and recently published NICE evaluations.[6, 21, 32, 33]

Conventional therapy

The first line of treatment for UC comprises a range of therapies collectively termed 'conventional therapy' which include aminosalicylates, corticosteroids and immunomodulators.[21, 27] Whilst conventional therapy is effective for the majority of patients with mild UC, a proportion of patients will relapse and some patients may develop moderately to severely active UC. Many patients will also present with moderately to severely active UC at diagnosis. The management of moderately to severely active UC is more challenging and requires the use of advanced therapies, described below.[21]

Advanced therapy

Advanced therapies are introduced if treatment with conventional therapy is associated with a poor response, is not tolerated, or is contraindicated.[6, 28-33] Advanced therapy treatment options that are recommended by NICE include a range of biologics and small molecule therapies, including: TNF-α inhibitors (infliximab, adalimumab, and golimumab [TA329][30]), JAK inhibitors (tofacitinib [TA547][28], filgotinib [TA792][31] and upadacitinib [TA856][32]), interleukin 12/23 and 23 inhibitors (ustekinumab [TA633][6] and mirikizumab [TA925][75]), an anti-integrin (vedolizumab [TA342][29]) and a S1P receptor modulator (ozanimod [TA828][33]). It should be noted that whilst all of these therapies are advanced therapies, the TNF-α inhibitors, interleukin inhibitors and anti-integrins are classed as 'biologic therapies', which are large molecules known as antibodies originally extracted from living organisms. JAK inhibitors and S1P receptor modulators are small molecule therapies which are small chemical structures and so are not classed as biological therapies (but are still advanced therapies).

Treatment with advanced therapies is individualised and the choice of advanced therapy is typically made according to a number of factors, including patient preference, patient history and presentation, cost, likely adherence, potential AEs and initial response to therapy.[6, 21, 27-33]

The majority of patients with moderately to severely active UC receive TNF-α inhibitors as a first-line advanced therapy, due to the wealth of experience and familiarity with their use in UK clinical

practice, as well as the availability and affordability of biosimilar products for both infliximab and adalimumab.[6, 21, 27, 30, 34, 35] However, primary failure of induction therapy with TNF-α inhibitors has been reported in 19–58% of patients in clinical trials, with a further 17–22% of patients having to discontinue due to secondary loss of response within the first 12 months, and dose escalation being required to maintain efficacy in 19–40% of patients.[36]

Feedback from UK clinical experts indicates that patients in whom TNF-α inhibitors are deemed unsuitable, or where patients have had an inadequate response to, lost response to, or were intolerant to a TNF-α inhibitor, are typically prescribed other advanced therapies with different mechanisms of action. However, as for all current advanced therapy options, patients will face a risk of relapse and non-response; many patients will need to cycle through various advanced therapies with different mechanisms of action in order to achieve clinical remission following relapse on previous treatments.[36]

Finally, surgery, most commonly a colectomy (removal of the large bowel) with formation of an ileostomy (where the end of the small intestine is brought out through an opening [stoma] in a patient's abdomen), is considered for patients with UC whose disease has not responded or is refractory to medical treatment. Approximately 20–30% of patients will eventually require surgery primarily due to failure of medical therapy.[76] However, surgery is usually considered as a last-line option due to the short-and long-term risks involved.[35] The long-term complications of surgery in UC include small bowel obstruction, and complications of ileoanal pouches such as pouch fistulas, pouchitis and pouch failure.[77] Although there is not an impact on life expectancy associated with UC,[78] there is a potential increase in the risk of mortality associated with post-operative complications particularly in patients aged >50 years.[79] One of the ultimate UC treatment goals agreed in the 2019 BSG guidelines was to prevent surgery,[27] highlighting that surgery is usually considered as a last resort only when all therapeutic options have failed. The availability of new treatments for UC therefore offers patients additional therapeutic options before the need to consider surgery.

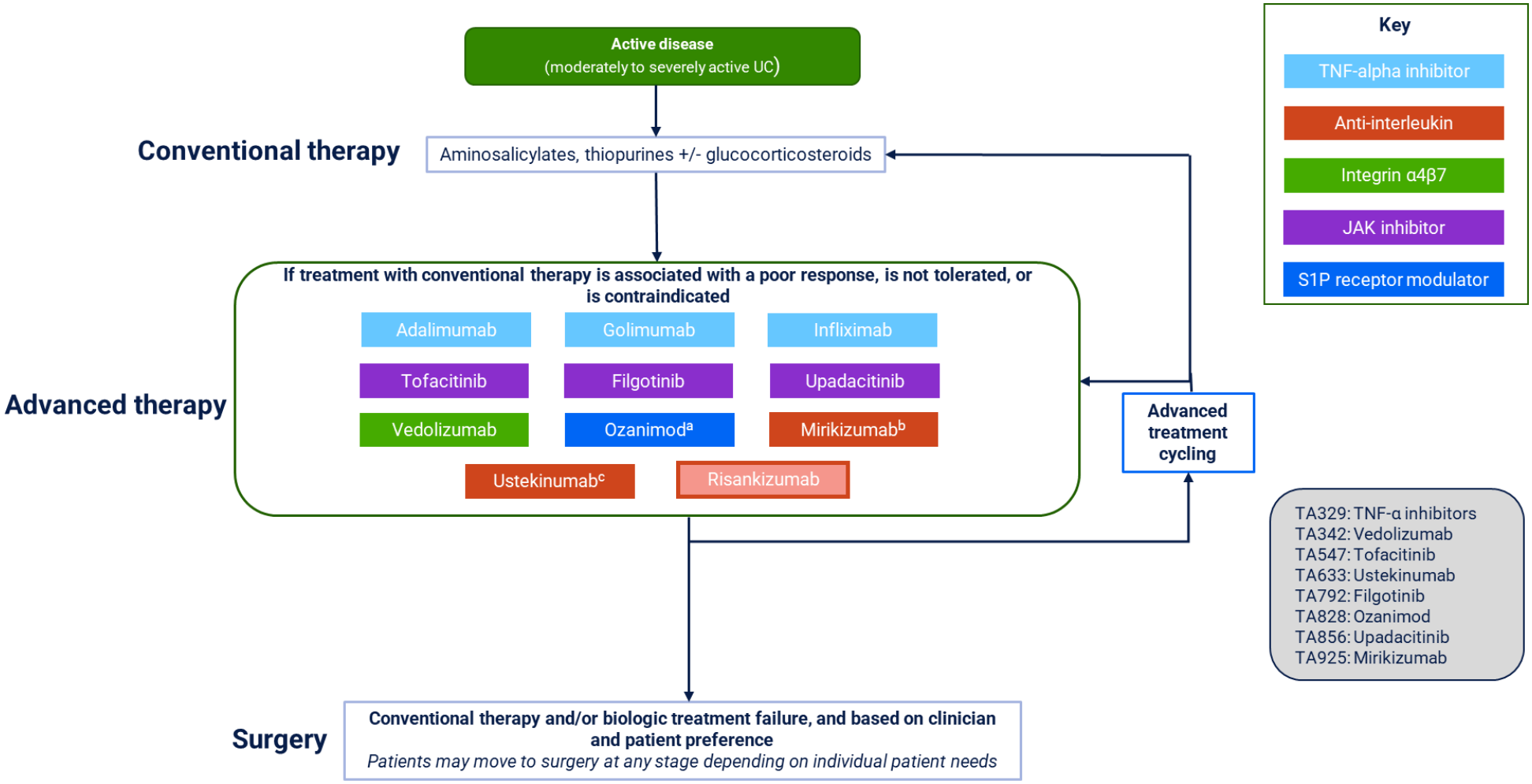
Anticipated positioning of risankizumab

The proposed positioning of risankizumab in the UC treatment pathway is displayed in Figure 3. Risankizumab is expected to be used in adults with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

This positioning represents a subpopulation of the anticipated licensed indication and the population specified in the NICE final scope for this evaluation. This is in line with the population recommended by NICE for ustekinumab (TA633),[6] which is considered the most relevant comparator to risankizumab in this submission.

Ustekinumab represents established clinical practice in the proposed target population; both treatments have a related mechanism of action of targeting ILs and both treatments have a similar mode of administration. Feedback from UK clinical experts also supports that risankizumab would be considered as an alternative treatment to ustekinumab in the proposed target population.

Figure 3: UK treatment pathway for moderately to severely active UC and the anticipated positioning of risankizumab



Footnotes: [a] Ozanimod is recommended only if infliximab is not suitable or biological treatment cannot be tolerated or is not working well enough. [b] Mirikizumab is recommended only if a TNF-α inhibitor has not worked or cannot be tolerated or is not suitable. [c] Ustekinumab is recommended only if TNF-α inhibitor has failed or cannot be tolerated or is not suitable.
Abbreviations: IR: inadequate response; JAK: Janus kinase; S1P: sphingosine 1-phosphate; TNF-α: tumour necrosis factor-alpha; UC: ulcerative colitis.
Sources: NICE guideline NG130.[21]

B.1.4 Equality considerations

It is not anticipated that the provision (or non-provision) of risankizumab would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

As described in Section B.1, risankizumab is anticipated to represent an alternative treatment option to ustekinumab, which has received a positive recommendation for reimbursement by NICE in TA633.[6]

The following section provides an overview of the key clinical outcomes and measures considered in the ustekinumab cost-effectiveness evaluation. As stated in Section B.1, for this submission, a cost-comparison analysis has been conducted between risankizumab and ustekinumab which assumes comparable efficacy and safety between the two treatments; therefore, clinical outcomes discussed in this section are not considered in the cost-comparison model for this submission (presented in Section B.4).

Two measures of clinical effectiveness were considered in the ustekinumab evaluation: clinical response and remission, as defined by the Mayo scoring system, to assess patients' disease activity after the induction treatment period and during the maintenance phase. Surgery and post-surgery were included in the economic analysis with the Committee-accepted approach of modelling surgery as a distinct health state. Separate post-surgery health states were modelled dependent upon whether patients experienced post-surgery complications or not.

The health state utility values (HSUVs) considered in the ustekinumab evaluation were sourced from the literature, with values derived from Woehl *et al.* (2008),[80] supplemented by values from Arseneau *et al.* (2006).[81] Utility values derived from the key pivotal trial were also considered by the Committee.

In the ustekinumab evaluation, it was assumed that 30% of patients received an escalated dose in the maintenance period at any one time, and the corresponding higher drug acquisition costs were applied to these patients. Feedback from clinical experts is that the proportion of patients requiring dose escalation with ustekinumab is now much higher and closer to 100% of patients; indeed, in the NICE evaluation for risankizumab in Crohn's disease, the proportion of patients receiving an escalated dose of ustekinumab was assumed to be 92.5%.

Finally, a constant risk of discontinuation in the maintenance phase was assumed, but scenario analyses were presented at which a 25% reduction in the loss of response rate after the first year or two years was implemented. The impact of these scenarios was minimal, and the Committee accepted the constant risk as per the Company's approach.

Further detail on clinical outcomes and measures used in the ustekinumab evaluation are presented in Table 4. As highlighted above, some of these outcomes are only relevant to a cost-effectiveness analysis and are therefore not relevant to this appraisal.

Table 4: Clinical outcomes and measures appraised in NICE TA633 (ustekinumab)

Outcomes	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee preferred assumption	Uncertainties
Clinical remission and clinical response without remission	Clinical remission and clinical response without remission were defined based on the Mayo scoring system as implemented in the UNIFI trial.	Clinical trial data relating to the proportions of patients with clinical remission or clinical response without remission were included in the economic model. It was assumed that patients with disease that did not respond or lost response to initial therapy remained in the active UC health state (i.e. assumed a 0% response rate).	N/A	The Committee considered the approach implemented by the Company to be appropriate.	The ERG noted that the relapsing and remitting nature of UC means there is a chance some patients could improve without treatment. The Committee agreed with this but emphasised a lack of data to inform the model otherwise.
Loss of response in maintenance phase	The proportion of patients who are in the 'clinical remission' or 'clinical response without remission' health states who lose response to treatment during the maintenance phase.	A loss of response analysis was implemented which took clinical remission and response data directly from the individual trial arms. In the initial base case economic analysis, the calculated probability of loss of response was extrapolated beyond the trial periods and a constant loss or response rate over time was assumed.	The Company presented a scenario analysis implementing a one-time 25% reduction in loss of response after the first two years of treatment initiation. The impact on the ICERs was minimal.	Despite acknowledging uncertainty, the Committee preference was to use the ERG's maintenance-only NMA and to assume a constant risk of loss of response throughout the maintenance treatment.	The ERG argued that the use of direct trial data was associated with bias, such as bias related to differences in baseline factors in the trials. As such, the ERG preferred the Company's maintenance NMA as the source of maintenance phase response data to the unadjusted indirect comparison methods. The Company provided an updated base case

					using a one-year NMA conditional on response which aligned with the preferences of the ERG. The committee agreed that the results of the Company's maintenance NMA were highly uncertain.
Dose escalation	The proportion of patients who receive dose escalation due to loss of response.	In the initial approach, the Company assumed 30% of patients receiving all included biologics except for infliximab, with the latter justified by the SmPC for infliximab not permitting dose escalation. Based on clinical feedback that infliximab dose escalation does occur in clinical practice, the ERG preferred to implement the same assumption of 30% of patients receiving the escalated dose to infliximab. This change was accepted by the Company.	N/A	The Company's revised assumption was accepted by the Committee.	The Committee recognised there was some uncertainty about this issue but noted it not to be a major driver of cost effectiveness.
Surgery	First and second surgeries were modelled as distinct health states	The model included two health states for surgery (first surgery and second surgery) and three health states for post-surgery (post-first surgery remission,	N/A	The Committee concluded the model could be used for decision-making, and the appropriateness of the surgery and post-surgery health	N/A

		post-first surgery complications, and post-second surgery remission). These health states were selected in order to reflect the natural history of UC and to align with the definitions used in the UNIFI trial as closely as possible.		states was not discussed.	
HSUVs	EQ-5D data derived from key clinical trials or published literature sources.	The Company and the ERG both used utility values sourced from Woehl *et al.* (2008)[80]	The Company explored scenario analyses in which utility values derived from the UNIFI trial were implemented for all non-surgery health states, and in which utility values related to surgery health states from Swinburn *et al.* were implemented. Both increased the ICERs; the UNIFI scenario considerably, the Swinburn *et al.* scenario modestly.	The Committee concluded that utility values derived from Woehl *et al.* (2008)[80]and the UNIFI trial were equally appropriate, and thus considered both in its decision-making.	The Committee acknowledged the use of values derived from Woehl *et al.* (2008)[80] in previous appraisals, but highlighted its limited sample size as compared with the UNIFI trial, and that assessment of its appropriateness was challenging due to it being an abstract rather than a full publication. However, limitations of the UNIFI trial utility data, such as potential placebo effects and the limited time period over which they were collected, were also acknowledged.
Adverse events	Only serious infection adverse events were modelled.	Serious infection rates were informed by a real-world study in psoriasis patients. Rates were applied in	The ICERs were not sensitive to scenarios explored by the company or ERG, including a scenario	This was not discussed by the Committee.	The ERG noted uncertainty regarding the use of the literature data in psoriasis patients; however, it

		the induction and maintenance phases of the model as one-time events, and patients were assumed to be at constant risk of experiencing the adverse event.	in which all treatments were assumed to have the same rate of serious infection as ustekinumab.		was agreed that this was the most appropriate source of data available.
Delayed response	Delayed response was assessed using clinical remission or clinical response without remission.	Patients who did not respond after the initial induction period for vedolizumab, golimumab, ustekinumab, infliximab or tofacitinib remained on treatment for an additional cycle, based on the respective SmPCs, to allow for a delayed response. In the base case, delayed response data were assumed to be the same as early responders as reported in clinical trials.	Scenario analyses in which delayed responder efficacy was derived from individual trials and in which delayed responders were excluded from the analysis both resulted in lower ICERs.	This was not discussed by the Committee.	The ERG noted that maintenance efficacy may differ between initial and delayed responders; however, a paucity of evidence is available to inform this and was acknowledged.

Abbreviations: ERG: Evidence Review Group; EQ-5D: European Quality of Life 5 Dimensions; HSUV: health state utility value; ICER: incremental cost-effectiveness analysis; NICE: National Institute of Health and Care Excellence; NMA: network meta-analysis; SmPC: summary of product characteristics; TA: technology appraisal; UC: ulcerative colitis.
Source: NICE TA633.[6]

B.2.2 Resource use assumptions

Resource use and cost elements included in the ustekinumab evaluation (TA633) that are most relevant to the current evaluation were:[6]

- Drug acquisition costs
- Drug administration costs
- Disease-related costs
    - Costs associated with each health state in the model were considered, including the costs associated with remission, response no remission, and active UC (including consultant visit, endoscopies, care without colectomy, and stoma care)
    - Frequency of resource use was mostly based on Tsai *et al*. (2008)[82], consistent with previous appraisals for moderately severely active UC,[29, 32, 33] and hospitalisation rates for the pre-surgery health states were obtained from Sandborn *et al*. (2016)[83]
- Averse event costs
    - Only costs associated with serious infections were considered due to the high costs associated with their management.

A summary of the healthcare resource use and related cost assumptions from the ustekinumab evaluation are presented below in Table 5.

For this submission, a cost-comparison analysis has been conducted between risankizumab and ustekinumab. The model adopts a ten-year time horizon and incorporates drug acquisition and drug administration costs for risankizumab and ustekinumab only, as these are the only costs assumed to differ substantially between the two treatments over the modelled time horizon. Full details of the methodology and results of the cost-comparison analysis are presented in Section B.3.12.

Table 5: Healthcare resource use and related costs appraised in NICE TA633 (ustekinumab)

Resource use	Company submission	Committee preferred/ alternative assumptions
Drug acquisition costs	• Drug acquisition costs for active treatments were included in the cost-effectiveness analysis. The costs for concomitant therapies were not included in the company base case. • Unit costs were derived from standard sources including the BNF, the Drugs and Pharmaceutical eMIT, MIMS, previous NICE submission and published literature. • Costs were modelled separately during the induction phase and maintenance phase of the treatment cycles.	• The ERG preferred that drug acquisition costs for concomitant therapies were also included in the company base case.
Dose escalation	• A modelling of 30% dose escalation in the maintenance phase for ustekinumab was assumed.	• N/A
Conventional therapy costs	• Patients on active treatment were expected to receive concomitant treatment, which included a basket of azathioprine, 6-mercopturine, methotrexate, 5-aminosalicylate, prednisolone, and budesonide. Upon discontinuation of active treatment, patients were modelled to proceed to conventional therapy. As such, costs of conventional therapy were applied to patients both in the "active treatment" and "post-active treatment" states of the model. • The proportion of patients modelled to be receiving conventional therapy were derived from TA342.[29]	• N/A
Administration costs	• As ustekinumab requires IV administration in the induction setting, it was assumed to incur the cost of an outpatient visit, based on a weighted average of the NHS reference costs for consultant-led non-admitted, face-to-face follow-up appointments and non-consultant led non-admitted, face-to-face follow-up appointments. • Subcutaneous administration of ustekinumab was assumed to have no cost to the NHS, besides the initial cost associated with a nurse training the patient in how to self-administer treatment, due to the possibility of self-administration	• N/A
Health state costs	• Various health states were modelled, including: Active UC, Response without remission, Remission, first surgery, Post-first surgery, Post-first surgery complications, Second surgery and Post-second surgery. • A cost-effectiveness study by Tsai *et al* (2008)[82] represented the accepted source of health care resource use and costs for all non-surgery health states, for which no costs were reported. • It was assumed that the resource use for first and second surgery health states would be equivalent to the active UC health state.	• N/A

Abbreviations: BNF: British National Formulary; eMIT: Electronic Market Information Tool; ERG: Evidence Review Group; IV: intravenous; MIMS: Monthly Index of Medical Specialities; NHS: National Health Service; UC: ulcerative colitis.
Source: NICE TA633.[6]

B.3 Clinical effectiveness

Clinical effectiveness

Study identification

- A systematic literature review (SLR) identified two Phase III randomised controlled trials (RCTs) investigating the efficacy and safety of risankizumab in patients with moderately to severely active UC: INSPIRE (NCT03398148)[84] and COMMAND (NCT03398135).[85] These trials form the pivotal evidence base informing the efficacy and safety of risankizumab in this submission

Induction phase (INSPIRE)

- INSPIRE was an induction trial which evaluated the efficacy and safety of induction treatment with risankizumab IV in patients with moderately to severely active UC. The trial comprised two sub-studies:
    - INSPIRE sub-study 1 was a Phase IIb dose-finding induction study. Results for this sub-study are not presented in this submission as results from the Phase III trial are now available (see INSPIRE sub-study 2 below)
    - INSPIRE sub-study 2 was a Phase III placebo-controlled induction study. Sub-study 2 of INSPIRE is the pivotal induction clinical trial for risankizumab in this indication and results for this sub-study are presented in Section B.3.6.1
- The primary endpoint of INSPIRE sub-study 2 was the achievement of clinical remission per Adapted Mayo score at Week 12. Key secondary endpoints included the achievement of clinical response per Adapted Mayo score, the achievement of endoscopic improvement and the achievement of histologic endoscopic mucosal improvement (all at Week 12)

INSPIRE enrolment into COMMAND

- Both INSPIRE sub-study 1 and sub-study 2 consisted of two induction periods. Patients from either study who achieved clinical response at Week 12 of the initial induction period (Induction Period 1) were eligible to be enrolled into the COMMAND maintenance trial
- Patients who did not achieve clinical response in either sub-study were eligible to receive blinded risankizumab treatment in a second 12-week induction period (Induction Period 2) for that sub-study, which evaluated 12-week reinduction with risankizumab. Patients who achieved clinical response at Week 24 (at the end of Week 12 of Induction Period 2) were also eligible to be enrolled into the COMMAND maintenance trial

Maintenance phase (COMMAND)

- COMMAND was a 52-week maintenance and open-label extension trial which evaluated the efficacy and safety of maintenance treatment with risankizumab in patients with moderately to severely active UC. The trial comprised three sub-studies: sub-study 1, sub-study 2 and sub-study 3
- COMMAND sub-study 1 was a double-blind, placebo-controlled Phase III maintenance study which forms the pivotal maintenance clinical trial for risankizumab in this indication and results for this sub-study are presented in Section B.3.6.2

- Sub-study 2 and sub-study 3 were exploratory and open-label long-term extension trials, respectively. Results for these sub-studies are not currently available and so are not presented in this submission. In addition, these sub-studies do not form part of the primary efficacy analysis and sub-study 3 is still ongoing.
- The primary efficacy population of COMMAND sub-study 1 consisted of patients enrolled from both INSPIRE sub-study 1 and INSPIRE sub-study 2 who achieved clinical response per Adapted Mayo score to 12 weeks of IV risankizumab treatment at either Week 12 (Induction Period 1) or Week 24 (Induction Period 2)
- The primary endpoint of COMMAND sub-study 1 was the proportion of patients with clinical remission per Adapted Mayo score at Week 52. Key secondary endpoints included the proportion of patients with endoscopic improvement, the proportion of patients with histological-endoscopic mucosal improvement and the proportion of patients with endoscopic remission (all at Week 52)

INSPIRE efficacy

- In INSPIRE sub-study 2, induction treatment with risankizumab resulted in statistically significantly greater proportions of patients achieving the primary endpoint and key secondary endpoints versus placebo (Table 6)

Table 6: INSPIRE key efficacy endpoints (sub-study 2)

Key endpoint (Week 12)	Placebo	RZB 1200 mg IV	p-value
Proportion of patients achieving clinical remission[a] (Adapted Mayo score)	6.2%	20.3%	p<0.00001
Proportion of patients achieving clinical response (Adapted Mayo score)	35.7%	64.3%	p<0.00001
Proportion of patients achieving endoscopic improvement	12.1%	36.5%	p<0.00001
Proportion of patients achieving histologic-endoscopic mucosal remission	7.7%	24.5%	p<0.00001

Footnotes: [a] Primary efficacy endpoint.
Abbreviations: RZB: risankizumab.

- Subgroup analyses were conducted in the advanced therapy-IR and non-advanced therapy-IR populations and results in both subgroups were consistent with the overall population. Clinical remission rates in patients treated with risankizumab 1200 mg IV versus placebo at Week 12 were 11.4% versus 4.3%, respectively for advanced therapy-IR patients and 29.7% versus 8.4%, respectively for non-advanced therapy-IR patients

COMMAND efficacy

- In COMMAND sub-study 1, maintenance treatment with risankizumab 180 mg SC and risankizumab 360 mg SC resulted in statistically significantly greater proportions of patients achieving the primary endpoint and a number of key secondary endpoints versus placebo (Table 7)

Table 7: COMMAND key efficacy endpoints (sub-study 1)

Key endpoint (Week 52)	Placebo	RZB 180 mg SC	RZB 360 mg SC	RZB 180 mg SC p-value	RZB 360 mg SC p-value

Proportion of patients achieving clinical remission[a] (Adapted Mayo score)	25.1%	40.2%	37.6%	p=0.0004	p=0.0019
Proportion of patients achieving endoscopic improvement	31.7%	50.8%	48.3%	p<0.0001	p=0.0003
Proportion of patients achieving histologic-endoscopic mucosal improvement	23.5%	42.8%	42.2%	p<0.0001	p<0.0001
Proportion of patients with endoscopic remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Primary efficacy endpoint.
Abbreviations: RZB: risankizumab; SC: subcutaneous.

- Subgroup analyses were conducted in the advanced therapy-IR and non-advanced therapy-IR populations and results in both subgroups were consistent with the overall population. Clinical remission rates for advanced therapy-IR patients were [redacted] and [redacted] for risankizumab 180 mg and 360 mg SC, respectively, compared to [redacted] for placebo. In non-advanced therapy-IR patients, clinical remission rates were [redacted] and [redacted] for risankizumab 180 mg and 360 mg SC, respectively, compared to [redacted] for placebo.

INSPIRE safety

- The safety profile of risankizumab was assessed in both INSPIRE and COMMAND and was consistent with the known tolerable safety profile for risankizumab in other indications
- In INSPIRE sub-study 2, treatment with risankizumab 1200 mg IV was well-tolerated, with a similar overall incidence of treatment-emergent adverse events (TEAEs) in both the risankizumab and placebo arms and a lower incidence of severe (2.5% versus 10.2% respectively) and serious (2.3% versus 10.2% respectively) adverse events (AEs) compared to placebo
- In addition, the incidence of serious infections was lower in the risankizumab 1200 mg IV arm compared to placebo (0.6% versus 1.2%, respectively). No major adverse cardiovascular events (MACE) occurred in either arm. One death was reported in the risankizumab 1200 mg IV arm which was assessed by investigator to be COVID-19 related

COMMAND safety

- In COMMAND sub-study 1, the overall incidence of TEAEs were comparable between the risankizumab 180 mg SC, risankizumab 360 mg SC and placebo arms, with a similar incidence of severe TEAEs observed ([redacted] respectively)
- The incidence of serious infections was lower in the risankizumab 180 mg SC and 360 mg SC arms versus placebo ([redacted] respectively) at Week 52. No MACE events were reported any arm. One death was reported in the risankizumab 360 mg SC arm, which occurred >140 days after the last dose of risankizumab and was considered by the investigator as having no reasonable possibility of relationship to the study drug

Conclusion

- Risankizumab is an effective treatment option in patients with moderately to severely active UC; the pivotal Phase III studies INSPIRE and COMMAND met all primary efficacy

endpoints. INSPIRE also met all secondary endpoints and COMMAND met a number of secondary endpoints

- Risankizumab is also well tolerated, with a favourable safety profile and no new safety concerns identified versus placebo

B.3.1 Identification and selection of relevant studies

An SLR was conducted on June 27th 2023 to identify relevant clinical evidence in the form of RCTs for the efficacy and safety of treatments for moderately to severely active UC. Overall, the SLR identified 404 relevant publications, reporting on 57 unique studies.

Full details of the SLR methodology used to identify the clinical evidence relevant to risankizumab and ustekinumab in this submission, including the search strategy, preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram, list of included studies, and list of excluded studies at full-text review, is provided in Appendix D.

B.3.2 List of relevant clinical effectiveness evidence

The SLR identified two RCTs investigating the efficacy and safety of risankizumab for the treatment of moderately to severely active UC: INSPIRE (NCT03398148; M16-067) and COMMAND (NCT03398135; M16-066).

INSPIRE (induction study)

INSPIRE was an induction trial which evaluated the efficacy and safety of induction treatment with risankizumab in patients with moderately to severely active UC. The trial comprised two sub-studies:

- INSPIRE sub-study 1 was a Phase IIb dose-finding induction study. Results for this sub-study are not presented in this submission as results from the Phase III trial are now available (see INSPIRE sub-study 2 below)
- INSPIRE sub-study 2 was a double-blind, placebo-controlled Phase III induction study. Sub-study 2 of INSPIRE is the pivotal induction clinical trial for risankizumab in this indication and results for this sub-study are presented in Section B.3.6.1

INSPIRE dose-selection analysis

INSPIRE sub-study 1 identified the risankizumab 1200 mg IV dose for evaluation in sub-study 2 following a dose exposure and response analysis for key efficacy and safety variables. During the analysis period, additional patients continued to be enrolled into the sub-study 1 risankizumab 1800 mg IV dosing group, on an open-label basis, to avoid interrupting the study activities during the analysis period and to generate a sufficient number of patients with clinical response to be enrolled into COMMAND. The data collected from these additional patients were not included in the primary analysis but are reported in the INSPIRE clinical study report (CSR).[84]

INSPIRE enrolment into COMMAND

Both INSPIRE sub-study 1 and sub-study 2 consisted of two induction periods. Patients from either study who achieved clinical response at Week 12 of the initial induction period (Induction Period 1) were eligible to be enrolled into the COMMAND maintenance trial. Results from sub-

study 2 Induction Period 1 form the principal evidence base for risankizumab from INSPIRE. Patients who did not achieve clinical response in either sub-study were eligible to receive blinded risankizumab treatment in a second 12-week induction period (Induction Period 2) for that sub-study, which evaluated 12-week reinduction with risankizumab. Patients who achieved clinical response at Week 24 (at the end of Week 12 of Induction Period 2) were also eligible to be enrolled into the COMMAND maintenance trial. Only patients achieving clinical response to 12 weeks of IV risankizumab in INSPIRE sub-study 1 or sub-study 2 (in either Induction Period 1 or Induction Period 2) could be re-randomised to either SC risankizumab or placebo in COMMAND sub-study 1 and were included in the primary efficacy analysis for COMMAND; patients achieving clinical response to SC risankizumab in INSPIRE sub-study 1 or sub-study 2 (Induction Period 2), or patients requiring a total of 24 weeks of risankizumab induction treatment in order to achieve response, were still enrolled in COMMAND, but excluded from the primary efficacy analysis.

Methodology and results for INSPIRE sub-study 2 (Induction Period 1) are presented in detail in this submission. Whilst no results for INSPIRE sub-study 1 are presented in this submission, methodology and baseline characteristics for INSPIRE sub-study 1 are presented in Appendix J for completeness, as some patients with a clinical response to IV risankizumab in either INSPIRE sub-study 1 or sub-study 2 at Week 12 or Week 24 were considered in the primary efficacy analysis for COMMAND.

COMMAND (maintenance study)

COMMAND was a 52-week maintenance and open-label extension trial which evaluated the efficacy and safety of maintenance treatment with risankizumab in patients with UC. The trial comprised three sub-studies: sub-study 1, sub-study 2 and sub-study 3:

- COMMAND sub-study 1 was a double-blind, placebo-controlled Phase III maintenance study which forms the pivotal maintenance clinical trial for risankizumab in this indication and results for this sub-study are presented in Section B.3.6.2
- COMMAND sub-study 2 and sub-study 3 were exploratory and open-label long-term extension trials, respectively. Sub-study 3 is ongoing and will last until approximately 240 weeks of individual follow-up or until the study is discontinued, whichever is earlier. Results for these sub-studies are not presented in this submission

In summary, the principal evidence base for risankizumab in moderately to severely active UC derives from the Phase III 12-week placebo-controlled induction sub-study 2 for INSPIRE (Induction Period 1) and the Phase III 52-week placebo-controlled maintenance sub-study 1 for COMMAND (which comprised IV risankizumab clinical responders from INSPIRE sub-study 1 or sub-study 2 who were re-randomised to maintenance SC risankizumab in COMMAND). The methodology, efficacy and safety results for sub-study 2 of INSPIRE (Induction Period 1) and sub-study 1 of COMMAND are therefore reported in detail in the submission.

An overview of all of the INSPIRE and COMMAND sub-studies is presented in Table 8 and a diagram of the trial design of INSPIRE and COMMAND is presented in Figure 4 below.

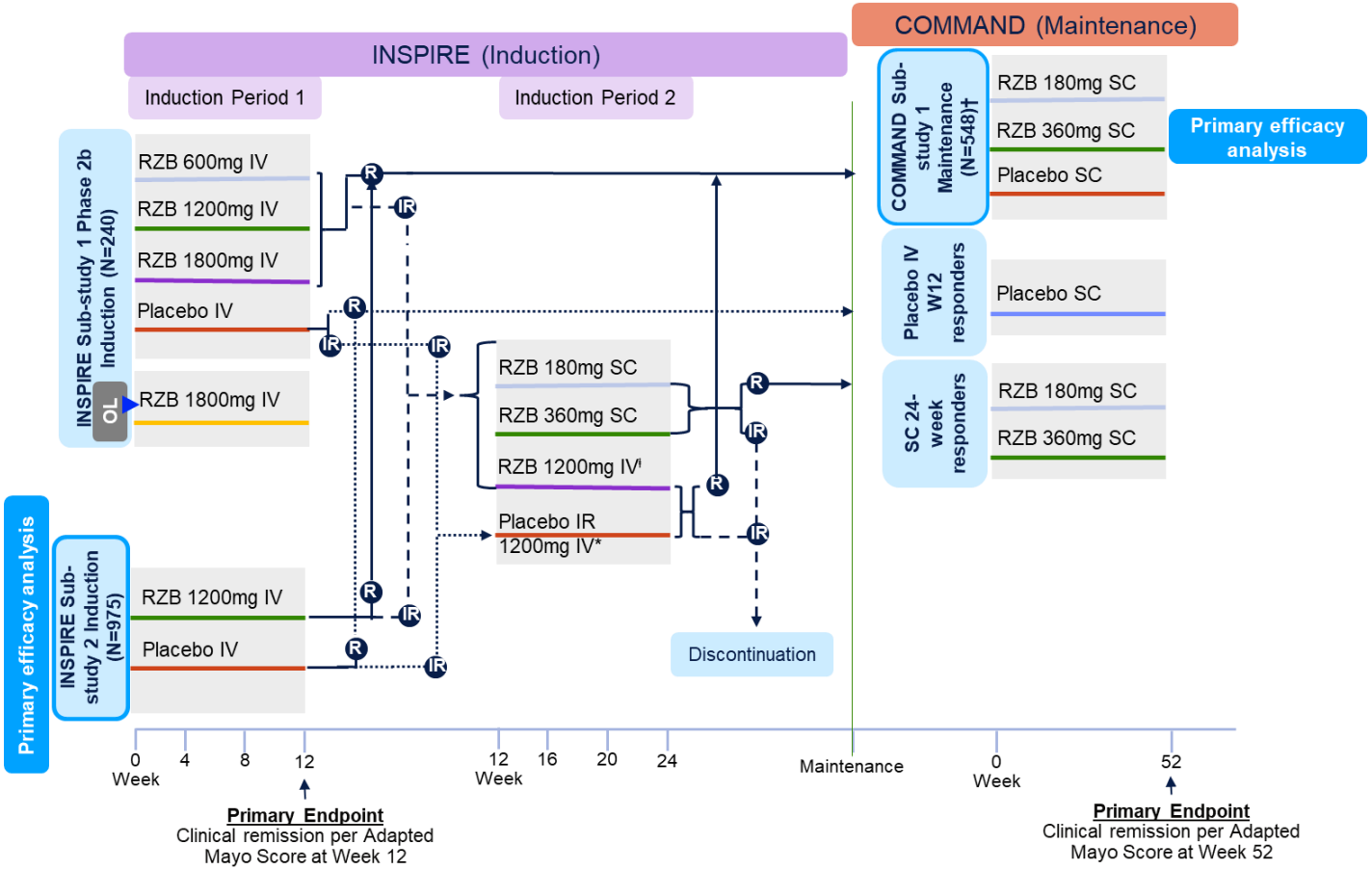
Table 8: INSPIRE and COMMAND sub-study and induction phase overview

INSPIRE (NCT03398148)	Sub-study 1: Phase IIb dose-ranging study consisting of two induction periods • Sub-study 1 Induction Period 1: 12-week placebo-controlled induction study (risankizumab 1800 mg, 1200 mg or 600 mg IV or placebo IV) • Sub-study 1 Induction Period 2: 12-week reinduction for patients who

	did not achieve clinical response in Induction Period 1 (risankizumab 1800 mg IV, 360 mg SC, or 180 mg SC for risankizumab IV non-responders or risankizumab 1800 mg IV for placebo IV non-responders)
	Sub-study 2: Phase III induction study consisting of two induction periods • **Sub-study 2 Induction Period 1:**[a] 12-week placebo-controlled induction study (risankizumab 1200 mg IV or placebo IV) • Sub-study 2 Induction Period 2: 12-week reinduction for patients who did not achieve clinical response in Induction Period 1 (risankizumab 1200 mg, 360 mg or 180 mg IV for risankizumab IV non-responders or risankizumab 1200 mg IV for placebo IV non-responders)
COMMAND (NCT03398135)	**Sub-study 1:**[a] 52-week placebo-controlled maintenance study (risankizumab 180 mg or 360 mg SC or placebo SC) for patients who achieved clinical response to 12 weeks of IV risankizumab in INSPIRE sub-study 1 or sub-study 2 in either Induction Period 1 or Induction Period 2
	Sub-study 2: An exploratory 52-week maintenance study for comparison of two treatment regimens for dose escalation, clinical assessment and therapeutic drug monitoring in patients receiving open label risankizumab 180 mg, initiating after the completion of COMMAND sub-study 1
	Sub-study 3: Open-label extension study (risankizumab 180 mg or 360 mg SC) for patients who completed COMMAND sub-study 1 or sub-study 2

Footnotes: [a] Sub-studies/induction periods **highlighted in bold** form the principal evidence base for risankizumab in moderately to severely active UC and are reported in detail in this submission.
Abbreviations: IV : intravenous; SC: subcutaneous.
Source: AbbVie. Data on File. INSPIRE CSR.[84] AbbVie. Data on File. COMMAND CSR.[85]

Figure 4: INSPIRE and COMMAND trial designs



Footnotes: INSPIRE sub-study 1 was a Phase 2b dose-finding study and evaluated the efficacy, safety and PK of risankizumab as induction treatment to identify the appropriate induction dose of risankizumab for further evaluation in INSPIRE sub-study 2. During analysis of INSPIRE sub-study 1, patients continued to enroll in the highest dosing arm (risankizumab 1800 mg IV Weeks 0, 4, 8) on an open-label basis. Patients receiving open label risankizumab would follow the same path through the trial as the blinded risankizumab 1800 mg IV arm mapped on this diagram. ǂ Risankizumab 1800mg IV Induction Period 2 from INSPIRE sub-study 1 was not included in the primary efficacy maintenance analysis. * Placebo IR patients in Induction Period 2 for INSPIRE sub-study 1 received risankizumab 1800 mg IV. † Patients who achieved clinical response to study drug after induction were to be enrolled until approximately 573 patients who achieved clinical response to IV risankizumab were randomised. A total of 548 patients were randomised in the intent-to-treat population in COMMAND sub-study 1 (ITT1RN_A).
Abbreviations: IR: inadequate response; IV: intravenous; OL: open label; R: response; RZB: risankizumab; SC: subcutaneous.

B.3.2.1 INSPIRE (induction study)

The INSPIRE trial comprised two sub-studies (as presented in Figure 4). As described above, INSPIRE sub-study 2 forms the principal clinical evidence base for induction treatment with risankizumab and the methodology and results of this study are described in more detail in the following sections.

INSPIRE sub-study 2 was a Phase III induction sub-study evaluating the efficacy and safety of induction treatment with risankizumab 1200 mg IV compared to placebo in inducing clinical remission in patients with moderately to severely active UC.

INSPIRE induction periods

INSPIRE sub-study 2 comprised two induction periods. Patients who achieved clinical response at Week 12 of the initial induction period (Induction Period 1) were eligible to be enrolled into the COMMAND maintenance trial. Patients who did not achieve clinical response in Induction Period 1 were eligible to receive blinded risankizumab treatment in a second 12-week induction period (Induction Period 2), which evaluated 12-week reinduction with risankizumab. Patients who achieved clinical response at Week 24 (at the end of Week 12 of Induction Period 2) were also eligible to be enrolled into the COMMAND maintenance trial. However, only patients achieving clinical response to 12 weeks of IV risankizumab in INSPIRE sub-study 1 or sub-study 2 (in either Induction Period 1 or Induction Period 2) could be re-randomised to either SC risankizumab or placebo in COMMAND sub-study 1 and were included in the primary efficacy analysis for COMMAND.

An overview of the INSPIRE sub-study 2 induction periods is presented in Table 9 below. Results are presented within this submission for INSPIRE sub-study 2 Induction Period 1 only, given these form the primary efficacy analysis of the INSPIRE trial and the principal evidence base for risankizumab from INSPIRE. Results for INSPIRE sub-study 2 Induction Period 2 are not presented.

Table 9: INSPIRE sub-study 2 induction periods

Induction Period 1[a]	Once the dose selection analysis in sub-study 1 (Phase IIb) was completed, patients who met all eligibility criteria were enrolled into the double-blind 12-week sub-study 2 (Induction Period 1) and randomised in a 2:1 ratio to one of the following treatment groups: • Group 1: Risankizumab 1200 mg IV Weeks 0, 4, 8 (n=650) • Group 2: Placebo IV Weeks 0, 4, 8 (n=325) Randomisation at baseline was stratified by number of prior failed biologic treatments (0, 1 versus >1), baseline steroid use (yes versus no), and baseline Adapted Mayo score (≤ 7 versus >7). Patients who achieved clinical response after completion of the 12-week Induction Period 1 were enrolled into the maintenance COMMAND study.
Induction Period 2	Patients who did not achieve clinical response after Induction Period 1 were randomised to Induction Period 2, a double-dummy 12-week treatment period (24-weeks total) to evaluate reinduction with risankizumab versus starting maintenance dosing on clinical response status. Induction Period 2 was an exploratory extended induction, as Week 24 was not a primary efficacy analysis timepoint for INSPIRE.

	Patients who received risankizumab 1200 mg IV in Induction Period 1 and did not achieve a clinical response were randomised in a 1:1:1 ratio to the following groups in Induction Period 2: • Group 1: Risankizumab 1200 mg IV Weeks 12, 16, and 20 (n=[redacted]) • Group 2: Risankizumab 360 mg SC Weeks 12 and 20 (n=[redacted]) • Group 3: Risankizumab 180 mg SC Weeks 12 and 20 (n=[redacted]) Patients who received placebo induction treatment in Induction Period 1 and did not achieve a clinical response received: • Group 4: Risankizumab 1200 mg IV Weeks 12, 16, and 20 (n=[redacted])

Footnotes: [a] Principal evidence base for risankizumab from INSPIRE.
Abbreviations: IV: intravenous; SC: subcutaneous.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

An overview of INSPIRE sub-study 2 (Induction Period 1) is presented in Table 10.

Table 10: Clinical effectiveness evidence (INSPIRE sub-study 2 [Induction Period 1])

Study	**INSPIRE (NCT03398148)[a] sub-study 2 (Induction Period 1)**
Study design	Phase III, randomised, double-blind, placebo-controlled trial
Population	Adults (or patients aged 16 to <18 years of age who met the definition of Tanner stage 5 development where locally permitted) with a diagnosis of moderately to severely active UC
Intervention(s)	Risankizumab 1200 mg IV at Weeks 0, 4, 8 (N=650)
Comparator(s)	Placebo IV Weeks 0, 4, 8 (N=325)
Indicate if study supports application for marketing authorisation	Yes
Outcomes specified in the decision problem reported in this submission	• Rate and duration of response, relapse and remission • Corticosteroid-free remission • Rate of endoscopic improvement • Rate of hospitalisation • Rate of surgical intervention • Mortality • Adverse effects of treatment • Health-related quality of life
All other outcomes reported in this submission	• Histologic-endoscopic mucosal improvement • Endoscopic remission • Bowel urgency • Abdominal pain • Histologic endoscopic musical remission • Nocturnal bowel movements • Tenesmus • Faecal incontinence episodes • Sleep interruption

Footnotes: [a] Risankizumab has also been evaluated in one Phase IIb study, INSPIRE sub-study 1, to identify the induction dose of risankizumab for further evaluation. This study does not form part of the principal clinical evidence base for risankizumab in the submission.
Abbreviations: IV: intravenous; UC: ulcerative colitis.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

B.3.2.2 COMMAND (maintenance study)

The COMMAND trial comprised three sub-studies. As described above, COMMAND sub-study 1 forms the principal clinical evidence base for maintenance treatment with risankizumab and the methodology and results of this study are described in more detail in the following sections.

COMMAND sub-study 1 investigated the efficacy and safety of maintenance treatment with risankizumab 180 mg SC or 360 mg SC versus placebo in patients who had completed INSPIRE sub-study 1 or INSPIRE sub-study 2 and had achieved clinical response to IV risankizumab. An overview of COMMAND sub-study 1 is presented in Table 11.

Table 11: Clinical effectiveness evidence (COMMAND sub-study 1)

Study	**COMMAND (NCT03398135) sub-study 1**
Study design	Phase III, randomised, double-blind, placebo-controlled maintenance trial
Population	Adults (or patients aged 16 to <18 years of age who met the definition of Tanner stage 5 development where locally permitted) with a diagnosis of moderately to severely active UC who had completed INSPIRE and achieved clinical response to IV risankizumab in either Induction Period 1 or Induction Period 2 of sub-study 1 or sub-study 2.
Intervention(s)	• Group 1: Risankizumab 180 mg SC Q8W (N=179) • Group 2: Risankizumab 360 mg SC Q8W (N=186)
Comparator(s)	• Placebo SC Q8W (N=183)
Indicate if study supports application for marketing authorisation	Yes
Outcomes specified in the decision problem reported in this submission	• Rate and duration of response, relapse and remission • Corticosteroid-free remission • Rate of endoscopic improvement • Rate of hospitalisation • Rate of surgical intervention • Mortality • Adverse effects of treatment, including nephrotoxicity • Health-related quality of life
All other outcomes reported in this submission	• Histologic-endoscopic mucosal improvement • Endoscopic remission • Bowel urgency • Abdominal pain • Histologic endoscopic musical remission • Nocturnal bowel movements • Tenesmus • Faecal incontinence episodes • Sleep interruption • Corticosteroid use discontinuation • Mucosal healing

Abbreviations: IV: intravenous; Q8W: once every 8 weeks; SC: subcutaneous; UC: ulcerative colitis.
Source: AbbVie. Data on File. COMMAND CSR.[85]

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Summary of trial methodology

INSPIRE (induction study)

A summary of the trial methodology for INSPIRE sub-study 2 (Induction Period 1) is presented in Table 12.

Table 12: Summary of INSPIRE methodology (sub-study 2 [Induction Period 1])

Trial name	INSPIRE; (sub-study 2 Induction Period 1)[a]
Location	Multinational study, with over 430 study locations across North America, Europe, South America, Asia Pacific, and Africa, including 10 UK study sites
Trial design	Phase III, multicentre, randomised, double-blind, placebo-controlled induction study
Eligibility criteria for participants	Key eligibility for the INSPIRE trial are summarised below. The full eligibility criteria can be found in Appendix K. *Inclusion criteria*: • Adults ≥18 and <80 years of age (or where locally permissible, patients 16 to <18 years of age who met the definition of Tanner Stage 5 for development at the baseline Visit, confirmed by central review) • Confirmed diagnosis of UC for at least 3 months prior to baseline • Active UC with an Adapted Mayo score of 5 to 9 points and an endoscopic subscore of 2 to 3 • Demonstrated intolerance[b] or inadequate response to one or more of the following categories of drugs: aminosalicylates[c], oral locally acting steroids[d], systemic steroids (prednisone or equivalent)[e], immunomodulators[e], and/or biologic therapies or tofacitinib[f] *Exclusion criteria:* • Patients with a current diagnosis of Crohn's disease, IBD-unclassified or a history of radiation colitis or ischemic colitis
Intervention and method of study drug administration	Risankizumab 1200 mg IV (N=650) or placebo IV (N=325) at Week 0, 4 and 8
Permitted and disallowed concomitant medication	*Permitted concomitant medications:* • Patients taking oral aminosalicylates, immunomodulators and/or UC-related antibiotics at baseline had to continue these treatments for the duration of the study • Patients taking oral corticosteroids at baseline had to continue their concomitant treatment at the baseline dose for the duration of Induction Period 1 *Prohibited concomitant medications:* • Patients initiating and/or on increasing doses of oral aminosalicylates, immunomodulators and/or UC-related antibiotics after baseline • Patients on decreasing doses of oral aminosalicylates, immunomodulators, immunomodulators and/or UC-related

	antibiotics during the study, except in the event of moderate-to-severe treatment related toxicities (e.g. leukopenia or elevated liver enzymes) • Patients initiating and/or on increasing doses of systemic and/or UC-related corticosteroids after baseline • Patients on decreasing doses of oral corticosteroids during Induction Period 1, except in the event of moderate-to-severe treatment related toxicities
Primary outcome	The achievement of clinical remission per Adapted Mayo score at Week 12
Secondary and exploratory outcomes	**Ranked secondary endpoints** • The achievement of clinical response per Adapted Mayo score at Week 12 • The achievement of endoscopic improvement at Week 12 • The achievement of histologic endoscopic mucosal improvement at Week 12 • The achievement of endoscopic remission at Week 12 • The achievement of clinical response per Partial Adapted Mayo score at Week 4 • The achievement of no bowel urgency at Week 12 • The achievement of no abdominal pain at Week 12 • The achievement of histologic endoscopic mucosal remission at Week 12 • Change from baseline to Week 12 in FACIT-Fatigue • Change from baseline to Week 12 in IBDQ total score • Occurrence of UC-related hospitalisations through Week 12 • The achievement of no nocturnal bowel movements at Week 12 • The achievement of no tenesmus at Week 12 • Change from baseline to Week 12 in number of faecal incontinence episodes per week • Change from baseline to Week 12 number of days per week with sleep interrupted due to UC symptoms **Additional secondary endpoints[g]** • The achievement of SFS = 0, RBS = 0, and endoscopic subscore = 0 at Week 12 • The achievement of SFS ≤ 1 at Week 4, Week 8, Week 12 respectively • The achievement of RBS = 0 at Week 4, Week 8, Week 12 respectively • The achievement of clinical response per Partial Adapted Mayo score at Week 8, Week 12 respectively • Change from baseline to Week 12 in Full Mayo score • Change from baseline in SFS at Week 4, Week 8, Week 12 respectively • Change from baseline in RBS at Week 4, Week 8, Week 12 respectively • Change from baseline in hs-CRP at Week 4, Week 8, Week 12 respectively • Change from baseline in FCP at Week 4, Week 12 respectively • Change from baseline to Week 12 in UCEIS

	• The achievement of histologic remission at Week 12 • Change from baseline to Week 12 in EQ-5D-5L • Change from baseline to Week 12 in WPAI-UC • Change from baseline to Week 12 in UC-SQ • The achievement of IBDQ remission (IBDQ total score ≥ 170) at Week 12 • The achievement of IBDQ response (increase of IBDQ ≥ 16 from baseline) at Week 12 • Time to clinical response per Partial Adapted Mayo • Change from baseline in PGIS at Week 4, Week 8, Week 12 respectively • PGIC at Week 4, Week 8, Week 12 respectively • UC-related surgeries through Week 12 • The achievement of clinical response per Adapted Mayo score at Week 12 in patients with pancolitis at baseline • Change from baseline to Week 12 in SF-36 • The achievement of clinical remission per Full Mayo score at Week 12 in patients with a Full Mayo score of 6 to 12 at baseline
Duration of study and follow-up	12-week induction (Week 0 to Week 12)

Footnotes: [a] Risankizumab has also been evaluated in one Phase IIb study, INSPIRE sub-study 1, to identify the induction dose of risankizumab for further evaluation. This study does not form part of the principal clinical evidence base for risankizumab in the submission.; [b] Demonstration of intolerance requires no minimum dose or duration of use; [c] Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine (2 g/day if controlled release), 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide; [d] Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone OR Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease; [e] Signs and symptoms of persistently active disease, in the opinion of the Investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone ≥ 40 mg/day orally for 3 weeks or intravenously for 1 week OR Inability to taper oral systemic steroids to at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease; [e] Signs and symptoms of persistently active disease, in the opinion of the Investigator, during a current or prior course of at least 90 days of treatment with one or more of AZA, 6-MP, MTX or Tacrolimus; [f] Signs and symptoms of persistently active disease despite a history of infliximab, adalimumab, golimumab, vedolizumab or tofacitinib; [g] Additional secondary endpoints are not reported in the submission but can be found in the INSPIRE CSR.
Abbreviations: AZA: azathioprine; EQ-5D-5L: European Quality of Life 5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; FCP: fecal calprotectin; hs-CRP: high-sensitivity CRP; IBD: irritable bowel disease; IBDQ: Inflammatory Bowel Disease Questionnaire; IV, intravenous; MTX, methotrexate; RBS: rectal bleeding subscore; SFS: stool frequency subscore; SF-36: Short Form-36; UC: ulcerative colitis; UCEIS: Ulcerative Colitis Endoscopic Index of Severity; UC-SQ: UC-Symptom Questionnaire; WPAI-UC: Work Productivity and Impairment Questionnaire – UC; 6-MP: mercaptopurine.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

COMMAND (maintenance study)

The first [redacted] patients who achieved clinical response to IV risankizumab in the INSPIRE Induction Period 1 of sub-study 1 or sub-study 2 were enrolled into COMMAND sub-study 1 and were re-randomised to receive SC risankizumab. These patients make up the ITT1RN_A population, which includes all randomised patients who received at least 1 dose of risankizumab in COMMAND sub-study 1 after receiving risankizumab IV (either 600 mg, 1200 mg or 1800 mg) for only 1 period of 12 weeks in INSPIRE sub-study 1 or sub-study 2. This is the primary analysis set for COMMAND sub-study 1.

A summary of the trial methodology for COMMAND is presented in Table 13.

Table 13: Summary of COMMAND methodology (sub-study 1)

Trial name	COMMAND; (sub-study 1)[a]
Location	Multinational study, with over 424 study locations across North America, Europe, South America, Asia Pacific, and Africa, including 10 UK study sites
Trial design	Phase III, multicentre, randomised, double-blind, placebo-controlled 52-week maintenance and open-label extension study
Eligibility criteria for participants	Patients were enrolled who had completed INSPIRE and had achieved a clinical response to risankizumab IV, defined as a decrease from baseline of induction study of Adapted Mayo score ≥2 points and ≥30%, plus a decrease in RBS≥1 or an absolute RBS≤1
Intervention and method of study drug administration	**Sub-**study 1 (N=548) • Group 1: Risankizumab 180 mg SC Q8W (N=179) • Group 2: Risankizumab 360 mg SC Q8W (N=186) • Group 3: Placebo (N=183)
Permitted and disallowed concomitant medication	*Permitted concomitant medications:* • Patients receiving stable doses of aminosalicylates and/or immunomodulators at Week 0 could maintain their concomitant treatments through the end of the study • Doses of aminosalicylates and/or immunomodulators could be decreased in the event of moderate-to-severe treatment related toxicities (e.g. leukopenia or elevated liver enzymes) • At Week 0, patients taking corticosteroid therapy could have their corticosteroid therapy tapered such that the taper is completed by Week 8 • Patients taking corticosteroids at Week 0 who have a loss of satisfactory clinical response per the Investigator's judgement after the steroid taper has been initiated could have their corticosteroid dose increased up to the dose used at baseline of INSPIRE *Prohibited concomitant medications:* • Increasing doses of or starting aminosalicylates, immunomodulators, and/or UC-related antibiotics • Rectal therapy with aminosalicylates or corticosteroids during the course of the study
Primary outcomes	Proportion of patients with clinical remission per Adapted Mayo score at Week 52
Secondary and exploratory outcomes	**Ranked secondary endpoints** • Proportion of patients with endoscopic improvement at Week 52 • Proportion of patients achieving clinical remission per Full Mayo score at Week 52 in patients with a Full Mayo score of 6 to 12 at induction baseline • Proportion of patients who discontinued corticosteroid use at Week 52 in patients taking steroids at induction baseline • Proportion of patients with clinical remission per Adapted Mayo score at Week 52 in patients with clinical remission at Week 0 • Proportion of patients who discontinued corticosteroid use, remained corticosteroid free for 90 days and achieved clinical remission at Week 52 in patients taking steroids at induction baseline • Proportion of patients with clinical response per Adapted Mayo score at Week 52 • Proportion of patients achieving histologic-endoscopic mucosal

	improvement at Week 52 • Proportion of patients with endoscopic remission at Week 52 • Proportion of patients with endoscopic improvement at Week 52 in patients with endoscopic improvement at Week 0 • Proportion of patients with UC-related hospitalisations through Week 52 • Proportion of patients with histologic remission at Week 52 • Proportion of patients who reported no abdominal pain at Week 52 • Proportion of patients who reported no bowel urgency at Week 52 • Proportion of patients with mucosal healing at Week 52 • Change from baseline (of induction) to Week 52 in IBDQ total score • Proportion of patients with UC-related surgeries through Week 52 • Change from baseline (of induction) to Week 52 in FACIT-Fatigue • Proportion of patients with clinical response per Adapted Mayo score at Week 52 in patients with pancolitis at baseline • Proportion of patients who reported no nocturnal bowel movements at Week 52 • Proportion of patients who reported no tenesmus at Week 52 • Change from baseline (of induction) to Week 52 in number of faecal incontinence episodes per week • Change from baseline (of induction) to Week 52 in number of days over a week with sleep interrupted due to UC symptoms • Change from baseline (of induction) to Week 52 in SF-36 **Additional endpoints[b]** • Proportion of patients with SFS = 0, RBS = 0, and endoscopic subscore = 0 at Week 52 • Proportion of patients with SFS ≤ 1 over time • Proportion of patients with RBS = 0 over time • Change from baseline of Induction in Partial Adapted Mayo score over time • Change from Week 0 to Week 52 in Full Mayo score • Change from Week 0 in SFS over time • Change from Week 0 in RBS over time • Change from Week 0 in hs-CRP over time • Change from Week 0 in FCP over time • Change from baseline to Week 52 in UCEIS • Change from Week 0 in EQ-5D-5L over time • Change from Week 0 in WPAI UC over time • Proportion of patients with IBDQ remission (IBDQ total score ≥ 170) over time • Proportion of patients with IBDQ response (increase of IBDQ ≥ 16 from induction baseline) over time • Change from Week 0 from baseline in UC-SQ over time • Time to loss of clinical response per Partial Adapted Mayo in patients with response per Partial Adapted Mayo at Week 0. • Change in PGIS from Week 0 over time • PGIC over time • Proportion of patients who discontinued corticosteroid use over time in patients taking steroids at baseline (of induction). • Proportion of patients who discontinued corticosteroid use and

	achieved clinical remission over time in patients taking steroids at baseline (of induction). • Proportion of patients who discontinued corticosteroid use for 90 days and achieved clinical remission at Weeks 0 and 52, in patients who were taking steroids at baseline (of induction) • Proportion of patients who discontinued corticosteroid use for 90 days and achieved a SFS ≤ 1 (and not worse than Baseline of induction) and RBS = 0 at Weeks 40 and 48 and clinical remission at Week 52, in patients who were taking steroids at baseline (of induction) • Proportion of patients with clinical remission per Adapted Mayo score summarized by concomitant corticosteroid dose at Week 52 • Proportion of patients with endoscopic remission per Adapted Mayo score summarized by concomitant corticosteroid dose at Week 52
Duration of study and follow-up	52-week maintenance period and a 140-day follow-up period

Footnotes: [a] Risankizumab has also been evaluated in two additional maintenance sub-studies, COMMAND sub-study 2 and sub-study 3. These sub-studies do not form part of the principal clinical evidence base for risankizumab in the submission. [b] Additional secondary endpoints are not reported in this submission but can be found in the COMMAND CSR.
Abbreviations: CA: clinical assessment; EQ-5D-5L: European Quality of Life 5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; FCP: faecal calprotectin; hs-CRP: high-sensitivity C-reactive protein; IBDQ: Inflammatory Bowel Disease Questionnaire; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; Q8W; once every 8 weeks; RBS: rectal bleeding subscore; SC: subcutaneous; SFS: stool frequency sub score; SF-36: Short Form-36; TDM: therapeutic drug monitoring; UCEIS: Ulcerative Colitis Endoscopic Index of Severity; UC: ulcerative colitis; UC-SQ: Ulcerative Colitis Symptoms Questionnaire; WPAI-UC: Work Productivity and Impairment Questionnaire – Ulcerative Colitis
Source: AbbVie. Data on File. COMMAND CSR.[85]

Outcome definitions

Outcomes in INSPIRE and COMMAND were measured using a range of scoring systems, full details of which are presented in Table 14.

Table 14: Endpoint definitions used in INSPIRE and COMMAND

Outcome	Definition
Clinical remission per Adapted Mayo	SFS ≤ 1, and not greater than baseline, RBS = 0, and endoscopic subscore ≤ 1 without the evidence of friability
Clinical response per Adapted Mayo	Decrease from baseline ≥ 2 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
Clinical remission per Partial Adapted Mayo	SFS ≤1 and not greater than baseline, RBS=0
Clinical response per partial Adapted Mayo (without endoscopy)	Decrease from baseline ≥ 1 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
Clinical remission per full Mayo	Full Mayo score ≤ 2 with no subscore > 1
Endoscopic improvement	Endoscopy subscore of 0 or 1 without the evidence of friability
Endoscopic remission	Endoscopic subscore = 0
Histologic remission	Geboes score of < 2.0
Histologic endoscopic mucosal remission (HEMR)	Endoscopy subscore of 0 and Geboes score < 2.0

Histologic endoscopic mucosal improvement (HEMI)	Endoscopic subscore of 0 or 1 without the evidence of friability and Geboes score ≤ 3.1

Abbreviations: RBS: rectal bleeding subscore; SFS: stool frequency subscore.

Note, in INSPIRE and COMMAND, the Adapted Mayo scoring system was primarily used for clinical remission and clinical response. The Adapted Mayo scoring system has also been used in previous trials for patients with moderately to severely active UC (upadacitinib [TA856][32]). A total score of 5 to 9 signifies that a patient has moderately to severely active UC, the indication of relevance for risankizumab in this submission. The partial Adapted Mayo score was used to calculate clinical response in patients in the INSPIRE and COMMAND trials in instances where an endoscopy had not yet been performed (e.g. proportion of subjects achieving clinical response at Week 4) or could not be performed due to COVID-19 pandemic restrictions or geo-political conflict in Ukraine.

Subgroup analyses

Across the INSPIRE and COMMAND trials, several pre-planned subgroup analyses of the primary efficacy outcome (clinical remission per Adapted Mayo score) were conducted to assess any treatment differences according to a range of different factors. These pre-planned subgroup analyses are presented in Table 15.

Table 15: Pre-planned subgroup analyses in INSPIRE and COMMAND

Subgroup factor	Categories
Age	18-40, 40-65 or ≥ 65
Sex	Male or Female
Baseline weight	< 60 kg or ≥ 60 kg
Race	White or non-White
Geographic region	North America, South/Central America, Western Europe, Eastern Europe, Asia, Other
Baseline corticosteroid use	Yes or No
Baseline immunosuppressant use	Yes or No
Baseline Adapted Mayo Score	≤ 7 or > 7
Baseline Partial Adapted Mayo Score	≤ 4 or > 4
Prior exposure to TNF-α inhibitor for UC for non-advanced therapy-IR population	Yes or No
Number of prior failed TNF-α inhibitor for UC for advanced therapy-IR population	0, 1, 2, > 2
Prior exposure to advanced therapy	0, 1, > 1
Number of prior failed advanced therapies	0 (non-advanced therapy -IR population), ≥ 1 (advanced therapy-IR population) (Then analyse 1, 2, > 2 within advanced therapy-IR population)
Presence of pancolitis at baseline	Yes or No
Disease duration at baseline	≤ median or > median
Disease duration at baseline	≤ 3 years or > 3 years
Baseline hsCRP	≤ median or > median

Baseline hsCRP	≤ 5 mg/L or > 5 mg/L
Baseline albumin	≤ median or > median
Baseline calprotectin	≤ median or > median
Baseline calprotectin	≤ 250 mg/kg or > 250 mg/kg

Abbreviations: hs-CRP: high-sensitivity C-reactive protein; TNF: tumour necrosis factor; UC: ulcerative colitis.
Source: AbbVie. Data on File. INSPIRE CSR[84]; AbbVie. Data on File. COMMAND CSR.[85]

B.3.3.2 Baseline characteristics and demographics

INSPIRE

The baseline characteristics and demographics were generally well balanced between the treatment groups in INSPIRE sub-study 2 Induction Period 1 (Table 16). Feedback from UK experts indicated that INSPIRE baseline characteristics could be considered generalisable to UK patients with moderately to severely active UC but highlighted the very refractory nature of the overall patient cohort.

For INSPIRE sub-study 2 (Induction Period 1), the mean age of patients ranged from [redacted] and the proportion of patients with over 3 years of UC disease ranged from [redacted] across both treatment arms. The mean duration of disease ranged from [redacted] years, highlighting the long disease duration within the overall patient cohort.

Disease severity baseline characteristics highlight the severity of the disease in the enrolled patient cohort; the mean Adapted Mayo Score across treatment arms ranged from [redacted] and [redacted] of patients were classed as having severe disease (Adapted Mayo score >7). Moreover, most patients had extensive UC/pancolitis with this proportion ranging from [redacted]. Extensive UC/pancolitis is the most severe form of the disease and is associated with a particularly poor prognosis.

Finally, approximately [redacted] of patients entering INSPIRE sub-study 2 (Induction Period 1) were classed as having prior advanced treatment failure (advanced therapy-IR), defined as documented intolerance or inadequate response to advanced therapy including one or more of the approved biologics for UC (infliximab, adalimumab, golimumab, ustekinumab, and/or vedolizumab), approved JAK inhibitors for UC (tofacitinib, filgotinib, upadacitinib), and/or ozanimod. The proportion of patients who had failed two advanced therapies ranged from [redacted] and the proportion of patients who had failed more than two advanced therapies ranged from [redacted]. This highlights the very refractory nature of the overall patient cohort.

Table 16: Baseline characteristics and demographics; INSPIRE (sub-study 2 [Induction Period 1]; ITT2 population)

Characteristic	PBO IV (N = 325)	RZB 1200 mg IV (N = 650)	Total (N = 975)
Sex – n %			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Ethnicity – n %			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]

Missing	[redacted]	[redacted]	[redacted]
Race – n %			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Age (year)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Age (year) – n %			
18-< 40	[redacted]	[redacted]	[redacted]
40-< 65	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]
Weight (kg)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Body Mass Index(kg/m^2) - n (%)			
Underweight [< 18.5]	[redacted]	[redacted]	[redacted]
Normal [≥ 18.5 and < 25]	[redacted]	[redacted]	[redacted]
Overweight [≥ 25 and < 30]	[redacted]	[redacted]	[redacted]
Obese [≥ 30]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
UC disease duration			
Mean – years (SD)	[redacted]	[redacted]	[redacted]
≤ 3 years – n (%)	[redacted]	[redacted]	[redacted]
> 3 years – n (%)	[redacted]	[redacted]	[redacted]
Disease extent- n (%)			
Left sided UC	[redacted]	[redacted]	[redacted]
Extensive UC/pancolitis	[redacted]	[redacted]	[redacted]
Limited to rectum	[redacted]	[redacted]	[redacted]
Number of prior failed advanced therapies – n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
>2	[redacted]	[redacted]	[redacted]
Advanced therapy – IR Status – n (%)			

Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Baseline corticosteroid use - Yes, n (%)	[redacted]	[redacted]	[redacted]
Baseline immunosuppressant use - Yes, n (%)	[redacted]	[redacted]	[redacted]
Baseline aminosalicylates use - Yes, n (%)	[redacted]	[redacted]	[redacted]
Adapted Mayo Score – n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
≤7 (%)	[redacted]	[redacted]	[redacted]
>7 (%)	[redacted]	[redacted]	[redacted]
Partial Adapted Mayo Score - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
hsCRP (mg/L) – n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Fecal calprotectin (mg/kg) - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Endoscopy subscore – n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IBDQ score – total – n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
FACIT-Fatigue Total Score - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Footnotes: ITT2 includes all randomised patients who received at least one dose of study drug during Induction Period 1 from sub-study 2.
Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy; hsCRP: high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IR: inadequate response; IV: intravenous; PBO, placebo; RZB: risankizumab; SD: standard deviation.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

COMMAND

The baseline characteristics and demographics were generally well balanced between treatment groups in COMMAND sub-study 1 (Table 17). Feedback from UK experts indicated that COMMAND baseline characteristics could be considered generalisable to UK patients with moderately to severely active UC.

For COMMAND sub-study 1, the mean age of patients ranged from [redacted] and the proportion

of patients with over 3 years of UC disease ranged from [redacted], across treatment arms. The mean duration of disease ranged from [redacted] years.

Disease severity baseline characteristics highlight the severity of the disease in the enrolled patient cohort; the mean Adapted Mayo Score across treatment arms ranged from [redacted] and [redacted] of patients were classed as having severe disease (Adapted Mayo score >7). Moreover, similar to INSPIRE, most patients had extensive UC/pancolitis (the most severe form of UC) with the proportion of patients ranging from [redacted]. Extensive UC/pancolitis is the most severe form of the disease and is associated with a particularly poor prognosis.

Finally, approximately [redacted] of patients entering COMMAND sub-study 1 were classed as having prior advanced treatment failure (advanced therapy-IR), defined as documented intolerance or inadequate response to advanced therapy including one or more of the approved biologics for UC (infliximab, adalimumab, golimumab, ustekinumab, and/or vedolizumab), approved JAK inhibitors for UC (tofacitinib, filgotinib, upadacitinib), and/or ozanimod. The proportion of patients who had failed two advanced therapies ranged from [redacted] and the proportion of patients who had failed on more than two advanced therapies ranged from [redacted]. As for INSPIRE, this highlights the very refractory nature of the overall patient cohort.

Table 17: Baseline and demographic characteristics; COMMAND (sub-study 1; ITT1RN_A population)

Characteristic	PBO (N = 183)	Risankizumab 180 mg IV (N = 179)	RZB 360 mg IV (N=186)
Sex – n %			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Race – n %			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Age (year)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Age (year) – n %			
18-< 40	[redacted]	[redacted]	[redacted]
40-< 65	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]

Weight (kg)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Body Mass Index(kg/m^2) - n (%)			
Underweight [< 18.5]	[redacted]	[redacted]	[redacted]
Normal [≥ 18.5 and < 25]	[redacted]	[redacted]	[redacted]
Overweight [≥ 25 and < 30]	[redacted]	[redacted]	[redacted]
Obese [≥ 30]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Ulcerative colitis (UC) disease duration			
Mean – years (SD)	[redacted]	[redacted]	[redacted]
≤ 3 years – n (%)	[redacted]	[redacted]	[redacted]
> 3 years– n (%)	[redacted]	[redacted]	[redacted]
Disease extent- n (%)			
Left sided UC	[redacted]	[redacted]	[redacted]
Extensive UC/pancolitis	[redacted]	[redacted]	[redacted]
Limited to rectum	[redacted]	[redacted]	[redacted]
Number of prior failed advanced therapies – n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
>2	[redacted]	[redacted]	[redacted]
Advanced therapy – IR status – n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Baseline corticosteroid use - Yes, n (%)	[redacted]	[redacted]	[redacted]
Baseline immunosuppressant use - Yes, n (%)	[redacted]	[redacted]	[redacted]
Baseline aminosalicylates use - Yes, n (%)	[redacted]	[redacted]	[redacted]
Adapted Mayo Score - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
≤7 (%)	[redacted]	[redacted]	[redacted]
>7 (%)	[redacted]	[redacted]	[redacted]
Partial Adapted Mayo Score - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
hsCRP (mg/L) - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

Median	[redacted]	[redacted]	[redacted]
Faecal calprotectin (mg/kg) - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Endoscopy subscore - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IBDQ score – total - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
FACIT-Fatigue Total Score - n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Footnotes: ITT1RN_A includes all randomised patients who received at least one dose of study drug in sub-study 1 after receiving IV risankizumab induction dose of 600 mg, 1200 mg or 1800 mg for only one period of 12 weeks in INSPIRE.
Abbreviations: hsCRP: high-sensitivity C-reactive protein; IR: inadequate response; IV: intravenous; RZB: risankizumab; SD: standard deviation
Source: AbbVie. Data on File. COMMAND CSR.[85]

B.3.4 Statistical analysis and definition of study groups

B.3.4.1 Analysis sets in INSPIRE and COMMAND

The data sets analysed in INSPIRE and COMMAND, including the number of patients in each analysis set, are presented in Table 18 and Table 19, respectively.

Table 18: Analysis sets used in the analysis of outcomes in INSPIRE (sub-study 2)

Analysis set	Description
Intention-to-treat (ITT) population	**Induction Period 1** • **ITT2:** All randomised patients who received at least one dose of study drug during Induction Period 1 (risankizumab [n=650] or placebo [n=325]). **This is the principal efficacy analysis set presented in this submission for INSPIRE**
Safety population	**Induction Period 1** **SA2:** All patients who received at least one dose of study drug during Induction Period 1 (risankizumab [n=[redacted]] or placebo [n=[redacted]]). **This is the principal safety analysis set presented in this submission for INSPIRE**

Abbreviations: ITT: intention-to-treat; SA: safety analysis.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

Table 19: Analysis sets used in the analysis of outcomes in COMMAND (sub-study 1)

Analysis set	Description
Intention-to-treat (ITT) population	• **ITT1RN_A**: All randomised patients who received at least one dose of study drug in sub-study 1 after receiving IV risankizumab (either 600 mg, 1200 mg or 1800 mg) for only one period of 12 weeks in INSPIRE. **This is the principal efficacy analysis set presented in this submission for COMMAND**

	• ITT1NRN: All non-randomised patients who received at least one dose of study drug in COMMAND sub-study 1 after receiving risankizumab 180 mg or 360 mg SC during Induction Period 2 in INSPIRE or placebo during Induction Period 1 in INSPIRE. This analysis population was used for supplementary efficacy analysis reported in Appendix E (risankizumab [n=[redacted]] or placebo [n=[redacted]])
Safety population	• **SA1RN:** All randomised patients who received at least one dose of study drug in sub-study 1 (risankizumab [n=[redacted]] or placebo [n=[redacted]]) **This is the principal safety analysis set presented in this submission for COMMAND**

Abbreviations: ITT: intention-to-treat; ITT1RN_A: Intend-to-Treat Population in sub-study 1 for randomised patients, the primary analysis population [A]; ITT1NRN: Intend-to-Treat Population in sub-study 1 for non-randomised patients; IV: intravenous; SC: subcutaneous.
Source: AbbVie. Data on File. COMMAND CSR.[85]

B.3.4.2 Statistical methods for the primary analysis of INSPIRE and COMMAND

A summary of the statistical methods for the primary analyses of INSPIRE (sub-study 2) and COMMAND (sub-study 1) are provided in Table 20 and Table 21, respectively.

Table 20: Statistical methods for the primary analysis of INSPIRE (sub-study 2)

	INSPIRE
Hypothesis	The primary hypothesis was that the proportion of patients achieving clinical remission per Adapted Mayo score treated with risankizumab is greater than those treated with placebo at Week 12
Statistical Analysis	• All analyses for the primary and secondary efficacy endpoints were based on an ITT approach • In order to control the family-wise type I error rate at a significance alpha level of 0.05 (2-sided) a graphical multiple testing procedure was used to test the primary and secondary endpoints in the order as specified in Table 12 • The primary endpoint was tested at the pre-specified significant alpha level of 0.05 (2-sides) • The secondary efficacy endpoints are divided into two groups. The first group includes the first ten secondary endpoints. The second group includes all the remaining secondary endpoints which were be tested using the Holm procedure • If the primary endpoint achieved statistical significance, continued testing followed a pre-specified weight of α allocation **Primary endpoint: Induction Period 1** • The primary analysis compared the patients in risankizumab 1200 mg IV group and placebo group based on the ITT2 • The difference between the treatment groups in the primary efficacy endpoint was assessed using Cochran-Mantel-Haenszel (CMH) test stratified by advanced therapy-IR status (yes vs no), baseline steroid use (yes vs no), and baseline Adapted Mayo score (≤ 7 vs > 7) with two-sided alpha of 0.05. A two-sided 95% confidence interval for the difference between treatment groups was constructed **Secondary endpoints: Induction Period 1** • Categorical secondary efficacy endpoints were analysed using the same CMH test as that for primary endpoint
Sample size, power calculation	A total minimum sample of 966 patients (actual number N=975) allocated to risankizumab 1200 mg IV dose or placebo in a randomisation ratio of 2:1 was determined to provide adequate powers for the primary endpoint and select ranked secondary endpoints and adequate responders to meet the sample size requirement. An assumed clinical remission rate of 6% in the placebo arm and 16% of the risankizumab treatment arm at Week 12 with a planned sample size of 644:322 patients per arm provides at least 90% power to detect the 10% treatment difference in the primary endpoint using two sided Miettinen and Nurminen test at a 0.05 significant level.
Data management, patient withdrawals	**Handling of missing data** Missing data were imputed using one or more of the following methods. • Non-Responder Imputation (NRI): Patients who prematurely discontinued the study prior to efficacy assessment or with

	missing values at Week 12 or Week 24 in Induction Period 2 were considered non-responders for the categorical efficacy endpoints • Non-Responder Imputation while incorporating Multiple Imputation (NRI-MI) to handle missing data due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions (NRI-MI): Patients who did not have an evaluation at a scheduled assessment visit (either due to missing assessment or due to early withdrawal from the study) were considered as non-responders for the visit. The only exception is that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic or due to geo-political conflict in Ukraine and surrounding impacted regions were handled by MI • Observed Cases (OC): No impute values for missing evaluations, and thus a patient who did not have an evaluation on a scheduled visit was excluded from the OC analysis for that visit • Multiple Imputation Incorporating Return-to-Baseline (RTB-MI) to handle missing data in the analysis of continuous endpoints: to handle the potential departures from the missing-at-random (MAR) assumption for visits after intercurrent events, the Return-to-Baseline (RTB) approach, which assumes patients with intercurrent events had a washout "return to baseline" of any potential treatment effect, was performed • As Observed (AO): The AO analysis did not impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit was excluded from the AO analysis for that visit. AO included all values collected in the study regardless of intercurrent events • Tipping Point analysis was performed as sensitivity analysis for the primary endpoint in Sub-Study 2 to handle the potential departures from the missing-at-random (MAR) assumption

Abbreviations: AO: As Observed; CMH: Cochran-Mantel-Haenszel; IR: inadequate response; ITT: intention-to-treat; IV: intravenous; MAR: missing-at-random NRI: Non-Responder Imputation while incorporating Multiple Imputation; OC: Observed Cases; RBT: Return-to-Baseline.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

Table 21: Statistical methods for the primary analysis of COMMAND (sub-study 1)

	COMMAND
Hypothesis	The primary hypothesis was that the proportion of patients achieving clinical remission per Adapted Mayo score treated with risankizumab is greater than those treated with placebo at Week 52
Statistical Analysis	• In order to control the family-wise type I error rate at a significance level of 0.05 (2-sided), a graphical multiple testing procedure was used to test the primary and secondary endpoints for each risankizumab dose group in the order specified in Table 13. The secondary efficacy endpoints were divided into two groups. The first group included the first twelve secondary endpoints and the second group included all other five secondary endpoints which were tested using the Holm procedure. Specifically, the testing began with testing the primary endpoint at the pre-specified significant level of 0.025 (2-sided) for each risankizumab dose group compared to placebo. If the primary endpoint achieved statistical significance, continued testing followed a pre-specified weight of α allocation • All efficacy analyses were conducted based on the ITT1RN_A population • When all patients in sub-study 1 complete their Week 52/prematurely discontinued (PD)visit, the database was locked and

	analysis was performed for sub-study 1. This was the only and final analysis for sub-study 1 • Unless otherwise specified, categorical variables were analysed using Cochran-Mantel-Haenszel (CMH) test stratified by induction baseline bio/JAK-IR status (bio/JAK-IR vs non-bio/JAK-IR), clinical remission status per Adapted Mayo score at Week 0 (per central read) and last risankizumab IV induction dose (600 mg vs 1200 mg vs 1800 mg) • Continuous variables collected longitudinally (more than one post-baseline visits) were analysed using a Mixed-Effect Model Repeat Measurement (MMRM) method. Continuous variables collected at only one post-baseline visit were analysed using an Analysis of Covariance (ANCOVA) model
Sample size, power calculation	**Sub-study 1** Assuming clinical remission rate of 22% in the placebo arm and 42% in one of the risankizumab treatment arms at Week 52, a planned sample size of 191 patients in placebo and 191 patients in each of the risankizumab groups was planned have more than 90% power to detect the 20% treatment difference in the primary endpoint between a risankizumab dose and placebo using two sided Miettinen and Nurminen test at a 0.025 significant level with multiplicity adjustment
Data management, patient withdrawals	• Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 (NRI-C): Patients who did not have an evaluation at a scheduled assessment visit (either due to missing assessment or due to early withdrawal from the study) were considered as non-responders for the visit. The only exception is that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic were handled by MI • Observed Cases (OC): No impute values for missing evaluations, and thus a patient who did not have an evaluation on a scheduled visit was excluded from the OC analysis for that visit

Abbreviations: ANCOVA: Analysis of Covariance; CMH: Cochran-Mantel-Haenszel; IR: inadequate response; ITT1RN_A: Intend-to-Treat Population in sub-study 1 for randomised patients, the primary analysis population [A]; JAK: Janus kinase; MI: Multiple Imputation; MMRM: Mixed-Effect Model Repeat Measurement; OC: Observed Cases; PD, prematurely discontinued.
Source: AbbVie. Data on File. COMMAND CSR.[85]

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

The primary evidence base for the efficacy and safety of risankizumab in patients with moderately to severely active UC comprises the INSPIRE induction trial (sub-study 2) and the COMMAND maintenance trial (sub-study 1).

INSPIRE sub-study 2 and COMMAND sub-study 1 were large, randomised, double-blind, placebo-controlled Phase III studies. The study protocols and amendments were approved by an independent ethics committee or institutional review board, and the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practise. Randomisation to study drugs was achieved via a web-based interactive response technology (IRT), and an Independent Data Monitoring Committee was established to monitor data on an ongoing basis to ensure the continuing safety of the study patients.

A summary of the quality assessments conducted based on the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs assessment is provided in Table 22. Overall, both trials are considered to be robust and of high quality.

Full details of the quality assessment for each trial are provided in Appendix D.

Table 22: Quality assessments of INSPIRE (sub-study 2) and COMMAND (sub-study 1)

Trial	INSPIRE (sub-study 2)	COMMAND (sub-study 1)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

B.3.6 Clinical effectiveness results of the relevant studies

Clinical efficacy results summary

- The efficacy of risankizumab has been demonstrated versus placebo in the pivotal induction study (INSPIRE) and the pivotal maintenance study (COMMAND). In both INSPIRE sub-study 2 and COMMAND sub-study 1 the primary endpoints were met. All ranked secondary endpoints were met for INSPIRE and a number of key secondary endpoints were met for COMMAND.

Key results from INSPIRE

- In INSPIRE sub-study 2, induction treatment with risankizumab 1200 mg IV was associated with statistically significant and clinically meaningful differences compared to placebo for the primary endpoint (clinical remission per Adapted Mayo score at Week 12) and all secondary endpoints
- Clinical remission rates were also greater in both advanced therapy-IR patients (11.4% versus 4.3% respectively) and non-advanced therapy-IR patients (29.7% versus 8.4% respectively) treated with risankizumab versus placebo at Week 1

Key results from COMMAND

- In COMMAND sub-study 1, maintenance treatment with risankizumab 180 mg SC or risankizumab 360 mg SC resulted in a statistically significantly greater proportion of patients achieving the primary endpoint and a number of key secondary endpoints versus placebo
- Clinical remission rates were also greater in advanced therapy-IR patients treated with risankizumab 180 mg versus placebo ([redacted] respectively) and for patients treated with risankizumab 360 mg versus placebo ([redacted] respectively) at Week 52

B.3.6.1 INSPIRE

In INSPIRE sub-study 2, the primary endpoint (clinical remission per Adapted Mayo score at Week 12) and all ranked secondary endpoints were met for risankizumab 1200 mg IV when compared with placebo in the ITT2 population. The primary endpoints and ranked secondary endpoints are presented in Table 23 and Table 24, respectively.

Primary efficacy outcome: Clinical remission per Adapted Mayo score at Week 12

In INSPIRE sub-study 2 at Week 12, a statistically significantly greater (p<0.00001) proportion of patients in the risankizumab 1200 mg IV arm achieved the primary endpoint of clinical remission per Adapted Mayo score compared to the placebo arm (Table 23).

Table 23: Proportion of patients achieving clinical remission per Adapted Mayo score at Week 12; INSPIRE sub-study 2, ITT2, NRI-MI

Treatment	N	Missing due to COVID/GP	Responder		Response rate difference compared to placebo		
			n (%)	[95% CI][a]	Adjusted difference[b]	[95% CI][b]	P value[c]
Placebo	325	1	20 (6.2)	[3.6, 8.9]	14.0	[10.0, 18.0]	<0.00001[S]
Risankizumab 1200 mg IV	650	1	132 (20.3)	[17.2, 23.4]			

Footnotes: [a] 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure; [b] Adjusted risk difference and 95% CI for adjusted difference are calculated based on Mante-Haenszel common rate difference; c Analysis based on Cochran-Mantel-Haenszel (CMH) test stratified by advanced therapy-IR status (yes versus no), baseline steroid use (yes versus no) and baseline Adapted Mayo score (≤7, >7) [S] Achieved statistical significance at the 2-sided α level of 0.05 under overall Type I error rate control; NRI-MI: Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data

due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area.
Abbreviations: CMH: Cochran-Mantel-Haenszel; CI: confidence interval; GP: geopolitical conflict; NRI-MI: Non-Responder Imputation while incorporating Multiple Imputation.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

Secondary outcomes

The superiority of risankizumab 1200 mg IV arm compared to placebo was demonstrated across all secondary endpoints of INSPIRE sub-study 2, evaluating several types of improvement: symptomatic, endoscopic, endoscopic-histologic, and patient-reported quality of life outcomes (Table 24). Differences in response were observed as early as Week 4.

Patients receiving risankizumab 1200 mg IV achieved clinically meaningful and statistically significant improvements in all endoscopic outcomes compared to placebo: 36.5% versus 12.1%, respectively for endoscopic improvement, 24.5% versus 7.7%, respectively for histological-endoscopic mucosal improvement, 10.6% versus 3.4%, respectively for endoscopic remission and 6.3% versus 0.6%, respectively for histologic-endoscopic mucosal remission.

Multiple other clinical meaningful outcomes were [redacted] for patients receiving risankizumab 1200 mg IV compared to placebo. Occurrence of UC-related hospitalisations was [redacted] for risankizumab 1200 mg IV compared to [redacted] for placebo. Clinical response was 64.3% versus 35.7%, respectively, for risankizumab 1200 mg IV and placebo and the incidence of no abdominal pain, which has been reported to have one of the greatest impacts on patient HRQoL,[61] was [redacted] versus [redacted], respectively.

Table 24: Summary of secondary endpoints; INSPIRE sub-study 2, ITT2, NRI/RBT-MI

Endpoint	N	Within group	Difference between risankizumab and placebo	P value
		Point estimate [95% CI]		
Clinical response per Adapted Mayo Score at Week 12 (NRI-MI) (%)				
Placebo	325	35.7 [30.5, 40.9]	28.6 [22.3, 34.8]	< 0.00001[S]
Risankizumab 1200 mg IV	650	64.3 [60.6, 67.9]		
Endoscopic improvement at Week 12 (NRI-MI) (%)				
Placebo	325	12.1 [8.5, 15.6]	24.3 [19.3, 29.4]	< 0.00001[S]
Risankizumab 1200 mg IV	650	36.5 [32.8, 40.2]		
Histological-endoscopic mucosal improvement at Week 12 (NRI-MI) (%)				
Placebo	325	7.7 [4.8, 10.6]	16.6 [12.3, 21.0]	< 0.00001[S]
Risankizumab 1200 mg IV	650	24.5 [21.2, 27.8]		
Endoscopic remission at Week 12 (NRI-MI) (%)				
Placebo	325	3.4 [redacted]	7.2 [4.2, 10.2]	[redacted]
Risankizumab 1200 mg IV	650	10.6 [redacted]		
Clinical response per Partial Adapted Mayo Score at Week 4 (NRI-MI) (%)				
Placebo	325	30.5 [redacted]	[redacted]	[redacted]

Risankizumab 1200 mg IV	650	52.2 [redacted]		
No bowel urgency at Week 12 (NRI-MI) (%)				
Placebo	325	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	650	[redacted]		
No abdominal pain at Week 12 (NRI-MI) (%)				
Placebo	325	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	650	[redacted]		
Histologic endoscopic mucosal remission at Week 12 (NRI-MI) (%)				
Placebo	325	0.6 [redacted]	5.6 [3.5, 7.7]	[redacted]
Risankizumab 1200 mg IV	650	6.3 [redacted]		
Change from Baseline to Week 12 FACIT-Fatigue (RTB-MI) (LS mean)				
Placebo	308	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	614	[redacted]		
Change from Baseline to Week 12 IBDQ total score (RTB-MI) (LS mean)				
Placebo	310	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	619	[redacted]		
Occurrence of UC-related hospitalisations through Week 12 (AO) (%)				
Placebo	325	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	650	[redacted]		
No nocturnal bowel movements at Week 12 (NRI-MI) (%)				
Placebo	325	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	650	[redacted]		
No tenesmus at Week 12 (NRI-MI) (%)				
Placebo	325	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	650	[redacted]		
Change from Baseline in number of faecal incontinence episodes per week at Week 12 (RTB-MI) (LS mean)				
Placebo	288	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	602	[redacted]		
Change from Baseline in number of days per week with sleep interrupted due to UC symptoms at Week 12 (RTB-MI) (LS mean)				
Placebo	288	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	602	[redacted]		

Footnotes: [S] Achieved statistical significance at the 2-sided α level of 0.05 under overall Type I error rate control;

NRI-MI used to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area; Categorical endpoints (except occurrence of UC-related hospitalisation) were analysed based on CMH test. Point estimate and 95% CI are the synthetic results based on Student's t-distribution from PROC MIANALYZE procedure; For continuous endpoints, the LS mean and 95% CI are the synthetic results based on ANCOVA/MMRM from PROC MIANALYZE.
Abbreviations: AO: As Observed; CI: confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ: Inflammatory Bowel Disease Questionnaire; IV: intravenous; LS: least squares; NRI-MI: Non-Responder Imputation while incorporating Multiple Imputation; RBT-MI: Multiple Imputation Incorporating Return-to-Baseline.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

B.3.6.2 COMMAND

In COMMAND sub-study 1, the primary endpoint (clinical remission per Adapted Mayo score at Week 52) a number of key secondary endpoints were met for risankizumab 180 mg SC and risankizumab 360 mg when compared with placebo.

Primary efficacy outcome: Clinical remission per Adapted Mayo score at Week 52

In COMMAND sub-study 1 at Week 52, a statistically significantly greater proportion of patients in the risankizumab 180 mg SC (p=0.0004) and risankizumab 360 mg SC (p=0.0019) arms achieved the primary endpoint of clinical remission per Adapted Mayo score compared to the placebo arm (Table 25).

Table 25: Proportion of patients achieving clinical remission per Adapted Mayo score at Week 52, COMMAND sub-study 1, ITT1RN_A

Treatment	N	Missing due to COVID/GP	Responder		Response rate difference compared to placebo		
			n (%)	[95% CI][a]	Adjusted difference[b]	[95% CI][b]	P value[b]
Placebo	183	[redacted]	[redacted] (25.1)	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg SC	179	[redacted]	[redacted] (40.2)	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	186	[redacted]	[redacted] (37.6)	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure. [b] Adjusted risk difference and 95% CI for adjusted difference are calculated based on Mantel-Haenszel common rate difference. P-value is calculated according to the Cochran-Mantel-Haenszel (CMH) test adjusted for strata (induction baseline advanced therapy-IR status [yes versus no], clinical remission status per adapted Mayo score at Week 0 [per central read; yes versus no] and last IV risankizumab induction dose [600 mg versus 1200 mg versus 1800 mg]. [S] Achieved statistical significance at the 2-sided α level of 0.05 under overall Type 1 error rate control.
Abbreviations: CI, confidence interval; GP, geopolitical conflict; SC, subcutaneous.
Source: AbbVie. Data on File. COMMAND CSR.[85]

Secondary outcomes

A number of secondary endpoints for the risankizumab 180 mg and 360 mg SC arms were met and showed statistical significance for endoscopic improvement, histologic-endoscopic improvement, endoscopic remission and corticosteroid-free remission compared to placebo in COMMAND sub-study 1 (Table 26). Feedback from UK clinical experts noted that endoscopic outcomes are a positive predictor of long-term outcomes for patients. As highlighted in Section B.1.3.3, current guidance by the British Society of Gastroenterologists (BSG) recognises the importance of endoscopic outcomes such as mucosal healing in addition to controlling clinical

symptoms.[27] Mucosal healing typically refers to the absence of macroscopic mucosal inflammation of ulceration, which can be captured by endoscopic outcomes such as endoscopic improvement +/- histologic remission.[27] Inducing mucosal healing is associated with reduced relapses, reduced colectomy rates, improved patients' HRQoL and the achievement of long-term corticosteroid-free remission.[23, 69] In addition, steroid-free remission is a clinically meaningful outcome for patients and clinicians due to the burden of steroid usage;[74] steroid sparing results are therefore particularly meaningful for UK clinical practice.

Multiple other [redacted] in outcomes were observed for patients receiving risankizumab 180 mg or 360 mg SC compared to placebo. Occurrence of UC-related hospitalisations was [redacted] and [redacted] for risankizumab 180mg and 360 mg SC, respectively, compared with [redacted] for placebo. Clinical response was [redacted] and [redacted] for risankizumab 180 mg and 360 mg SC, respectively, compared with [redacted] for placebo, with [redacted]. In addition, the proportion of patients with no abdominal pain, which has been reported to have one of the greatest impacts on patient HRQoL,[61] was [redacted] and [redacted] for risankizumab 180 mg and 360 mg SC, respectively, compared to [redacted] for placebo. The 180 mg dose [redacted] for this endpoint.

Long elimination half-life of risankizumab

As patients re-randomised to receive placebo in sub-study 1 of COMMAND had previously achieved clinical response to IV risankizumab in INSPIRE sub-study 1 or sub-study 2, the COMMAND placebo group may have continued to respond to residual risankizumab. Consequently, the benefit of risankizumab maintenance therapy over placebo may appear lower.

Risankizumab serum concentrations at planned visits for COMMAND sub-study 1 are presented in Appendix J.2, which show that placebo patients had measurable serum exposures to risankizumab, particularly at Week 16, indicating a prolonged drug washout from the previous IV induction treatment due to the long elimination half-life of risankizumab. The long elimination half-life of risankizumab (approximately 28 days)[10] is as a result of the engineered nature of risankizumab to enable the drug to persist within the body and support continued efficacy.[86]

Suppression of inflammatory markers (high sensitivity C-reactive protein [hs-CRP] and faecal calprotectin [FCP]) from Week 0 also remained in the placebo group, as shown by the results presented in Appendix J. Together, these data suggest that the long elimination half-life of risankizumab contributed to higher response rates for the placebo group for key endpoints in COMMAND sub-study 1, therefore reducing the relative efficacy for risankizumab versus placebo in the maintenance phase. The long elimination half-life of risankizumab is a known phenomenon and has been highlighted in the submission for previous treated moderately to severely active Crohn's disease (TA888).[4]

Table 26: Summary of secondary endpoints at Week 52; COMMAND sub-study 1, ITT1RN_A

Endpoint [a]	N	Within group	Difference between risankizumab and placebo[b]	P value[c]
		Point estimate [95% CI]		
Endoscopic improvement at Week 52 (%)				

Placebo	183	31.7 [redacted]	-	-
Risankizumab 180 mg SC	179	50.8 [redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	186	48.3 [redacted]	[redacted]	[redacted]
Histologic-endoscopic mucosal improvement at Week 52 (%)				
Placebo	183	23.5 [redacted]	-	-
Risankizumab 180 mg SC	179	42.8 [redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	186	42.2 [redacted]	[redacted]	[redacted]
Endoscopic remission at Week 52 (%)				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission per Adapted Mayo score at Week 52 with no corticosteroid use for 90 days (%)				
Placebo	183	25.1 [redacted]	-	-
Risankizumab 180 mg SC	179	39.6 [redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	186	37.1 [redacted]	[redacted]	[redacted]
Clinical remission per Adapted Mayo score at Week 52 in patients with clinical remission at Week 0 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
No bowel urgency at Week 52 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
No abdominal pain at Week 52 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Histologic endoscopic mucosal remission at Week 52 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic improvement at Week 52 in patients with endoscopic improvement at Week 0 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response per Adapted Mayo score at Week 52 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]

Change from baseline in FACIT-Fatigue at Week 52				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in IBDQ – total score at Week 52				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
No nocturnal bowel movements at Week 52 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
No tenesmus at Week 52 (%)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in number of fecal incontinence episodes per week at Week 52				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in number of days per week with sleep interrupted due to UC symptoms at Week 52				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Exposure adjusted occurrence of UC-related hospitalisations from Week 0 through Week 52 (n/100 PYs)				
Placebo	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [S]Achieved statistical significance at the 2-sides α level of 0.05 under overall Type I error rate control. [a] Results for categorical endpoints (except occurrence of UC-related hospitalisation) are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impact regions) (NRI-MI). Results for continuous endpoints are based on RTB-MI. [b] Between-group difference and 95% CI are calculated using Mantel-Haenszel common rate difference with NRI-MI for categorical endpoints (normal approximation to binomial distribution for occurrence of hospitalisation) and ANCOVA/MMRM with RTB-MI for continuous endpoints. [c] Statistical significance is determined via the graphical multiple procedure controlling the overall type I error rate of primary and secondary endpoints at the 0.05 level.
Abbreviations: CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; IBDQ, Inflammatory Bowel Disease Questionnaire; NRI-MI: Non-responder Imputation while incorporating Multiple Imputations; SC, subcutaneous; UC, ulcerative colitis.
Source: AbbVie. Data on File. COMMAND CSR.[85]

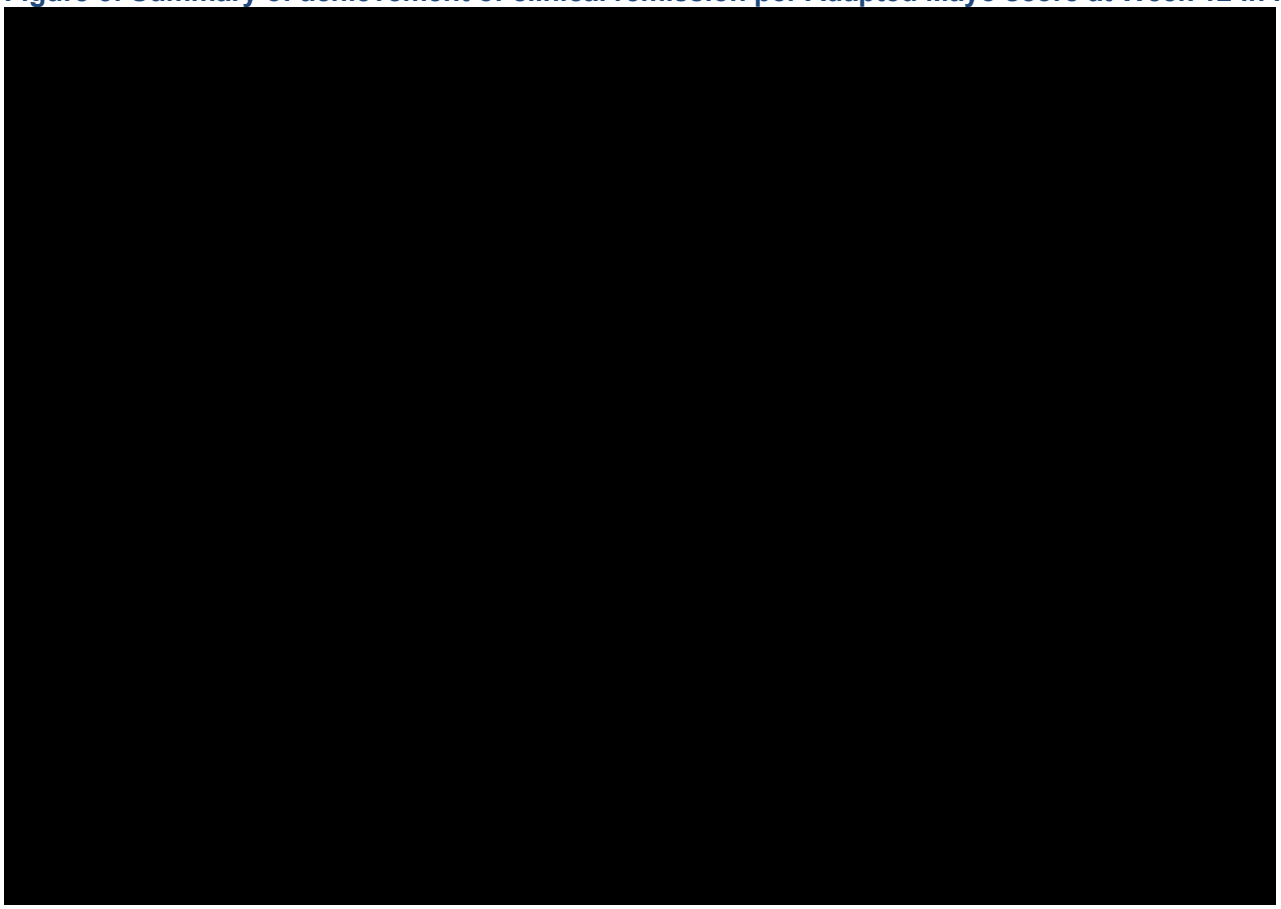
B.3.7 Subgroup analysis

B.3.7.1 Primary efficacy endpoint subgroup analysis

Subgroup analysis was performed for the primary efficacy endpoint of clinical remission for the pre-defined subgroups presented in Figure 5 for INSPIRE and Figure 6 for COMMAND.

In both INSPIRE and COMMAND, efficacy results for the primary endpoint of clinical remission per Adapted Mayo score at Week 12 across most subgroups were consistent with the full ITT2 population.

Figure 5: Summary of achievement of clinical remission per Adapted Mayo score at Week 12 in INSPIRE by subgroups, ITT2, NRI-MI



Footnotes: ITT2 includes all randomised patients who received at least one dose of study drug during Induction Period 1 from sub-study 2; Clinical remission per Adapted Mayo score is defined as SFS ≤1 , and not greater than baseline, RBS=0 , and endoscopic subscore ≤1 without the evidence of friability; If any of the resulting subgroups except for age, sex and race has fewer than 10% of the planned size, the subgroup analyses for that category are not presented; risk difference=(risankizumab – placebo); 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to logistic restrictions (COVID-19 or geo-political restrictions) or is based on the normal approximation to the binomial distribution if there are no missing data due to logistic restrictions (COVID-19 or geo-political restrictions).
Abbreviations: RBS: rectal bleeding subscore; SFS: stool frequency subscore
Source: AbbVie. Data on File. INSPIRE CSR.[84]

Figure 6: Summary of achievement of clinical remission per Adapted Mayo score at Week 12 in COMMAND by subgroups, ITT1RN_A, NRI-MI

The ITT1RN_A Population includes all randomised subjects who received at least one dose of study drug in Sub-study 1 after received IV risankizumab (either 600 mg, 1200 mg or 1800 mg) for only one period of 12 weeks in INSPIRE. Risk difference = (Risankizumab - Placebo). If any of the resulting subgroups except for age, sex and race has fewer than 10% of the planned study size, the subgroup analyses for that category are not presented. Clinical remission per Adapted Mayo score is defined as stool frequency subscore (SFS) <= 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore <= 1 without the evidence of friability.
Abbreviations: IR: inadequate responder; IV: intravenous; SC: subcutaneous; TNF: tumour necrosis factor; UC: ulcerative colitis.
Source: AbbVie. Data on File. COMMAND CSR.[85]

B.3.7.2 Subgroup analyses by prior advanced therapy response

Subgroup analyses based on prior inadequate response to advanced therapy are presented for INSPIRE and COMMAND in this section. Further subgroup analyses based on prior TNF-α inhibitor exposure and prior advanced therapy exposure are presented in Appendix E.

- ***Advanced therapy-IR population:*** Patients who have had an intolerance or inadequate response to advanced therapy, including one or more of the approved biologics for UC (TNF-α inhibitors [infliximab, adalimumab or golimumab], ustekinumab, and/or vedolizumab), approved JAK inhibitors for UC (tofacitinib, filgotinib, upadacitinib), and/or the approved S1P inhibitor for UC (ozanimod).
    - Around [redacted] of patients in the advanced therapy-IR population had previously failed a biologic therapy
- ***Non-advanced therapy-IR population:*** Patients who have had an inadequate response or intolerance to conventional therapy, defined as one or more of the following treatments: aminosalicylates, oral locally acting steroids (e.g. budesonide, beclomethasone), systemic corticosteroids (e.g. prednisone or equivalent), or immunomodulators (e.g. azathioprine, mercaptopurine, methotrexate)
    - This population also included some patients who had previously been exposed to biologic therapy (infliximab, adalimumab, golimumab, ustekinumab, and/or vedolizumab) or tofacitinib but had stopped therapy based on reasons other than inadequate response or intolerance (e.g. change in reimbursement coverage). However, the proportion of these patients was small, with only [redacted] having prior exposure to TNF-α inhibitors, [redacted] having prior exposure to tofacitinib and [redacted] prior receipt of vedolizumab for INSPIRE sub-study 2

INSPIRE

Primary efficacy outcome by advanced therapy status

In general, similar trends were observed in the subgroups of advanced-therapy-IR and non-advanced therapy-IR as compared to the full ITT2 population for the primary endpoint (Table 27) and secondary endpoints (Table 28).

Table 27: Proportion of patients achieving clinical remission per Adapted Mayo score at Week 12 by advanced therapy-IR status; INSPIRE sub-study 2 ITT2, NRI-MI

Treatment	N	Missing due to COVID/GP	Responder		Response rate difference compared to placebo	
			n (%)	[95% CI][a]	Adjusted difference[b]	[95% CI][a]
Advanced therapy-IR						
Placebo	170	[redacted]	[redacted] (4.3)	[redacted]	7.2	[2.6, 11.8]
Risankizumab 1200 mg IV	333	[redacted]	[redacted] (11.4)	[redacted]		
Non advanced therapy-IR						
Placebo	155	[redacted]	[redacted] (8.4)	[redacted]	21.3	[14.6, 27.9]

Risankizumab 1200 mg IV	317	[redacted]	[redacted] (29.7)	[redacted]		

Footnotes: [a] 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure; [b] Risk difference = (risankizumab – placebo); NRI-MI: NRI-MI: Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 or due to geo-political conflict in Ukraine or surrounding area.
Abbreviations: CI: confidence interval; GP: geopolitical conflict; NRI-MI: Non-Responder Imputation while incorporating Multiple Imputation
Source: AbbVie. Data on File. INSPIRE CSR.[84]

Secondary outcomes by advanced therapy status

Table 28: Secondary endpoint results by advanced therapy-IR and non-advanced therapy-IR subgroups; INSPIRE sub-study 2, ITT2 population

Endpoint [a]	Advanced therapy-IR			Non-advanced therapy-IR		
	N	Within group Point estimate [95% CI]	Difference between risankizumab and placebo[b]	N	Within group Point estimate [95% CI]	Difference between risankizumab and placebo[b]
Clinical response per Adapted Mayo Score at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Endoscopic improvement at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Histological-endoscopic mucosal improvement at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Endoscopic remission at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Clinical response per Partial Adapted Mayo Score at Week 4 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
No bowel urgency at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
No abdominal pain at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Histologic endoscopic mucosal remission at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Change from Baseline to Week 12 FACIT-Fatigue (RTB-MI) (LS mean)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Change from Baseline to Week 12 IBDQ total score (RTB-MI) (LS mean)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Occurrence of UC-related hospitalisations through Week 12 (AO) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
No nocturnal bowel movements at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
No tenesmus at Week 12 (NRI-MI) (%)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Change from Baseline in number of faecal incontinence episodes per week at Week 12 (RTB-MI) (LS mean)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	
Change from Baseline in number of days per week with sleep interrupted due to UC symptoms at Week 12 (RTB-MI) (LS mean)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]		[redacted]	[redacted]	

Footnotes: [a] Results for categorical endpoints (except occurrence of UC-related hospitalisations) are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or geopolitical restrictions) (NRI-MI). Results for continuous endpoints are based on RTB-MI. [b] 95% CI are calculated using Normal approximation to binomial distribution with NRI-MI for categorical endpoints, and ANCOVA/MMRM with RTB-MI for continuous endpoints.

Abbreviations: CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, inflammatory bowel disease questionnaire; IV, intravenous; LS, least squares; NRI-MI, Non-Responder Imputation while incorporating missing data due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions; RTB-MI: Multiple Imputation Incorporating Return-To-Baseline; UC, ulcerative colitis.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

COMMAND

Primary efficacy outcome by advanced therapy status

In general, similar trends were observed in the advanced therapy-IR and non-advanced therapy-IR subgroups from COMMAND sub-study 1 as compared to the full ITT1RN_A population for the primary endpoint (Table 29) and secondary endpoints (Table 30).

Table 29: Proportion of patients achieving clinical remission per Adapted Mayo score at Week 52 by advanced therapy-IR status; COMMAND sub-study 1, ITT1RN_A

Treatment	N	Missing due to COVID/GP	Responder		Response rate difference compared to placebo	
			n (%)	[95% CI][a]	Difference (%)[b]	[95% CI][c]
Advanced therapy-IR						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non advanced therapy-IR						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure. [b] Risk difference = (risankizumab – placebo). [c] 95% CI for difference are calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions) or non-responder imputation only if there are no missing data due to logistic restrictions (COVID-19 or the geo-political conflict in Ukraine and surrounding impacted regions).
Abbreviations: CI, confidence interval; GP, geopolitical conflict; SC, subcutaneous.
Source: AbbVie. Data on File. COMMAND CSR.[85]

Table 30: Secondary endpoint results by advanced therapy-IR and non-advanced therapy-IR subgroups; COMMAND sub-study 1, ITT1RN_A

Endpoint [a]	Advanced therapy-IR			Non-advanced therapy-IR		
	N	Within group	Difference between risankizumab and placebo[b]	N	Within group	Difference between risankizumab and placebo[b]
		Point estimate [95% CI]			Point estimate [95% CI]	
Achievement of endoscopic improvement at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of histological-endoscopic mucosal improvement at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of endoscopic remission at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of clinical remission per adapted Mayo score at Week 52 with no corticosteroid sue for 90 days (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of clinical remission per adapted Mayo score at Week 52 in patients with clinical remission at Week 0 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of no bowel urgency at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-

Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of no abdominal pain at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of histologic endoscopic mucosal remission at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of endoscopic improvement at Week 52 in patients with endoscopic improvement at Week 0 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of clinical response per adapted Mayo score at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline of INSPIRE in FACIT-Fatigue at Week 52						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline of INSPIRE in IBDQ total score at Week 52						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of no nocturnal bowel movements at Week 52 (%)						

Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Achievement of no tenesmus at Week 52 (%)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline of INSPIRE in number of faecal incontinence episodes per week at Week 52						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline of INSPIRE in number of days per week with sleep interrupted due to UC symptoms at Week 52						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exposure adjusted occurrence of UC-related hospitalisations from Week 0 through Week 52 (n/100PYs)						
Placebo	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Risankizumab 180 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Results for categorical endpoints (except occurrence of UC-related hospitalisations) are based on non-responder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or geopolitical restrictions) (NRI-MI). Results for continuous endpoints are based on RTB-MI. [b] 95% CI are calculated using Normal approximation to binomial distribution with NRI-MI for categorical endpoints, and ANCOVA/MMRM with RTB-MI for continuous endpoints.
Abbreviations: CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, inflammatory bowel disease questionnaire; LS, least squares; NRI-MI, Non-Responder Imputation while incorporating missing data due to COVID-19 or geo-political conflict in Ukraine and surrounding impacted regions; RTB-MI, Multiple Imputation Incorporating Return-To-Baseline; SC, subcutaneous; UC, ulcerative colitis.
Source: AbbVie. Data on File. COMMAND CSR.[85]

B.3.8 Meta-analysis

No meta-analyses were conducted for this submission.

B.3.9 Indirect and mixed treatment comparisons

Comparative efficacy summary

- As described in Section B.1, risankizumab is anticipated to present an alternative treatment to ustekinumab for patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.
- In the absence of head-to-head data between risankizumab and ustekinumab, a series of NMAs were conducted to assess the relative efficacy and safety of risankizumab compared with ustekinumab in adults with moderately to severely active UC.

NMA methodology

- NMAs were conducted for induction and maintenance treatment in three populations:
    - Overall population, defined as patients with moderately to severely active UC regardless of prior biologic therapy exposure. NMA results for this population are presented in Section B.3.9.5 to Section B.3.9.8
    - Bio-exposed population, defined as patients with moderately to severely active UC who have received one or more prior biologic therapies and had an inadequate response or intolerance; and those who stopped prior biologic therapy for reasons other than inadequate response or intolerance. This population is considered analogous to the advanced therapy-IR population in the risankizumab trials; as such, this population also included a small proportion of patients who had prior exposure to non-biologic advanced therapies (a JAK inhibitor or ozanimod). NMA results for this population are presented in Section B.3.9.5 to Section B.3.9.8
    - Bio-naïve population, defined as patients with moderately to severely active UC with no prior biologic therapy or other advanced therapy exposure. This population is considered analogous to the non-advanced therapy-IR population in the risankizumab trials. NMA results for this population are presented in Appendix D
- To keep the NMA comparable in terms of trial populations, patient-level data from the risankizumab trials were used to separate patients into the bio-naïve and bio-exposed populations
- The NMAs included all biologic therapies which are positioned in patients who have failed a biologic therapy, or for whom TNF-α inhibitors are not suitable: risankizumab, ustekinumab, vedolizumab and mirikizumab. Further interventions were not included for a number of reasons, including that they have very different mechanisms of action, so as to not introduce additional heterogeneity into the network
- Outcomes assessed within the NMAs included both efficacy (clinical remission, clinical response and endoscopic improvement) and safety (serious infections and serious AEs) endpoints that are important and clinical meaningful goals in the treatment of UC

- All NMAs were conducted under a Bayesian framework, and for all networks, both fixed (FE) and random (RE) effect models were conducted

NMA results

- Across all of the NMAs conducted, risankizumab was associated with comparable efficacy and safety in terms of clinical response, clinical remission, endoscopic improvement, serious infections and serious AEs compared with ustekinumab. Based on this, a cost-comparison approach was considered suitable for this submission

As described in Section B.3.1, an SLR was conducted on June 27th 2023 to identify relevant clinical evidence in the form of RCTs for the efficacy and safety of treatments for moderately to severely active UC. Full details of the methodology and results of this SLR are presented in Appendix D.

Overall, of the 404 records reporting on 57 unique studies included in the clinical SLR, 118 records (reporting on 39 unique studies) were considered for extraction. Of these, no head-to-head RCTs between risankizumab and ustekinumab were identified in the SLR. As such, a series of NMAs were conducted to assess the relative efficacy and safety of risankizumab compared with ustekinumab in adults with moderately to severely active UC.

B.3.9.1 NMA populations

As described in Section B.1, risankizumab is positioned as a treatment for patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough. In this position, it is anticipated that risankizumab will represent an alternative treatment option to ustekinumab only.

For completeness, a series of NMAs were conducted in three patient populations: an overall population, a bio-exposed population, and a bio-naïve population. An overview of these populations is summarised below. Results for the overall and bio-exposed NMAs are presented in Section B.3.9.5 and B.3.9.6, results for the bio-naïve NMAs are presented in Appendix D.

- **Overall population**: Patients with moderately to severely active UC regardless of prior biologic therapy exposure
- **Bio-exposed population**: Patients with moderately to severely active UC, who have received one or more prior biologic therapies and had an inadequate response or intolerance; and those who stopped prior biologic therapy for reasons other than inadequate response or intolerance
- **Bio-naïve population:** Patients with moderately to severely active UC with no prior biologic therapy or other advanced therapy exposure

The overall population reflects the entire target population for risankizumab in patients with moderately to severely active UC in this submission as this population captures both patients *in whom TNF-α inhibitors are deemed unsuitable* (bio-naïve) and patients *where biological treatment is not tolerated or not working well enough* (bio-exposed).

The bio-exposed population reflects the largest share of the target population for risankizumab in patients with moderately to severely active UC *where prior biological treatment is not tolerated or*

not working well enough. This population is analogous to the advanced therapy-IR population evaluated in INSPIRE and COMMAND, results for which are presented in Section B.3.7.2. It should be noted that the advanced therapy-IR population in INSPIRE and COMMAND considered prior advanced therapy 'inadequate response', rather than 'exposure'. As such, individual patient-level data (IPD) from the risankizumab clinical trials were re-analysed to expand the advanced therapy-IR subgroup to align with the bio-exposed subgroup of the relevant comparator clinical trials. In addition, whilst the bio-exposed subgroups of the relevant comparator trials considered prior exposure to biologic therapy only, the advanced therapy-IR populations evaluated in INSPIRE and COMMAND included a small proportion of patients with prior exposure to any advanced therapy (including JAK inhibitors and ozanimod). However, feedback from UK clinical experts indicated that the inclusion of this small number of patients within the risankizumab bio-exposed subgroup of the NMA would not bias results and indicated that the efficacy of risankizumab would not be expected to differ in patients who had prior exposure to biologic therapy versus other non-biologic advanced therapies such as JAK inhibitors or ozanimod. This is supported by the comparison of results for patients with prior TNF-α inhibitor or prior advanced therapy exposure (presented in Appendix E), which show similar efficacy for risankizumab versus placebo regardless of the type of prior therapy exposure.

The bio-naïve population reflects the smallest share of the target patient population for risankizumab in patients with moderately to severely active UC *in whom TNF-α inhibitors are deemed unsuitable*. The bio-naïve population is analogous to the non-advanced therapy-IR population evaluated in INSPIRE and COMMAND, results for which are presented in Section B.3.7.2. Patients in the bio-naïve population are naïve to any advanced therapy, including JAK inhibitors or ozanimod.

B.3.9.2 NMA study selection and feasibility assessment

As described in Appendix D, of the 404 records reporting on 57 unique studies included in the clinical SLR, 118 records (reporting on 39 unique studies) were considered for extraction.

These 118 records (reporting on 39 unique studies) considered for extraction in the clinical SLR were then assessed for inclusion within the NMAs based on the inclusion/exclusion criteria for the NMA detailed in Table 31.

The NMAs included all biologic therapies which are positioned in patients who have failed a biologic therapy, or for whom TNF-α inhibitors are not suitable: risankizumab, ustekinumab, vedolizumab and mirikizumab. Further interventions were not included for a number of reasons, including that they have very different mechanisms of action, so as to not introduce additional heterogeneity into the network, and it is not anticipated that risankizumab would be considered an alternative treatment to these therapies.

Table 31: Study selection criteria for the NMAs

Criteria	Inclusion criteria	Exclusion criteria
Population	Adults (≥16 years) with moderately-to-severely active UC[a] who have had an inadequate response, lost response, intolerance, or medical contraindication to either conventional therapy or a biologic agent	Paediatric or adolescent (<16 years) populations
Intervention(s)	• Risankizumab	Conventional therapy only

	• Ustekinumab • Vedolizumab • Mirikizumab	
Comparators	Head-to-head comparison and/or placebo-controlled	No comparator (i.e. single-arm RCTs)
Outcomes	The following efficacy and/or safety outcomes if reported after 6 to 12 weeks of induction treatment OR after 40 to 54 weeks of maintenance treatment: • Clinical remission (Full Mayo score [FMS] ≤2 with no subscore >1), results presented for the maintenance NMA only • Clinical response (decrease from baseline in FMS≥3 points and ≥30%, accompanied by a decrease in RBS of ≥1 or an absolute RBS≤1) • Endoscopic improvement • Serious AEs (SAEs) • Serious infections	• Patient-reported outcomes • Pharmacokinetics
Study design	Phases 3+ randomised and double-blinded (only outcomes during randomised, double-blinded phases were assessed)	• Phase 1, 2 • Non-randomised • Open-label • Observational
Others	English language	• Animal studies

[a] Defined as a FMS of 6 to 12 or an AMS (i.e. Full Mayo Score minus the PGA component) of 5 to 9, along with an EMS of 2 to 3.
Abbreviations: AMS: Adapted Mayo score; EMS: endoscopic Mayo subscore; FMS: Full Mayo score; NMA: network meta-analysis; PGA: Physician's Global Assessment; UC: ulcerative colitis.

Feasibility assessment

In addition, the feasibility of the NMAs based on the included RCTs was assessed as described in Cope *et al*. (2014).[87] First, the network connectivity of all included induction and maintenance RCTs was checked and illustrated using a network plot, with each node representing a treatment regimen included in the network and lines representing direct comparisons between nodes.

Then, relevant study and patient characteristics were considered and reviewed across the included induction and maintenance RCTs to get a sense of their comparability and identify potential sources of cross-RCT heterogeneity. The following baseline characteristics were identified a priori to be potential treatment effect modifiers in UC:

- Age (years)
- Gender (% male)
- Weight (kg)
- Duration of disease (years)
- Extent of disease (% extensive colitis or pancolitis)
- Baseline Full and Adapted Mayo Score

- Baseline C-reactive protein (CRP; some may be high sensitivity)
- Concurrent medications for UC (% corticosteroids, % immunomodulators)

After applying the inclusion/exclusion criteria for the NMAs and conducting the feasibility assessment, 8 unique studies were included for analysis within the NMAs. Full details of the feasibility assessment and the comparison of baseline characteristics between the trials considered in the NMAs is presented in Appendix D.

Summary of studies included in the NMAs

An overview of the studies included in the NMAs is presented in Table 32. A list of all studies excluded from the NMA (including reasons for exclusion) is available in Appendix D. For the interventions included in the NMAs, only licensed doses were included in the analysis.

Table 32: Summary of the trials used in the NMAs

Study	Phase	UC severity	NMA population	Induction phase			Maintenance phase					
				Duration (weeks)	Total N	Included regimen(s) (+PBO)	RCT design	Induction treatment(s)	Induction status	Duration (weeks)	Total N	Included regimen(s) (+PBO)
GEMINI 1 (NCT00783718)	3	FM6/12; EMS2	Overall (I) Bio-exposed (I/M) Bio-naïve (I/M)	6	374	VED300	RR	VED300	FM response	46	373	VED300Q8W VED300Q4W
LUCENT-1 (NCT03518086)	3	AM4/9; EMS2	Overall (I) Bio-exposed (I) Bio-naïve (I)	12	1,281	MIR300	*Maintenance in LUCENT-2*					
LUCENT-2 (NCT03524092)	3	AM4/9; EMS2	Overall (M) Bio-exposed (M) Bio-naïve (M)	*Induction in LUCENT-1*			RR	MIR300	AM response	40	644	MIR200
INSPIRE (NCT03398148) Sub-Study 2 Induction Period 1	3	AM5/9; EMS2	Overall (I) Bio-exposed (I) Bio-naïve (I)	12	975	RIS1200	*Maintenance in COMMAND*					
COMMAND (NCT03398135) Sub-Study 1	3	AM5/9; EMS2	Overall (M) Bio-exposed (M) Bio-naïve (M)	*Induction in INSPIRE*			RR	RIS1200 RIS600 RIS1800	AM response	52	548	RIS180 RIS360
NCT02039505	3	FM6/12; EMS2	Overall (I/M) Bio-exposed (I/M) Bio-naïve (I/M)	10	246	VED300	RR	VED300	FM response	50	83	VED300Q8W
UNIFI (NCT02407236)	3	FM6/12; EMS2	Overall (I/M) Bio-exposed (I/M)	8	961	UST6 (UST130 excluded)	RR	UST130 UST6	FM response	44	523	UST90Q12W UST90Q8W

			Bio-naïve (I/M)									
VISIBLE 1 (NCT02611830)	3	FM6/12; EMS2	Overall (M) Bio-exposed (M) Bio-naïve (M)	Excluded: Open-label			RR	VED300	FM response	46	216	VED300Q8W (VED108Q2W SC excluded)

Abbreviations: AMS: Adapted Mayo score; AM4/9=AMS 4 to 9; AM5/9=AMS 5 to 9; AM response: decrease in AMS ≥2 points and ≥30% from baseline, and a decrease in RBS ≥1 or an absolute RBS ≤1; AM2 remission: SFS≤1 and ≥1-point decrease from baseline, RBS=0, and EMS≤1; EMS: endoscopic Mayo subscore; EMS2: EMS≥2; FMS: Full Mayo score; FM6/12: FMS 6 to 12; FM response: decrease in FMS ≥3 points and ≥30% from baseline, and a decrease in RBS ≥1 or an absolute RBS ≤1; HIR: higher induction dosing regimen; N: number of patients randomised; NR: not reported; PBO: placebo; PGA: Physician's global assessment subscore; PGA2: PGA≥2; RBS: Rectal bleeding subscore; RBS1: RBS≥1; RCT: randomised clinical trial; RR: re-randomised responder; SFS: Stool frequency subscore; SFS1: SFS≥1; TDM: therapeutic drug monitoring; TT: treat-through; UC: ulcerative colitis; X: applicable.

B.3.9.3 NMA methodology

NMA methodology

All NMAs were conducted under a Bayesian framework. For each feasible network, NMAs were conducted in a Generalised Linear Model (GLM) framework using Bayesian Markov Chain Monte Carlo (MCMC) simulations and three chains with 100,000 runs each, with a burn-in that was half of the convergence sequence (set size of 10,000). Convergence was assessed with the Brooks-Gelman-Rubin method using the Potential Scale Reduction Factor (PSRF). The PRSF should gradually shrink to one with increasing numbers of iterations; a value of <1.05 was used to indicate convergence.

In line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2,[88] all binary response outcomes were modelled with a binomial likelihood and logit link function. For all networks, both fixed (FE) and random (RE) effect models were conducted.

For some RE models, the credible intervals produced were implausibly large; as such, NMA results from the FE models only are presented in the following sections. NMA results from the RE models are presented in Appendix D for completeness.

Outcomes assessed in the NMA

The outcomes considered in the NMA are detailed below, and were assessed for both induction and maintenance, with the exception of clinical remission in the induction phase. Clinical remission was not assessed in the induction NMAs given this is a longer-term outcome that is more relevant to the maintenance treatment phase. Additionally, feedback from UK clinical experts indicated that the principal purpose of induction therapy is to induce clinical response and enable patients to go on to receive maintenance treatment.

Efficacy outcomes (all populations)

- Clinical remission (Full Mayo score [FMS] ≤2 with no subscore >1)
- Clinical response (decrease from baseline in Full Mayo Score ≥3 points and ≥30%, accompanied by a decrease in rectal bleeding score (RBS) of ≥1 or an absolute RBS≤1)
- Endoscopic improvement (endoscopic Mayo subscore [EMS] ≤1)

Safety outcomes (overall population only)

- Serious infections
- Serious AEs (SAEs)

Full details of the methodology for the NMAs are provided in Appendix D.

Results presented for the NMA

For each NMA population and outcome, the following results were derived:

- Surface under the cumulative ranking curve (SUCRA) values for each treatment. This value represents the average proportion of the treatments that are worse than each intervention. These are presented in Appendix D.

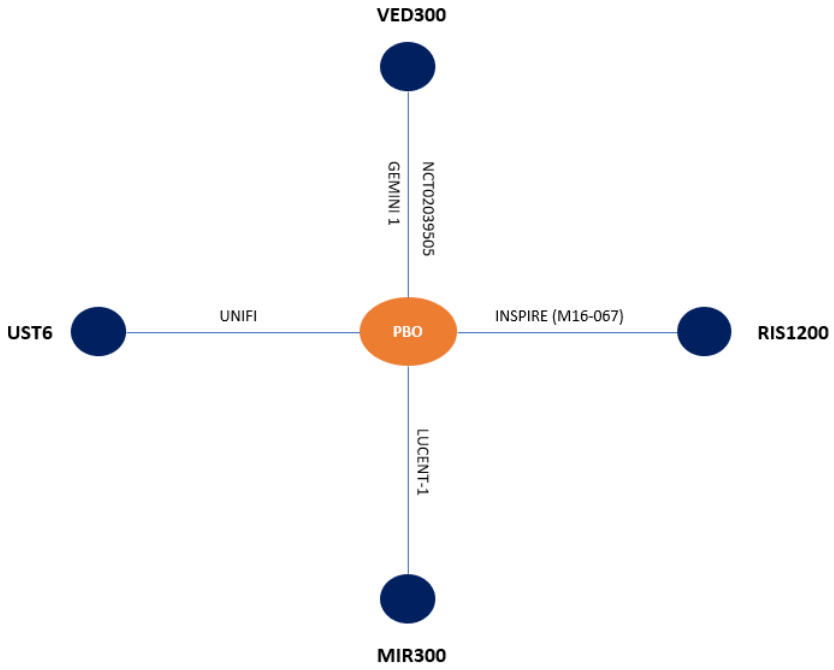
- Predicted absolute outcomes for each treatment. These are presented in Appendix D.
- Relative effect estimates for each treatment (league tables). These are presented below in Section B.3.9.5, Section B.3.9.6, Section B.3.9.7 and Section B.3.9.8.

Given the overall population reflects the entire target population for risankizumab in patients with moderately to severely active UC in this submission, and the bio-exposed population reflects the largest share of the target population for risankizumab in patients with moderately to severely active UC *where prior biological treatment is not tolerated or not working well enough*, NMA results for the overall population and bio-exposed populations are presented in the following sections. NMA results for the bio-naïve population, which reflects the smallest share of the target patient population for risankizumab in patients with moderately to severely active UC *in whom TNF-α inhibitors are deemed unsuitable*, are presented in Appendix D.

B.3.9.4 NMA networks

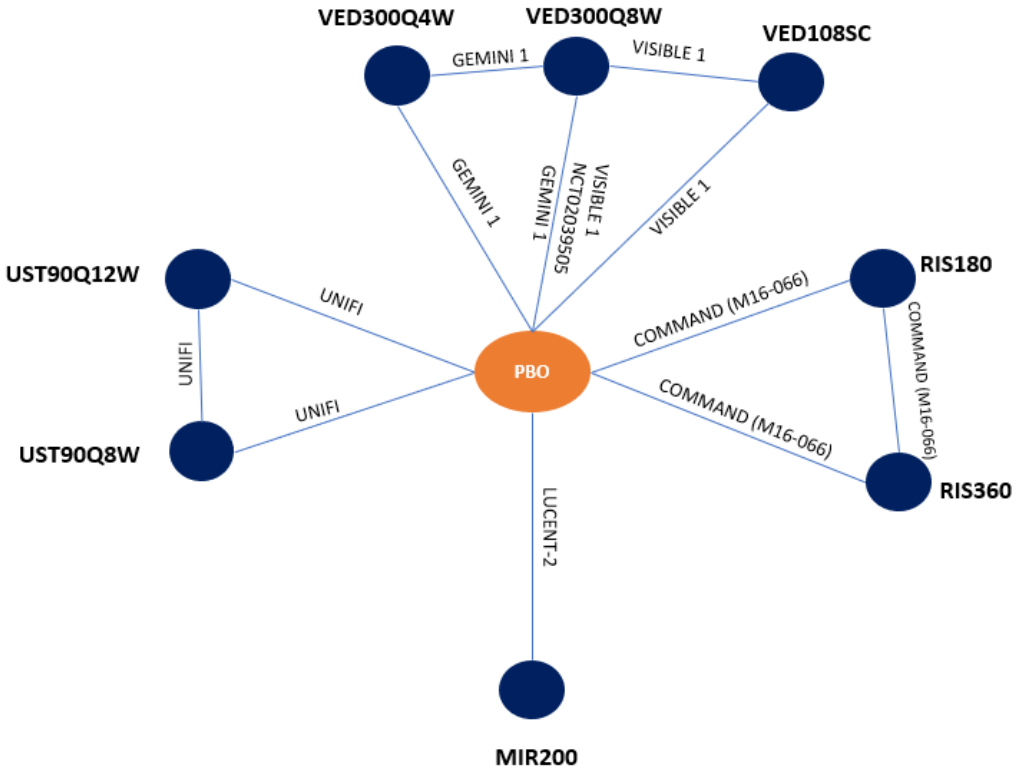
Network diagrams for the induction and maintenance phase NMAs are presented in Figure 7 and Figure 8, respectively.

Figure 7: Induction phase network diagram



Abbreviations: MIR300: mirikizumab 300 mg; PBO: placebo; RIS1200: risankizumab 1200 mg; UST6: ustekinumab 6 mg; VED300: vedolizumab 300 mg.

Figure 8: Maintenance NMA network diagrams



Abbreviations: MIR200: mirikizumab 200 mg; PBO: placebo; RIS180: risankizumab 180 mg; RIS360: risankizumab 360 mg; UST90Q12W: ustekinumab 90 mg every 8 weeks; UST90Q12W: ustekinumab 90 mg every 12 weeks; VED108SC: vedolizumab 108 mg subcutaneous; VED300Q4W: vedolizumab 300 mg every 4 weeks; VED300Q8W: vedolizumab 300 mg every 8 weeks.

B.3.9.5 Efficacy NMA results: Induction phase

Results from the induction efficacy NMAs are presented in the following sections.

Clinical response

The induction NMA results for clinical response in the overall and bio-exposed populations are presented in Table 33 and Table 34 with risankizumab results presented in bold.

In terms of relative effect estimates for clinical response with induction treatment, the odds ratios for clinical response for risankizumab compared with ustekinumab were [redacted] in both the overall population and the bio-exposed population, showing that the rate of clinical response was comparable between the two treatments. The credible intervals for both comparisons of risankizumab versus ustekinumab [redacted], meaning that there was no statistically significant difference in terms of clinical response between the two treatments.

Overall population

Table 33: Induction NMA odds ratios league table for clinical response – overall population (FE)

Column vs row	Vedolizumab	Mirikizumab	Risankizumab	Ustekinumab	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Bio-exposed population

Table 34: Induction NMA odds ratios league table for clinical response – bio-exposed population (FE)

Column vs row	Vedolizumab	Mirikizumab	Risankizumab	Ustekinumab	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Endoscopic improvement

The induction NMA results for endoscopic improvement in the overall and bio-exposed populations are presented in Table 35 and Table 36, with risankizumab results presented in bold.

In terms of relative effect estimates for endoscopic improvement in the overall population, risankizumab was significantly superior to ustekinumab, with the odds ratio for endoscopic improvement being [redacted]. In the bio-exposed population, the odds ratio for endoscopic improvement for risankizumab compared with ustekinumab was [redacted], showing comparable rates of endoscopic improvement between the two treatments. The credible interval for the comparison versus ustekinumab in the bio-exposed population [redacted], meaning that there was no statistically significant difference in terms of endoscopic improvement between the two treatments.

Overall population

Table 35: Induction NMA odds ratios league table for endoscopic improvement – overall population (FE)

Column vs row	Vedolizumab	Mirikizumab	Risankizumab	Ustekinumab	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Bio-exposed population

Table 36: Induction NMA odds ratios league table for endoscopic improvement – bio-exposed population (FE)

Column vs row	Vedolizumab	Mirikizumab	Risankizumab	Ustekinumab	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

B.3.9.6 Efficacy NMA results: Maintenance phase

Results from the maintenance efficacy NMAs are presented in the following sections.

Clinical remission

The maintenance NMA results for clinical remission in the overall and bio-exposed populations are presented in Table 37 and Table 38, with risankizumab results presented in bold.

In terms of relative effect estimates for clinical remission with maintenance treatment, the odds ratio for clinical remission with risankizumab 180 mg versus ustekinumab 90 mg Q12W was [redacted] in the overall population; for all other comparisons versus ustekinumab, the odds ratios for clinical remission for risankizumab (both the 180 mg and 360 mg dose) were [redacted], in both the overall and bio-exposed populations. However, in both the overall and bio-exposed populations, the credible intervals for all comparisons of risankizumab versus ustekinumab [redacted], meaning that there was no statistically significant difference in clinical remission between the two treatments, and hence the rates of clinical remission can be considered comparable.

Overall population

Table 37: Maintenance NMA odds ratios league table for clinical remission – overall population (FE)

Column vs row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Ustekinumab 90 mg Q8W	Ustekinumab 90 mg Q12W	Vedolizumab 108 Q2W	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 108 Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Bio-exposed population

Table 38: Maintenance NMA odds ratios league table for clinical remission – bio-exposed population (FE)

Column vs. row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Ustekinumab 90 mg Q12W	Ustekinumab 90 mg Q8W	Vedolizumab 108 Q2W	Placebo

Placebo	[redacted]								
Vedolizumab 108 Q2W	[redacted]								
Ustekinumab 90 mg Q8W	[redacted]								
Ustekinumab 90 mg Q12W	[redacted]								
Risankizumab 360 mg	[redacted]								
Risankizumab 180 mg	[redacted]								
Mirikizumab	[redacted]								
Vedolizumab 300 mg Q8W	[redacted]								
Vedolizumab 300 mg Q4W	[redacted]								

Abbreviations: FE: fixed effects.

Clinical response

The maintenance NMA results for clinical response in the overall and bio-exposed populations are presented in Table 39 and Table 40, with risankizumab results presented in bold.

In terms of relative effect estimates for clinical response with maintenance treatment, the odds ratios for clinical response for risankizumab (both the 180 mg and 360 mg dose) compared with ustekinumab were [redacted] in both the overall population and the bio-exposed population; however, with the exception of the risankizumab 360 mg dose versus ustekinumab 90 mg Q8W in the overall population, the credible intervals for all comparisons of risankizumab versus ustekinumab [redacted], meaning there was no statistically significant difference in clinical response between the two treatments, and therefore the rates of clinical response can be considered comparable.

Overall population

Table 39: Maintenance NMA odds ratios league table for clinical response – overall population (FE)

Column vs row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Ustekinumab 90 mg Q8W	Ustekinumab 90 mg Q12W	Vedolizumab 108 Q2W	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 108 Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Bio-exposed population

Table 40: Maintenance NMA odds ratios league table for clinical response – bio-exposed population (FE)

Column vs row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Ustekinumab 90 mg Q12W	Ustekinumab 90 mg Q8W	Placebo

Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Endoscopic improvement

The maintenance NMA results for endoscopic improvement in the overall and bio-exposed populations are presented in Table 41 and Table 42, with risankizumab results presented in bold.

In terms of relative effect estimates for endoscopic improvement with maintenance treatment, the odds ratios for endoscopic improvement for risankizumab (both the 180 mg and 360 mg dose) were [redacted] compared with the ustekinumab Q12W dose, and lower compared with the ustekinumab Q8W dose, in both the overall population and the bio-exposed populations. Overall, the credible intervals for all comparisons of risankizumab versus ustekinumab [redacted], meaning there was no statistically significant difference in clinical response between the two treatments. The rates of endoscopic improvement can therefore be considered comparable between risankizumab and ustekinumab.

Overall population

Table 41: Maintenance NMA odds ratios league table for endoscopic improvement – overall population (FE)

Column vs row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Ustekinumab 90 mg Q8W	Ustekinumab 90 mg Q12W	Vedolizumab 108 Q2W	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 108 Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Bio-exposed population

Table 42: Maintenance NMA odds ratios league table for endoscopic improvement – bio-exposed population (FE)

Column vs row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Ustekinumab 90 mg Q12W	Ustekinumab 90 mg Q8W	Placebo

Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

B.3.9.7 Safety NMA results: Induction phase

Serious infections

The induction NMA results for serious infections in the overall population are presented in Table 43.

In terms of relative effect estimates for the incidence of serious infections with induction treatment, the odds ratio for the incidence of serious infections was [redacted] for risankizumab versus ustekinumab. However, whilst the credible interval for this comparison [redacted] meaning there was no statistically significant difference in serious infections between the two treatments.

Table 43: Induction NMA odds ratios league table for serious infections – overall population (FE)

Column vs. row	Vedolizumab	Ustekinumab	Mirikizumab	Risankizumab	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects

Serious AEs

The induction NMA results for SAEs in the overall population are presented in Table 44, with risankizumab results presented in bold.

In terms of relative effect estimates for the incidence of SAEs with induction treatment, the odds ratio for the incidence of serious AEs was [redacted] for risankizumab versus ustekinumab; however, the credible interval for this comparison [redacted], meaning that there is no statistically significant difference in SAEs between the two treatments and the incidence of SAEs can therefore be considered comparable.

Table 44: Induction NMA odds ratios league table for SAEs – overall population (FE)

Column vs row	Placebo	Mirikizumab	Risankizumab	Ustekinumab	Vedolizumab
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects; SAE: serious adverse events.

B.3.9.8 Safety NMA results: Maintenance phase

Serious infections

The maintenance NMA results for serious infections in the overall population are presented in Table 27.

In terms of relative effect estimates for serious infections with maintenance treatment, across all comparisons with ustekinumab, the odds ratios for serious infections for risankizumab (both the 180 mg and 360 mg dose) were [redacted] in the overall population. For all comparisons the credible

intervals [redacted], meaning that there was no statistically significant difference in serious infections between the two treatments, and hence the rates of serious infections can be considered comparable.

Table 45: Maintenance NMA odds ratios league table for serious infections – overall population (FE)

Column vs. row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Ustekinumab 90 mg Q12W	Ustekinumab 90 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Placebo
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 360 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 180 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90 mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects.

Serious AEs

The maintenance NMA results for serious AEs in the overall population are presented in Table 46, with risankizumab results presented in bold.

In terms of relative effect estimates for SAEs with maintenance treatment, across all comparisons with ustekinumab, the odds ratios for SAEs for risankizumab (both the 180 mg and 360 mg dose) were [redacted] in the overall population. For all comparisons the credible intervals [redacted], meaning that there was no statistically significant difference in SAEs between the two treatments, and hence the rates of serious infections can be considered comparable.

Table 46: Maintenance NMA odds ratios league table for SAEs – overall population (FE)

Column vs row	Vedolizumab 300 mg Q4W	Vedolizumab 300 mg Q8W	Mirikizumab	Risankizumab 180 mg	Risankizumab 360 mg	Ustekinumab 90 mg Q12W	Ustekinumab 90 mg Q8W	Vedolizumab 108 Q2W	Placebo
Placebo									
Vedolizumab 108 Q2W									
Ustekinumab 90 mg Q8W									
Ustekinumab 90 mg Q12W									
Risankizumab 360 mg									
Risankizumab 180 mg									
Mirikizumab									
Vedolizumab 300 mg Q8W									
Vedolizumab 300 mg Q4W									

Abbreviations: FE: fixed effects; SAE: serious adverse events.

B.3.9.9 Conclusion of the NMA

As described in Section B.1.3.3, ustekinumab represents the most relevant comparator for this submission. Both treatments have a related mechanism of action of targeting ILs and inhibiting IL-23, both treatments have a similar mode of administration, and feedback from UK clinical experts supports that risankizumab would be considered as an alternative treatment to ustekinumab in the proposed target population. In the absence of head-to-head data between risankizumab and ustekinumab, a series of NMAs were conducted to assess the relative efficacy and safety of risankizumab compared with ustekinumab in adults with moderately to severely active UC.

NMAs were conducted for induction and maintenance treatment in three populations: an overall population, a bio-exposed population and a bio-naïve population. The overall population can be considered to reflect the entire target population for risankizumab in patients with moderately to severely active UC in this submission. The bio-exposed population reflects the largest share of the target population for risankizumab in patients with moderately to severely active UC *where prior biological treatment is not tolerated or not working well enough*, and the bio-naïve population reflects the smallest share of the target patient population for risankizumab in patients with moderately to severely active UC *in whom TNF-α inhibitors are deemed unsuitable*. NMA results for the bio-exposed and overall populations are presented in Section B.3.9.5 to B.3.9.8. Supporting results from the bio-naïve population are presented within Appendix D.

Outcomes assessed within the NMAs included both efficacy (clinical remission, clinical response and endoscopic improvement) and safety (serious infections and SAEs) endpoints that are important and clinically meaningful goals in the treatment of UC.

Across all the NMAs conducted, in both induction and maintenance, efficacy and safety outcomes were considered comparable between risankizumab and ustekinumab. Based on this, a cost-comparison approach was considered suitable for this submission.

Uncertainties and limitations of the NMA

As it is the case with any NMA, the key uncertainties and limitations of the NMA relate to heterogeneity. Whilst outcome definitions were mostly consistent across trials, differing definitions of clinical response in terms of Full versus Adapted Mayo Score were used for some studies. In addition, while the designs of the induction phase studies were consistent, the length of the induction period varied from 6 to 12 weeks.

Another source of heterogeneity was that the inclusion criteria for the bio-naïve and bio-exposed populations varied across studies. In the bio-naïve population, most studies recruited or analysed patients who had failed conventional therapy, such as corticosteroids or immunomodulators like azathioprine, 6-MP, or methotrexate, but had not yet been treated with a biologic or small molecule. However, the exact composition of prior conventional therapy varied across studies. Moreover, the included studies varied in their approach to permitting concomitant medication during the trial.

In the bio-exposed population, studies differed in terms of the definition of ‘exposure’ to prior therapies. For risankizumab, whilst the bio-exposed population is analogous to the advanced therapy-IR population evaluated in INSPIRE and COMMAND, the advanced therapy-IR population considered prior advanced therapy ‘inadequate response’, rather than ‘exposure’. As

such, IPD from the risankizumab clinical trials had to be re-analysed to expand the advanced therapy-IR subgroup to align with the bio-exposed subgroup of the relevant comparator clinical trials.

In addition, in the bio-exposed population, studies varied with respect to whether they recruited patients previously exposed to a biologic therapy such as TNF-α inhibitor, and/or vedolizumab, and/or ustekinumab, or if they also recruited patients who had exposure to a small molecule such as a JAK inhibitor. Indeed, as described in Section B.3.9.1, whilst the bio-exposed subgroups of the relevant comparator trials considered prior exposure to biologic therapy only, the advanced therapy-IR populations evaluated in INSPIRE and COMMAND included a small proportion of patients with prior exposure to any advanced therapy (including JAK inhibitors and ozanimod). This was also the case for the mirikizumab trials. However, feedback from UK clinical experts indicated that the inclusion of these patients within the risankizumab bio-exposed subgroup of the NMA would not bias results and indicated that the efficacy of risankizumab would not be expected to differ in patients who had prior exposure to biologic therapy versus other advanced therapies such as JAK inhibitors or ozanimod. This is supported by the comparison of results for patients with prior TNF-α inhibitor or prior advanced therapy exposure (presented in Appendix E), which show similar efficacy for risankizumab versus placebo regardless of the type of prior therapy exposure.

Despite these sources of heterogeneity, the feasibility assessment performed as part of this analysis and the approaches undertaken with the aim of aligning the data to allow for robust like-for-like comparisons are considered strengths which address the potential uncertainties and limitations of the NMA. Indeed, previous NICE evaluations have identified and accepted that trials in UC are heterogeneous, but that data obtained from rigorous NMAs based on high-quality RCT evidence nonetheless represent the best available estimates of relative efficacy and safety and are appropriate to inform decision-making.[6, 33] After the completion of the feasibility assessment, it was concluded that the baseline populations of the studies included in the analyses were sufficiently comparable to provide meaningful indirect clinical data.

Finally, potential uncertainty in the NMAs for the maintenance phase could be linked to the long elimination half-life of risankizumab. As discussed in Section B.3.6.2, patients re-randomised to receive placebo in sub-study 1 of COMMAND had previously achieved clinical response to IV risankizumab in INSPIRE sub-study 1 or sub-study 2. Given the long elimination half-life of risankizumab, the COMMAND placebo group may have continued to respond to residual risankizumab and consequently the benefit of risankizumab maintenance therapy over placebo may appear lower. Indeed, across all of the trials included in the NMA, the response rates for placebo in the maintenance phase are the highest across all of the trials (see Appendix D).

Risankizumab serum concentrations at planned visits for COMMAND sub-study 1 are presented in Appendix J.2, which show that placebo patients had measurable serum exposures to risankizumab, particularly at Week 16, indicating a prolonged drug washout from the previous IV induction treatment due to the long elimination half-life of risankizumab. Suppression of inflammatory markers (high sensitivity C-reactive protein [hs-CRP] and faecal calprotectin [FCP]) from Week 0 also remained in the placebo group, as shown by the results presented in Appendix J. Together, these data suggest that the long eliminating half-life of risankizumab may have contributed to higher response rates for the placebo group for key endpoints in COMMAND sub-study 1.

B.3.10 Adverse reactions

Summary of safety

Across the risankizumab INSPIRE and COMMAND studies, no new safety risks were observed versus placebo, and the overall safety profile was consistent with the known safety profile of risankizumab.

INSPIRE

- Safety data for all patients who received at least 1 dose of study drug indicated that induction treatment with risankizumab 1200 mg IV for 12 weeks (sub-study 2 Induction Period 1) was generally safe and well tolerated
- There was a similar incidence of TEAEs observed during sub-study 2 Induction Period 1 in patients treated with risankizumab 1200 mg IV and placebo (42.1% and 49.7%, respectively)
- The proportions of patients with severe AEs, serious AEs (SAEs) and AEs that led to study drug discontinuation were lower in the risankizumab 1200 mg IV arm compared to the placebo arm in sub-study 2 (Induction Period 1)
- Incidence of serious infections were lower in the risankizumab 1200 mg IV arm compared to placebo (0.6% versus 1.2%, respectively) and no MACE events occurred in either arm in sub-study 2 (Induction Period 1)
- One death was reported in sub-study 2 Induction Period 1, which occurred ≤140 days after the last dose of study drug and was COVID-19 related

COMMAND

- During sub-study 1, the proportions of patients with TEAEs with reasonable possibility of being drug-related, severe AEs and SAEs were all numerically lower in both the risankizumab 180 mg SC and risankizumab 360 mg SC arms compared to the placebo arm
- Incidence of serious infections were lower in the risankizumab 180 mg SC and 360 mg SC arms compared to placebo ([redacted] respectively) at Week 52 and no MACE events were reported any arm in sub-study 1
- One death was reported in the risankizumab 360 mg SC arm in sub-study 1, which occurred >140 days after the last dose of study drug and was considered by the investigator as having no reasonable possibility of relationship to the study drug

The incidence of TEAEs was a primary safety outcome in INSPIRE and COMMAND and was assessed throughout both studies. All AEs reported in this section were treatment-emergent.

B.3.10.1 INSPIRE

TEAEs for Induction Period 1 were defined as events that begin either on or after the first dose of the study drug in Induction Period 1 of sub-study 2.

During Induction Period 1, the proportion of patients with AEs was comparable in the risankizumab 1200 mg IV arm and the placebo arm. The proportion of patients with severe AEs,

SAEs, and AEs that led to study drug discontinuation were lower in the risankizumab arm compared to the placebo arm. One death was reported, which occurred ≤ 140 days after the last dose of study drug and was COVID-19 related. An overview of TEAES and all deaths is provided in Table 47.

The most commonly reported (≥1% of patients in the risankizumab arm) TEAESs are presented in Table 48), with the most common being COVID-19, anemia and arthralgia in the risankizumab 1200 mg IV arm and colitis ulcerative, anemia, COVID-19 and pyrexia in the placebo arm.

An overview of treatment-emergent SAEs occurring in ≥2 patients in any treatment arm in INSPIRE sub-study 2 is presented in Table 49. The proportion of patients with TEAEs was lower in the risankizumab 1200 mg IV arm compared to the placebo arm.

Table 47: Overview of TEAEs and all deaths; INSPIRE sub-study 2, SA2

	Placebo IV (N=[redacted]) (PY=[redacted])		Risankizumab 1200 mg IV (N=[redacted]) (PY=[redacted])	
	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)
Patients with any treatment-emergent:				
AE	[redacted] (49.7)	[redacted]	[redacted] (42.1)	[redacted]
AE with reasonable possibility of being drug-related[a]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AE	[redacted] (10.2)	[redacted]	[redacted] (2.5)	[redacted]
SAE	[redacted] (10.2)	[redacted]	[redacted] (2.3)	[redacted]
AE leading to discontinuation of study drug	[redacted] (3.7)	[redacted]	[redacted] (0.6)	[redacted]
AE resulting in death	[redacted]	[redacted]	[redacted]	[redacted]
Any COVID-19 related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
All deaths[b]	[redacted]	[redacted]	[redacted]	[redacted]
Any COVID-19 related death	[redacted]	[redacted]	[redacted]	[redacted]
Deaths occurring ≤ 140 days after last dose of study drug	[redacted]	[redacted]	1 [redacted]	[redacted]
Deaths occurring > 140 days after last dose of study drug	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] As assessed by investigator; [b] Includes non-treatment-emergent deaths; SA2 consists of all patients who received at least 1 dose of study drug during Induction Period 1 in sub-study 2; Patients are counted once in

each row, regardless of number of events they may have had; E/100PY = Events per 100 patient-years.
Abbreviations: AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

Table 48: TEAEs occurring in ≥1% of patients in the risankizumab arm; INSPIRE sub-study 2, SA2

MedDRA Preferred Term	Placebo IV (N = [redacted]) n (%)	Risankizumab 1200 mg IV (N = [redacted]) n (%)
Any AE	[redacted](49.7)	[redacted](42.1)
COVID-19	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Colitis ulcerative	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]

Footnotes: SA2 consists of all patients who received at least 1 dose of study drug during Induction Period 1 in sub-study 2; Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: AE: adverse event; IV: intravenous.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

Table 49: Patients with treatment-emergent SAEs occurring in ≥2 patients in any treatment arm; INSPIRE sub-study 2, SA2

MedDRA system organ class preferred term	Placebo IV (N = [redacted]) n (%)	Risankizumab 1200 mg IV (N = [redacted]) n (%)
Any AE	[redacted](10.2)	[redacted](2.3)
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Anal fistula	[redacted]	[redacted]
Colitis ulcerative	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]

Footnotes: SA2 consists of all patients who received at least 1 dose of study drug during Induction Period 1 in sub-study 2; Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: AE: adverse event; IV: intravenous; SAE: serious adverse event.
Source: AbbVie. Data on File. INSPIRE CSR.[84]

B.3.10.2 COMMAND

In COMMAND sub-study 1, TEAEs were defined as AEs that begin or worsen either on or after the first dose of the study drug. Comparisons between risankizumab and placebo are made on the randomised population (SA1RN) – see Table 19 for the definition of this analysis set.

An overview of TEAEs and all deaths observed in COMMAND sub-study 1 is provided in Table 50. The most commonly reported (≥2% of patients in the risankizumab arm) TEAEs in COMMAND sub-study 1 are presented in Table 50.

In summary, the proportion of patients with AEs, AEs related to the study drug and AEs leading to discontinuation of the study drug in each risankizumab SC arm (180 mg and 360 mg) were generally comparable to the placebo arm with no consistent dose-dependent pattern between the risankizumab arms. The proportion of patients with SAEs and severe AEs and the exposure-adjusted event rate of SAEs and severe AEs were lower in the risankizumab arms compared to the placebo arm, with no dose-dependent pattern, which was predominately due to higher rates of UC-related events in the placebo arm.

In the risankizumab 180 mg and 360 mg SC arms, [redacted] of patients ([redacted] events per 100 PY) and [redacted] of patients ([redacted] events per 100 patient-years [PY]), respectively, experienced at least 1 AE, compared to [redacted] of patients ([redacted] events per 100 PY) in the placebo arm. One death was reported in COMMAND, a patient in the randomised safety population whose death occurred > 140 days after the last dose of study drug.

Table 50: Overview of TEAEs and all deaths; COMMAND sub-study 1, SA1RN

	Placebo SC (N=[redacted]) (PY=[redacted])		Risankizumab 180 mg SC (N=[redacted]) (PY=[redacted])		Risankizumab 360 mg SC (N=[redacted]) (PY=[redacted])	
	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)	n (%)	Events (E/100 PY)
Patients with any treatment-emergent:						
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE related to COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE related to study drug according to the investigator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted] (8.2)	[redacted]	[redacted] (5.2)	[redacted]	[redacted] (5.1)	[redacted]
AE leading to discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All deaths						
Any COVID-19 related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths occurring ≤ 140 days after	[redacted]	[redacted]	[redacted]	[redacted]	1 [redacted]	[redacted]

last dose of study drug						
Deaths occurring > 140 days after last dose of study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: SA1RN population includes the randomised patients who received IV risankizumab in INSPIRE and at least 1 dose of study drug in sub-study 1; Patients are counted once in each row, regardless of the number of events they may have had; E/100 PY = Events per 100 patient-years; n/100 PY = Number of patients with at least 1 event per 100 patient-years; [a] Represented as EAIR: n/PY (n/100 PY).
Abbreviations: AE: adverse event; EAIR: exposure adjusted incidence rate; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: AbbVie. Data on File. COMMAND CSR.[85]

Table 51: TEAEs occurring in ≥2% of patients in the total risankizumab group by decreasing frequency; COMMAND, SA1RN

MedDRA Preferred Term	Placebo SC (N = [redacted]) n (%)	Risankizumab 180 mg SC (N = [redacted]) n (%)	Risankizumab 360 mg SC (N = [redacted]) n (%)	Risankizumab total (N = [redacted]) n (%)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
UC	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: SA1RN is defined as all randomised patients who received at least one dose of study drug in COMMAND sub-study 1; Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: AE: adverse event; IV: intravenous; UC, ulcerative colitis.
Source: AbbVie. Data on File. COMMAND CSR.[85]

B.3.11 Ongoing studies

COMMAND sub-study 2 and 3 are ongoing open-label long-term extension studies which is to continue until approximately 240 weeks of individual follow-up have elapsed or until the study is discontinued, whichever is earlier. Beyond the sub-studies of COMMAND, no further studies investigating the efficacy and safety of risankizumab in moderately to severely active UC are currently ongoing or planned.

B.3.12 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence base

Clinical efficacy

The clinical benefits of risankizumab versus placebo have been demonstrated in the pivotal induction study (INSPIRE) and a pivotal maintenance study (COMMAND).

Across both INSPIRE and COMMAND, risankizumab demonstrated a statistically significant and clinically meaningful difference compared to placebo for the primary endpoint of clinical remission per Adapted Mayo score at Week 12 (risankizumab 1200 mg IV) and Week 52 (risankizumab 180 mg SC/360 mg SC) (20.3% vs 6.2% of patients [p<0.00001] and 40.2% vs 25.1% [p=0.0004]/37.6% vs 25.1% [p=0.0019], respectively).

In the INSPIRE trial, superiority was also demonstrated across all secondary endpoints evaluating several types of improvement: symptomatic, endoscopic, endoscopic-histologic, and patient-reported quality of life outcomes. In the COMMAND trial, superiority was demonstrated across a number of key secondary endpoints including endoscopic improvement and remission.

Safety

In both INSPIRE and COMMAND, treatment with risankizumab was generally well tolerated with no new safety risks identified. In INSPIRE, there was a similar incidence of TEAEs observed in patients treated with risankizumab 1200 mg IV and placebo (42.1% and 49.7%, respectively). In COMMAND, the proportions of patients with TEAEs with reasonable possibility of being drug-related, severe AEs and SAEs were all numerically lower in both the risankizumab 180 mg SC and risankizumab 360 mg SC arms compared to the placebo arm. The overall safety profile was consistent with the known safety profile of risankizumab.

Comparative efficacy

In the absence of head-to-head data between risankizumab and ustekinumab, a series of NMAs were conducted to assess the relative efficacy and safety of risankizumab compared with ustekinumab in adults with moderately to severely active UC.

NMAs were conducted for induction and maintenance treatment in three populations: an overall population, a bio-exposed population and a bio-naïve population. Outcomes assessed within the NMAs included both efficacy (clinical remission, clinical response and endoscopic improvement) and safety (serious infections and serious AEs) endpoints that are important and clinical meaningful goals in the treatment of UC.

Across all the NMAs conducted, efficacy and safety outcomes were considered comparable between risankizumab and ustekinumab. Based on this, as well as clinical expert feedback indicating that this pathway would be appropriate, a cost-comparison approach was considered suitable for this submission.

Strengths and limitations of the clinical evidence base

The global Phase III induction (INSPIRE) and maintenance (COMMAND) studies of the

risankizumab clinical development programme were large, multinational, placebo-controlled, well-conducted and methodologically robust studies, designed and adequately powered to demonstrate that risankizumab provides superior differences in clinical remission. The studies were all placebo-controlled, with the placebo design similar to other recently approved biologics for moderately to severely active UC.

The study entry criteria were relevant and appropriate, and the study population included patients similar to those expected to be treated within UK clinical practice. Both INSPIRE and COMMAND included UK study sites with [redacted] and [redacted] UK patients enrolled in each trial respectively. Feedback from UK clinical experts highlighted that the patient population from INSPIRE and COMMAND were considered generalisable to UK clinical practice.

Both studies provide efficacy and safety data of direct relevance to the anticipated licence for risankizumab with endpoints investigated that are clinically relevant and of importance to patients with moderately to severely active UC. INSPIRE and COMMAND evaluated several secondary endpoints where mucosal healing (absence of macroscopic mucosal inflammation or ulceration) was assessed through endoscopic outcomes; mucosal healing is associated with improved long-term outcomes (e.g. reduced risk of relapse, decreased hospitalisations rates, steroid-free remission, and fewer bowel resections) and is now considered a major treatment objective in clinical trials and clinical practice.[89, 90, 27]

A key limitation of the evidence base was the lack of direct comparison versus the relevant comparator to this appraisal (ustekinumab). To address this limitation, an NMA was conducted in order to obtain relative efficacy estimates to inform the economic analysis. As it the case with any NMA, the key uncertainties and limitations of the NMA relate to heterogeneity and these limitations are summarised in detail in Section B.3.9.9.

Conclusions

The clinical effectiveness evidence presented above demonstrates that risankizumab is an effective therapy for patients with moderately to severely active UC. Across all of the NMAs conducted, the efficacy and safety of risankizumab and ustekinumab were considered to be comparable. The clinical evidence presented supports a cost-comparison analysis between risankizumab and ustekinumab and suggests that risankizumab represents an important additional treatment option for patients with UC in the UK.

B.4 Cost-comparison analysis

Summary of cost-comparison analysis

- A cost-comparison analysis was conducted to estimate the economic value of risankizumab in patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.
- As described in Section B.1, risankizumab is anticipated to represent an alternative treatment option to ustekinumab only; ustekinumab represents established clinical practice in this population and both treatments have a related mechanism of action of targeting ILs
- Evidence from a series of NMAs, conducted in an overall population of patients with moderately to severely active UC regardless of prior biologic therapy exposure and in the subgroups of patients both with/without prior exposure to biologic therapies (see Section B.3.9), showed comparable efficacy and safety in terms of clinical remission, clinical response, endoscopic improvement, serious infections and serious AEs between risankizumab and ustekinumab. Therefore, a cost-comparison approach between the two treatments was deemed appropriate for this submission.
- A cost-comparison model was developed in Microsoft Excel in line with the NICE reference case. The model adopted a ten-year time horizon and incorporated drug acquisition and drug administration costs for risankizumab and ustekinumab only, as these are the only costs assumed to differ substantially between the two treatments over the modelled time horizon.

Cost-comparison results

- Over the model time horizon of 10 years, when considering the PAS discount for risankizumab, risankizumab was associated with cost savings versus ustekinumab (at list price) of [redacted] per person.
- It should be noted that ustekinumab has a confidential PAS, which should be taken into account when interpreting the results of this analysis. However, the expectation is that when the net price of ustekinumab is considered, risankizumab remains a cost-saving option for patients with moderately to severely active UC
- Scenario analyses were conducted to consider alternative time horizons, and the proportion of patients receiving dose escalation in the maintenance phase. In the vast majority of scenarios (with risankizumab at PAS price) risankizumab remained cost-saving versus ustekinumab (at list price).
- Overall, the cost-comparison analysis demonstrates that the use of risankizumab over ustekinumab may provide cost-savings to the NHS in patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

B.4.1 Changes in service provision and management

As risankizumab shares a similar method of administration to ustekinumab, IV administration in the induction phase and SC administration in the maintenance phase, it is not anticipated that the introduction of risankizumab to clinical practice would require any changes to current service provision or management.

B.4.2 Cost-comparison analysis inputs and assumptions

As described in Section B.1, the target population for risankizumab is patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

In this population, risankizumab represents an alternative treatment option to ustekinumab which is considered the principal comparator within this cost-comparison analysis for the following reasons:

- Ustekinumab represents established UK clinical practice in the proposed target population. Additionally, feedback from UK clinical experts is that risankizumab would be considered as an alternative treatment to ustekinumab in the proposed target population
- Both treatments have a related mechanism of action of targeting ILs and both treatments inhibit IL-23. They also have a similar route of administration; IV in the induction phase and SC in the maintenance phase
- As described in Section B.3.9, a series of NMAs were conducted in an overall population of patients with moderately to severely active UC regardless of prior biologic therapy exposure and in the subgroups of patients both with/without prior exposure to biologic therapies. Results from these NMAs showed comparable efficacy and safety in terms of clinical remission, clinical response, endoscopic improvement, serious infections and serious AEs between risankizumab and ustekinumab

Therefore, a cost-comparison approach between the two treatments was deemed appropriate for this submission. The methodology and results of the cost-comparison analysis are presented below.

B.4.2.1 Features of the cost-comparison analysis

Population

The target population for risankizumab is patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

Intervention and comparators

The intervention is risankizumab, administered according to the dosing regimen in the draft SmPC (see Section B.4.2.2).[5] The comparator is ustekinumab, according to the dosing regimen in the ustekinumab SmPC (see Section B.4.2.2).[91]

Model structure

A cost-comparison model was developed in Microsoft Excel. The analysis included all relevant costs that would be expected to differ substantially between people receiving risankizumab and ustekinumab in the target patient population. As such, the cost-comparison analysis included drug acquisition costs and drug administration costs only.

Beyond drug acquisition costs and drug administration costs, all other costs, such as resource use/monitoring costs, adverse event costs and subsequent treatment costs are assumed to be equal between patients receiving risankizumab and patients receiving ustekinumab across all treatment years and were therefore not included within the cost-comparison analysis. This is because, inherent to the cost-comparison approach, no difference in health benefits is assumed between the two treatments.

The cost-comparison analysis was conducted in line with the NICE reference case and from an NHS/PSS perspective. A 10-year time horizon was used in the base case, in line with recent cost-comparison models in autoimmune inflammatory disorders submitted to NICE.[2, 3] Other time horizons were explored in scenario analyses. Discounting was not applied, as recommended by NICE in the user guide applicable to cost-comparison analyses.[7]

B.4.2.2 Intervention and comparator drug acquisition costs

Table 52 shows the key inputs, assumptions and acquisition costs included for risankizumab and ustekinumab within the model.

Table 52: Acquisition costs of the intervention and comparator technologies

	Risankizumab	Ustekinumab
Pharmaceutical formulation	**Induction:** Risankizumab is available as a 600 mg solution for IV infusion **Maintenance:** Risankizumab is available as a 180 mg and 360 mg SC injection	**Induction:** Ustekinumab is available as a 130 mg solution for IV infusion **Maintenance:** Ustekinumab is available as a 90 mg SC injection
(Anticipated) care setting	Secondary care	
Acquisition cost (excluding VAT) *	**Induction:** The list price of risankizumab 600 mg IV is £3,326.09 **Maintenance:** The list price of risankizumab 180 mg SC is [redacted] and of 360 mg SC is £3,326.09	**Induction:** The list price of ustekinumab 130 mg/26mL solution is £2,147.00 **Maintenance:** The list price of ustekinumab 90 mg SC is £2,147.00
Method of administration	**Induction:** IV **Maintenance:** SC	**Induction:** IV **Maintenance:** SC
Doses	**Induction:** The induction dose of risankizumab is 1200 mg (2 x 600 mg) administered IV at Week 0, Week 4, and Week 8, **Maintenance:** The maintenance dose is 180	**Induction:** The induction dose of ustekinumab at Week 0 is administered IV based on body weight: • ≤55 kg: 260 mg • >56 to ≤85 kg: 390 mg

	mg (standard dose) or 360 mg (dose escalation) SC at Week 12 then Q8W	• >85 kg: 520 mg **Maintenance:** The maintenance dose is 90 mg SC Q12W (standard dose) or 90 mg Q8W (dose escalation), starting from Week 8
Average length of a course of treatment	N/A. UC is a chronic disease; treatment is long-term or until the patient's clinician determines the treatment should be discontinued.	

Abbreviations: IV: intravenous; PAS: patient access scheme; SC: subcutaneous; VAT: value-added tax.

Drug acquisition costs were calculated for the whole induction duration and per year of maintenance treatment. Dosing regimens used to calculate the total drug cost were obtained from the SmPC for ustekinumab and the draft SmPC for risankizumab.[5, 91]

All drug acquisition unit costs were sourced from the British National Formulary (BNF).[11] As ustekinumab is a weight-based drug, the weights presented in Table 53 were used to calculate the number of vials needed to provide the required dose during induction.

Table 53: Weight distribution characteristics and corresponding ustekinumab induction doses

Weight	Proportion	Ustekinumab induction dose (IV)	Source
< 55kg*	[redacted]	260 mg	Baseline characteristics of the INSPIRE trial (bio-exposed population)
>55kg and ≤85kg*	[redacted]	390 mg	
>85kg*	[redacted]	520 mg	

Abbreviations: IV: intravenous.

Total maintenance costs were derived by calculating the cost for each treatment dosing regimen (either standard or escalated dose), and then applying the proportion of patients who were on the 'standard' or 'escalated' maintenance dose, respectively.

In the base case, 70% of patients receiving risankizumab were assumed to receive the standard (180 mg) dose in the maintenance phase, and 30% of patients were assumed to receive the escalated dose of 360 mg. For ustekinumab, feedback from clinical experts is that the proportion of patients requiring dose escalation with ustekinumab is now much higher and closer to 100% of patients; indeed, in the NICE evaluation for risankizumab in Crohn's disease, the proportion of patients receiving an escalated dose of ustekinumab was assumed to be 92.5%. Therefore, in the base case, 7.5% of patients receiving ustekinumab in the maintenance phase were assumed to receive the standard dose (90 mg Q12W), and 92.5% of patients were assumed to receive the escalated dose (90 mg Q8W).

Total drug acquisition costs for the induction and annual maintenance phases are presented in Table 54 and Table 55, respectively.

Table 54: Drug acquisition costs for the induction phase (risankizumab PAS price; ustekinumab list price)

Treatment	No. of units used during induction	Unit size	Unit price (£)	Total induction cost (£)
Risankizumab	3	600 mg	[redacted]	[redacted]
Ustekinumab†	[redacted]	130 mg	£2,147.00	£6,675.55

Footnotes: † Number of units based on the baseline characteristics of the INSPIRE bio-exposed population.

Table 55: Drug acquisition costs for the maintenance phase (risankizumab PAS price; ustekinumab list price)

Treatment	Maintenance phase dosage	Unit size	Unit price (£)	Total Year 1 maintenance cost (£)	Total Year 2+ maintenance cost (£)
Risankizumab	Standard: 180 mg Q8W (70%) Escalated: 360 mg Q8W (30%)	180 mg 360 mg	[redacted]	[redacted]	[redacted]
Ustekinumab	Standard: 90 mg Q12W (7.5%) Escalated: 90 mg Q8W (92.5%)	90 mg	£2,147.00	£12,559.95	£13,606.61

Abbreviations: Q8W: every 8 weeks; QD: once daily; SC: subcutaneous.

B.4.2.3 Intervention and comparator healthcare resource use and associated costs

An SLR was conducted on 27th June 2023 to identify studies reporting cost and resource use data in moderately to severely active UC. Full details of the methodology and results of the SLR are presented in Appendix G. In total, 208 publications reporting cost and resource use data were included in the SLR.

As described above, the costs considered in the base case cost-comparison analysis included drug acquisition costs and drug administration costs only. These costs were able to be sourced from NHS reference costs 2021/22 and the BNF (2023) and aligned with previous NICE evaluations (TA856,[32] TA828[33] and TA633[6]). As such, no costs were utilised from the cost and resource use data SLR.

Drug administration costs

In the induction phase, both risankizumab and ustekinumab are administered intravenously in an outpatient setting and were therefore costed as an outpatient visit. Consistent with NICE evaluation for ustekinumab (TA633), filgotinib (TA792), ozanimod (TA828) and mirikizumab (TA925), the costs for IV administration were calculated as the average of a consultant (£182.93) and a non-consultant led (£87.78), non-admitted, face-to-face, follow-up appointments (code WF01A) in gastroenterology.[6, 31, 33, 75] The unit costs were taken from the 2021/2022 NHS Reference Costs, and the cost per IV administration was estimated to be £135.36.[92]

In the maintenance phase, both risankizumab and ustekinumab are administered subcutaneously. Consistent with the approach taken in the NICE evaluation for ustekinumab (TA633), it was assumed that patients self-inject their medication and so there is no associated administration cost.[6]

Table 56 presents the number of administrations for risankizumab and ustekinumab during the induction and maintenance phase.

Table 56: Drug administrations for risankizumab and ustekinumab during the induction and maintenance phase

Treatment	Induction		Maintenance (Year 1)		Maintenance (Year 2+)	
	Number of administrations	Total administration costs	Number of administrations (per year)	Total administration costs	Number of administrations (per year)	Total administration costs
Risankizumab	3.00	£406.07	5.00	£0.00	6.50	£0.00
Ustekinumab	1.00	£135.36	5.85	£0.00	6.34	£0.00

Abbreviations: IV: intravenous.

B.4.2.4 Adverse reaction unit costs and resource use

Adverse events related to treatment were not included in the analysis, based on the NMA data (Section B.3.9) which demonstrated that the safety profiles of risankizumab and ustekinumab are broadly similar. Furthermore, the assumption of similar adverse event incidence across all treatments is in line with the assumption of similar efficacy and the overall cost-comparison approach.

B.4.2.5 Miscellaneous unit costs and resource use

All unit costs and resource use are detailed in the sections above; no additional unit costs or resources were considered in the cost-comparison model.

B.4.2.6 Clinical expert validation

Clinical validation

Clinical opinion was sought to gain feedback on the assumptions of the model. Feedback from UK clinical experts is that risankizumab would be considered as an alternative treatment to ustekinumab in the proposed target population. In addition, clinical expert feedback was also utilised to inform the dose escalation assumptions within the model.

Technical validation

In alignment with best practice, technical validation of the economic model was conducted by an independent expert health economist, not previously involved in the model conceptualisation or programming. Once fully developed, the model underwent independent quality control and technical validation processes which included checking of all model calculations including standalone formulae, equations and Excel macros programmed in visual basics for applications (VBA) for coding errors, inconsistencies, and the plausibility of inputs. The correct functioning of the scenario analyses was also reviewed, and two checklists (for technical and stress test checks), were completed to ensure that the model generated accurate results which were consistent with the input data.

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of the key model inputs and assumptions and any uncertainties in these is presented in Table 57.

Table 57: Key model assumptions

Assumption	Assumption and justification	Scenario analyses
Time horizon	A 10-year time horizon was adopted, in line with recent cost-comparison models in autoimmune inflammatory disorders submitted to NICE. It was also considered sufficiently long enough to capture all relevant differences in costs between risankizumab and ustekinumab.	To test the impact of the time horizon on the model results, scenario analyses adopting 5 year, 15 year and 20 year time horizons were conducted
Model perspective	In line with the NICE reference case, the model adopted the perspective of the NHS and PSS.	N/A
Discount rate	No discount rate was included as recommended by NICE in the user guide applicable to cost-comparison analyses.	N/A
All modelled treatments have the same efficacy	Inherent with the cost-comparison approach, all modelled treatments are assumed to have the same efficacy and safety. This is based on evidence from a series of NMAs conducted both in an overall population of patients with moderately to severely active UC regardless of prior therapy exposure and in patients who had prior exposure to biologic therapies (see Section B.3.9), which generally showed no statistically significant difference in efficacy or safety in terms of clinical remission, clinical response, endoscopic improvement, serious infections and serious AEs between risankizumab and ustekinumab.	N/A
Included costs	The model incorporated drug acquisition and drug administration costs for risankizumab and ustekinumab only, as these are the only costs assumed to differ substantially between the two treatments over the modelled time horizon. Adverse events related to treatment were not included based on the NMA data (Section B.3.9) which demonstrated that the safety profiles of risankizumab and ustekinumab are broadly similar, in line with the assumption of similar efficacy and the overall cost-comparison approach.	N/A
Dose escalation	In the base case, 70% of patients receiving risankizumab were assumed to receive the standard (180 mg) dose in the maintenance phase, and 30% of patients were assumed to receive the escalated dose of 360 mg. For ustekinumab, feedback from clinical experts is that the proportion of patients requiring dose escalation with ustekinumab is now much higher and closer to 100% of patients; indeed, in the NICE evaluation for risankizumab in Crohn's disease, the proportion of patients receiving an escalated dose of ustekinumab was assumed to be 92.5%. Therefore, in the	A scenario analysis was conducted to test the impact of these assumptions. The proportion of patients receiving standard dosing was assumed to be 50% for risankizumab and kept the same as the base case for ustekinumab (7.5%).

	base case, 7.5% of patients were assumed to receive the standard (90 mg Q12W) dose in the maintenance phase, and 92.5% of patients were assumed to receive the escalated dose of 90 mg Q8W.	
Extended induction	Consideration of extended induction was not included within the model as this is not explicitly specified in the SmPC for either therapy.	N/A
Vial sharing or wastage	Vial sharing or wastage was not considered within the model because it would not make a difference to the total number of vials required per patient; each ustekinumab weight-based dose in induction requires whole vials.	N/A

Abbreviations: AE: adverse event; N/A: not applicable; NICE: National Institute of Health and Care Excellence; NHS: National Health Service; NMA: network meta-analysis; PSS: Personal Social Services; Q8W: every 8 weeks; Q12W: every 12 weeks; SmPC: Summary of Product Characteristics; UC: ulcerative colitis.

B.4.3 Base case results

Base case results for the cost-comparison analysis of risankizumab (at PAS price) versus ustekinumab (at list price) are presented in Table 58.

Over the model time horizon of 10 years, risankizumab (at PAS price) was associated with cost savings versus ustekinumab (at list price) of [redacted] per person.

It should be noted that the net price of ustekinumab is confidential, which should be taken into account when interpreting the results of this analysis. However, the expectation is that when the net price for ustekinumab is considered, risankizumab remains a cost-saving option for patients with moderately to severely active UC.

Overall, the cost-comparison analysis demonstrated that the use of risankizumab over ustekinumab would provide cost-savings to the NHS in patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

B.4.4 Subgroup analysis

No economic subgroup analyses were conducted for this submission.

Table 58: Base case cost-comparison results (risankizumab PAS price; ustekinumab list price)

Treatment	Induction			Maintenance			Overall total costs[a]
	Drug acquisition costs	Drug administration costs	Total induction costs	Drug acquisition costs	Drug administration costs	Total maintenance costs	
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	£6,676	£135	£6,811	£135,019	£0	£135,019	£141,830
Incremental costs per patient (for risankizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Overall total costs over a 10 year time horizon.
Abbreviations: PAS: patient access scheme.

B.4.5 Sensitivity and scenario analyses

B.4.5.1 Scenario analyses

Scenario analyses were conducted to explore the impact of the base case cost-comparison analysis model inputs and assumptions. These scenario analyses are described in Table 59 and results of these scenario analyses are presented in Table 60 below.

Results from the scenario analyses show that risankizumab (at PAS price) remains cost-saving versus ustekinumab (at list price) in the majority of scenario analyses when alternative time horizons and assumptions relating to dose escalation were explored.

As for the base case, it should be noted that the net price of ustekinumab is confidential, which should be taken into account when interpreting the results of the scenario analyses. However, the expectation is that when the net price of ustekinumab is considered, risankizumab remains a cost-saving option for patients with moderately to severely active UC in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

Table 59: Scenario analyses

#	Model assumption	Base case	Scenario analysis
1	Time horizon	10 years	5 years
2			15 years
3			20 years
4	Dose escalation	Standard dosing for 70% of patients on risankizumab and 7.5% of patients on ustekinumab.	Standard dosing for 50% of patients on risankizumab and as per the base case for ustekinumab (7.5%)

Table 60: Results of scenario analyses (risankizumab PAS price; ustekinumab list price)

Scenario	Description	Risankizumab			Ustekinumab			Incremental costs per patient (for risankizumab)	
		Induction costs	Maintenance costs	Overall total costs[a]	Induction costs	Maintenance costs	Overall total costs[a]	Incremental costs	% Δ from base case
-	Base case	[redacted]	[redacted]	[redacted]	£6,811	£135,019	£141,830	[redacted]	[redacted]
1	Time horizon (5 years)	[redacted]	[redacted]	[redacted]	£6,811	£66,986	£73,797	[redacted]	[redacted]
2	Time horizon (15 years)	[redacted]	[redacted]	[redacted]	£6,811	£203,053	£209,863	[redacted]	[redacted]
3	Time horizon (20 years)	[redacted]	[redacted]	[redacted]	£6,811	£271,086	£277,896	[redacted]	[redacted]
4	Standard dose risankizumab (50%)	[redacted]	[redacted]	[redacted]	£6,811	£135,019	£141,830	[redacted]	[redacted]

[a] Overall total costs over a 10 year time horizon.
Abbreviations: PAS: patient access scheme.

B.4.6 Interpretation and conclusions of economic evidence

Risankizumab is an effective treatment option in patients with moderately to severely active UC with the pivotal Phase III studies INSPIRE and COMMAND meeting all primary efficacy endpoints. Improvements compared to placebo were also demonstrated in endoscopic improvement and endoscopic remission, which represent important endpoints to both patients and clinicians.

As shown by the NMAs presented in Section B.3.9, risankizumab has comparable health benefits in terms of efficacy and safety to ustekinumab for the treatment of moderate to severe UC. As confirmed by clinical expert feedback, ustekinumab is the most relevant comparator to risankizumab as it represents established clinical practice in the proposed target population, both treatments have a related mechanism of action of targeting ILs and inhibiting IL-23, and both treatments have a similar mode of administration.

The cost-comparison analysis further demonstrates that risankizumab (at PAS price) is cost-saving when compared to ustekinumab at list price. A number of scenario analyses demonstrate the robustness of the base case analysis, confirming risankizumab as a cost-saving option in this patient population. The Company acknowledges that the net price of ustekinumab is confidential, which should be taken into account when interpreting the results of this analysis. However, the expectation is that when the net price of ustekinumab is considered, risankizumab remains a cost-saving option for patients with moderately to severely active UC.

B.5 References

1. Medicines and Healthcare products Regulatory Agency. Risankizumab. Available at https://products.mhra.gov.uk/search/?search=risankizumab&page=1 [accessed 13 October 2023]
2. National Institute for Health and Care Excellence. Risankizumab for treating moderate to severe plaque psoriasis [TA596]. 2019. Available at https://www.nice.org.uk/guidance/ta596/resources/risankizumab-for-treating-moderate-to-severe-plaque-psoriasis-pdf-82607267096773 [accessed June 2022].
3. National Institute for Health and Care Excellence. Risankizumab for treating active psoriatic arthritis after inadequate response to DMARDs [ID1399]. Final appraisal document. 2022. Available at https://www.nice.org.uk/guidance/gid-ta10819/documents/final-appraisal-determination-document [accessed June 2022].
4. National Institute for Health and Care Excellence (NICE). Risankizumab for previously treated moderately to severly active Crohn's disease (TA888). Available at https://www.nice.org.uk/guidance/TA888/history [last accessed 23rd October 2023].
5. AbbVie Data on File. 2023. Draft Risankizumab SmPC.
6. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active ulcerative colitis [TA633] Technology appraisal guidance. London, UK: National Institute for Health and Care Excellence. 2020. Available at https://www.nice.org.uk/guidance/TA633 [accessed 16th October 2023].
7. National Institute for Health and Care Excellence (NICE). User guide for company evidence submission template. Fast track cost-comparison case. Available at https://www.nice.org.uk/process/pmg32/resources/user-guide-for-the-cost-comparison-company-evidence-submission-template-pdf-72286772526277 [accessed 28 June 2023].
8. Fitch E, Harper E, Skorcheva I, et al. Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. Curr Rheumatol Rep 2007;9:461-467.
9. Feng T, Qin H, Wang L, et al. Th17 cells induce colitis and promote Th1 cell responses through IL-17 induction of innate IL-12 and IL-23 production. J Immunol 2011;186:6313-6318.
10. Pang Y, Khatri A, Suleiman AA, et al. Clinical Pharmacokinetics and Pharmacodynamics of Risankizumab in Psoriasis Patients. Clinical Pharmacokinetics 2020;59:311-326.
11. British National Formulary (BNF). Risankizumab Medicinal Forms. Available at https://bnf.nice.org.uk/drugs/risankizumab/medicinal-forms/ [accessed 28th June 2023].
12. Crohn's and colitis UK. Ulcerative colitis. Available at https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/understanding-crohns-and-colitis/ulcerative-colitis [accessed 28th June 2023].
13. Ko CW, Singh S, Feuerstein JD, et al. AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterology 2019;156:748-764.
14. Ordás I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012;380:1606-1619.
15. Perler BK, Ungaro R, Baird G, et al. Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. BMC Gastroenterol 2019;19:47.
16. Revés J, Ungaro RC, Torres J. Unmet needs in inflammatory bowel disease. Curr Res Pharmacol Drug Discov 2021;2:100070.
17. Szende, A. Janssen, B. Cabases, J. 2014. Self-Reported Population Health: An International Perspective based on EQ-5D. Dordrecht (NL): Springer.

18. Piercy J, Ozbay A, Roughley A, et al. Tu1256 Comparison of Ulcerative Colitis With Crohn's Disease From the Perspective of Patient Burden. Gastroenterology 2015;148:S-839.
19. Devlen J, Beusterien K, Yen L, et al. The burden of inflammatory bowel disease: a patient-reported qualitative analysis and development of a conceptual model. Inflamm Bowel Dis 2014;20:545-552.
20. King D, Reulen RC, Thomas T, et al. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. Aliment Pharmacol Ther 2020;51:922-934.
21. National Institute for Health and Care Excellence (NICE). NG130. Ulcerative colitis: management. Available at https://www.nice.org.uk/guidance/ng130/resources/ulcerative-colitis-management-pdf-66141712632517 [accessed 3rd July 2023].
22. Hibi T, Ishibashi T, Ikenoue Y, et al. Ulcerative Colitis: Disease Burden, Impact on Daily Life, and Reluctance to Consult Medical Professionals: Results from a Japanese Internet Survey. Inflamm Intest Dis 2020;5:27-35.
23. Barreiro-de Acosta M, Vallejo N, de la Iglesia D, et al. Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 vs 1): A Longitudinal Cohort Study. Journal of Crohn's and Colitis 2015;10:13-19.
24. Cohen RD, Yu AP, Wu EQ, et al. Systematic review: the costs of ulcerative colitis in Western countries. Aliment Pharmacol Ther 2010;31:693-707.
25. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1-s106.
26. Raine T, Bonovas S, Burisch J, et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. Journal of Crohn's and Colitis 2021;16:2-17.
27. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1-s106.
28. National Institute for Health and Care Excellence. Tofacitinib for moderately to severly active ulcerative colitis. TA547. Available at https://www.nice.org.uk/guidance/ta547/resources/tofacitinib-for-moderately-to-severely-active-ulcerative-colitis-pdf-82606966445509 [accessed 3rd July 2023].
29. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active ulcerative colitis. TA342. Available at https://www.nice.org.uk/guidance/ta342/resources/vedolizumab-for-treating-moderately-to-severely-active-ulcerative-colitis-pdf-82602604482757 [accessed 3rd July 2023].
30. National Institute for Health and Care Excellence. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. TA329. Available at https://www.nice.org.uk/guidance/ta329/resources/infliximab-adalimumab-and-golimumab-for-treating-moderately-to-severely-active-ulcerative-colitis-after-the-failure-of-conventional-therapy-pdf-82602495307717 [accessed 3rd July 2023].
31. National Institute for Health and Care Excellence. Filgotinib for treating moderately to severly active ulcerative colitis. TA792. Available at https://www.nice.org.uk/guidance/TA792 [accessed 3rd July 2023].
32. National Institute for Health and Care Excellence. Upadacitinib for treating moderately to severly active ulcerative colitis. TA856. Available at https://www.nice.org.uk/guidance/TA856 [accessed 3rd July 2023].
33. National Institute for Health and Care Excellence. Ozanimod for treating moderately to severely active ulcerative colitis. TA828. Available at https://www.nice.org.uk/guidance/ta828 [accessed 3rd July 2023].

34. Adult Drugs Treatment Pathway for Moderately to Severey Active Ulcerative Colitis (UC)-based on NICE TAs. NHS Herts Valleys. Available at https://www.enhertsccg.nhs.uk/sites/default/files/content_files/Prescribing/Local_Decisions/Gastro_Intestinal_System/Ulcerative%20colitis%20in%20adults%20%E2%80%93%20Drug%20treatment%20pathway%20for%20moderately%20to%20severely%20active%20ulcerative%20colitis.pdf. [accessed 3rd July 2023].
35. Torres J, Billioud V, Sachar DB, et al. Ulcerative colitis as a progressive disease: the forgotten evidence. Inflamm Bowel Dis 2012;18:1356-63.
36. Gordon JP, McEwan PC, Maguire A, et al. 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;27:804-12.
37. Rogler G. Chronic ulcerative colitis and colorectal cancer. Cancer Lett 2014;345:235-41.
38. Grieco MJ, Remzi FH. Surgical Management of Ulcerative Colitis. Gastroenterol Clin North Am 2020;49:753-768.
39. M'Koma AE. Inflammatory Bowel Disease: Clinical Diagnosis and Surgical Treatment-Overview. Medicina (Kaunas) 2022;58.
40. Harvard Health Publishing. Ulcerative Colitis and Crohn's disease. Available at https://www.health.harvard.edu/digestive-health/ulcerative-colitis-and-crohns-disease. [accessed 11th July 2023].
41. Adams SM, Bornemann PH. Ulcerative colitis. Am Fam Physician 2013;87:699-705.
42. Office for National Statistics. ONS. Principal projection - England population in age groups. Available at https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/tablea24principalprojectionenglandpopulationinagegroups [accessed 28th June 2023].
43. National Institute for Health and Care Excellence. Ulcerative colitis. 2020. Available at https://cks.nice.org.uk/topics/ulcerative-colitis/background-information/prevalence/. [accessed 28th June 2023].
44. Pasvol TJ, Horsfall L, Bloom S, et al. Incidence and prevalence of inflammatory bowel disease in UK primary care: a population-based cohort study. BMJ Open 2020;10:e036584.
45. Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clin Gastroenterol Hepatol 2016;14:348-354.e17.
46. Pabla BS, Schwartz DA. Assessing Severity of Disease in Patients with Ulcerative Colitis. Gastroenterol Clin North Am 2020;49:671-688.
47. Sandborn WJ, Sands BE, Vermeire S, et al. Modified Mayo score versus Mayo score for evaluation of treatment efficacy in patients with ulcerative colitis: data from the tofacitinib OCTAVE program. Therap Adv Gastroenterol 2022;15:17562848221136331.
48. Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the mayo score to assess clinical response in Ulcerative Colitis. Inflammatory Bowel Diseases 2008;14:1660-1666.
49. Alexakis C, Davies G, Stephens J, et al. Perspectives and attitudes of young patients with inflammatory bowel disease: symptoms, burden of disease and communication with their healthcare professionals. Frontline Gastroenterol 2014;5:197-202.
50. Liverani E, Scaioli E, Digby RJ, et al. How to predict clinical relapse in inflammatory bowel disease patients. World J Gastroenterol 2016;22:1017-33.
51. National Institute for Health and Care Excellence (NICE). Quality standards and indicators - Briefing paper. Inflammatory bowel disease. 2014. Available at

https://www.nice.org.uk/guidance/qs81/documents/inflammatory-bowel-disease-briefing-paper2 [accessed 29th June 2023].
52. healthline. All About Ulcerative Colitis Symptoms. Available at https://www.healthline.com/health/ulcerative-colitis/ulcerative-colitis-symptoms [accessed 29th June 2023].
53. National Institute for Health and Care Excellence (NICE). What are the extra-intestinal manifestations? 2020. Available at https://cks.nice.org.uk/topics/ulcerative-colitis/background-information/extra-intestinal-manifestations/ [accessed 29th June 2023].
54. Marten K, Fend F, Hautmann H, et al. Case report: Fatal acute exacerbation of usual interstitial pneumonia in ulcerative colitis. Br J Radiol 2005;78:762-6.
55. Sange AH, Srinivas N, Sarnaik MK, et al. Extra-Intestinal Manifestations of Inflammatory Bowel Disease. Cureus 2021;13:e17187.
56. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol 2011;106:110-9.
57. Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal Manifestations of Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;21:1982-92.
58. Burisch J, Ungaro R, Vind I, et al. Proximal Disease Extension in Patients With Limited Ulcerative Colitis: A Danish Population-based Inception Cohort. J Crohns Colitis 2017;11:1200-1204.
59. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clinical Gastroenterology and Hepatology : the official clinical practice journal of the American Gastroenterological Association 2012;10 6:639-45.
60. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004;126:451-9.
61. Rubin DT, Sninsky C, Siegmund B, et al. International Perspectives on Management of Inflammatory Bowel Disease: Opinion Differences and Similarities Between Patients and Physicians From the IBD GAPPS Survey. Inflamm Bowel Dis 2021;27:1942-1953.
62. Larsson K, Lööf L, Nordin K. Stress, coping and support needs of patients with ulcerative colitis or Crohn's disease: a qualitative descriptive study. J Clin Nurs 2017;26:648-657.
63. Lönnfors S, Vermeire S, Greco M, et al. IBD and health-related quality of life -- discovering the true impact. J Crohns Colitis 2014;8:1281-6.
64. Armuzzi A, Liguori G. Quality of life in patients with moderate to severe ulcerative colitis and the impact of treatment: A narrative review. Digestive and Liver Disease 2021;53:803-808.
65. Vaizey CJ, Gibson PR, Black CM, et al. Disease status, patient quality of life and healthcare resource use for ulcerative colitis in the UK: an observational study. Frontline Gastroenterol 2014;5:183-189.
66. Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. Frontline Gastroenterol 2015;6:169-174.
67. Van Assche G, Peyrin-Biroulet L, Sturm A, et al. Burden of disease and patient-reported outcomes in patients with moderate to severe ulcerative colitis in the last 12 months - Multicenter European cohort study. Dig Liver Dis 2016;48:592-600.
68. Sammut J, Scerri J, Xuereb RB. The lived experience of adults with ulcerative colitis. J Clin Nurs 2015;24:2659-67.
69. Shah SC, Colombel JF, Sands BE, et al. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2016;14:1245-1255.e8.

70. Boal Carvalho P, Dias de Castro F, Rosa B, et al. Mucosal Healing in Ulcerative Colitis – When Zero is Better. Journal of Crohn's and Colitis 2015;10:20-25.
71. Feuerstein JD, Moss AC, Farraye FA. Ulcerative Colitis. Mayo Clin Proc 2019;94:1357-1373.
72. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. J Crohns Colitis 2007;1:10-20.
73. Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohns Colitis 2017;11:649-670.
74. Selinger CP, Parkes GC, Bassi A, et al. Assessment of steroid use as a key performance indicator in inflammatory bowel disease-analysis of data from 2385 UK patients. Aliment Pharmacol Ther 2019;50:1009-1018.
75. National Institute for Health and Care Excellence (NICE). Mirikizumab for treating moderately to severly active ulcerative colitis. Technology appraisal guidance [TA925] Available at: https://www.nice.org.uk/guidance/TA925 [last accessed 25th October 2023].
76. Kühn F, Klar E. Surgical Principles in the Treatment of Ulcerative Colitis. Viszeralmedizin 2015;31:246 - 250.
77. Cima RR, Pemberton JH. Medical and surgical management of chronic ulcerative colitis. Arch Surg 2005;140:300-10.
78. Manninen P, Karvonen A-L, Huhtala H, et al. Mortality in ulcerative colitis and Crohn's disease. A population-based study in Finland. Journal of Crohn's and Colitis 2012;6:524-528.
79. Winther KV, Jess T, Langholz E, et al. Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. Gastroenterology 2003;125:1576-82.
80. Woehl A, Hawthorne A, McEwan P. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis, In Gut, British Med Assoc House, Tavistock Square, London WC1H 9JR, England: BMJ Publishing Group, 2008.
81. Arseneau KO, Sultan S, Provenzale DT, et al. Do patient preferences influence decisions on treatment for patients with steroid-refractory ulcerative colitis? Clinical Gastroenterology and Hepatology 2006;4:1135-1142.
82. Tsai H, Punekar Y, Morris J, et al. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Alimentary Pharmacology & Therapeutics 2008;28:1230–1239.
83. Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis. N Engl J Med 2016;374:1754-62.
84. AbbVie. Data on file. INSPIRE CSR.
85. AbbVie. Data on file. COMMAND CSR.
86. Singh S, Kroe-Barrett RR, Canada KA, et al. Selective targeting of the IL23 pathway: Generation and characterization of a novel high-affinity humanized anti-IL23A antibody. MAbs 2015;7:778-91.
87. Cope S, Zhang J, Saletan S, et al. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer. BMC Medicine 2014;12:1–17.
88. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011.

89. Colombel JF, D'Haens G, Lee WJ, et al. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. J Crohns Colitis 2020;14:254-266.
90. Pineton de Chambrun G, Blanc P, Peyrin-Biroulet L. Current evidence supporting mucosal healing and deep remission as important treatment goals for inflammatory bowel disease. Expert Review of Gastroenterology & Hepatology 2016;10:915–927.
91. European Medicines Agency (EMA). Summary of product characteristics (SmPC). Stelara (ustekinumab) Available at https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf [last accessed 26th October 2023].
92. National Health Service (NHS). 2021/22 National Cost Collection 2021/22 Index. 2023. Available at https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication [accessed 16 August 2023].

B.6 Appendices

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Cost and healthcare resource identification, measurement and valuation
- Appendix H: Price details of treatments included in the submission
- Appendix I: Checklist of confidential information
- Appendix J: INSPIRE and COMMAND additional methodology and results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Risankizumab for people with previously treated moderately to severely active ulcerative colitis [ID6209]

Summary of Information for Patients (SIP)

November 2023

File name	Version	Contains confidential information	Date
ID6209_Risankizumab in UC_NICE SIP_NoCON	Final	No	3rd November 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Risankizumab

Brand name: SKYRIZI®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

Risankizumab is planned to be used in adults (people aged 18 or over) with moderately to severely active ulcerative colitis (UC) in whom tumour necrosis factor (TNF)-alpha inhibitors are deemed unsuitable; or where prior biological treatment (a group of advanced therapies) is not tolerated or not working well enough.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Risankizumab is currently pending marketing authorisation (approval) by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK for treating UC. The anticipated dates for approval are confidential and are presented in Section B.1.2 of the manufacturer submission (Document B).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie collaborates with a range of stakeholders with an interest in inflammatory bowel disease (IBD). This includes collaboration with patient groups to support improvements in health and care for individuals with IBD.

Where this includes any Transfer of Value, for example to support the development of information for people with UC and their families, this is declared on an annual basis and is available at: https://www.abbvie.co.uk/our-company/policies-disclosures.html.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is UC?

UC is a form of inflammatory bowel disease (IBD) where the large bowel (also known as the colon) and the rectum become swollen, inflamed, and affected by ulcers.[1, 2] This damage to the large bowel and rectum leads to highly debilitating symptoms that include diarrhoea (which may contain blood, mucus or pus), bowel urgency (suddenly needing to go to the toilet) and varying degrees of abdominal pain.[2] UC is a lifelong (chronic) condition that is associated with flare-ups (also known as relapses) where symptoms will return after periods of improvement.

Whilst the exact cause of UC is unknown, the damage to the large bowel is caused by a chronic and inappropriate response from the body's immune system.

A person's susceptibility to UC is thought to be increased by a number of factors, including certain genetic mutations, the environment, and bacteria in the gut.[1] Hundreds of genetic mutations have been identified as affecting the risk of developing UC. Many of these genetic mutations affect the immune system, which may alter the immune system's response to bacteria in the gut, leading to inflammation in the large bowel. Environmental factors that may increase the risk of developing UC include stress, diet and some viruses. Additionally, people with UC may also have fewer 'helpful' bacteria, viruses and fungi that live in the gut which can increase their susceptibility to the condition.

What are the signs and symptoms of UC?

For people with UC, the condition can be changeable and unpredictable. People may go for weeks or months with mild symptoms, or periods of time with no symptoms (also known as 'remission') followed by flare-ups (also known as 'relapse'). These flare-ups can vary in length

(lasting a few days to several months), symptoms and severity. This can depend on how much of the large bowel and/or rectum is inflamed and how severe the inflammation is.[1]

As described above, people with UC commonly report having recurring diarrhoea (which may contain blood, mucus or pus), bowel urgency (suddenly needing to go to the toilet) and varying degrees of abdominal pain.[2] In addition, some people with UC may experience symptoms elsewhere in their body (these are called extra-intestinal symptoms) which can include: painful and swollen joints (also called pauci-articular arthritis), mouth ulcers and bone problems (such as osteopenia or osteoporosis).

How many people get UC?

Around 570 per 100,000 adults are currently living with UC in England, which translates to approximately ~250,000 people.[3] While UC most commonly presents in adolescence and early adulthood (most people are diagnosed between 17–40 years of age), the condition can occur at any age.[4]

What is the impact of UC (burden of the condition)?

The physical impact of the intestinal and extra-intestinal symptoms of UC can result in debilitating pain and intense discomfort. This can prevent people with UC from carrying out everyday tasks, such as their ability to work, gain an education or carry out parenting tasks.[5]

In addition, symptoms such as bowel urgency, abdominal pain and diarrhoea can have a significant emotional impact on people with UC. For example, fear of losing control of bowel movements can mean individuals struggle to attend social events. This can increase isolation and a sense of loneliness, worsening the impact that UC has on people's quality of life.[6] As highlighted above, UC is most commonly diagnosed before the age of 30,[1] meaning that people can live with these negative impacts of the condition for a significant proportion of their life.

As there is no cure for UC, people may worry about how the condition will affect their future health and lifestyle. This further increases the emotional burden and impact of UC on people's quality of life.

What is the economic burden of UC (cost of the condition to the NHS and society)?

People with UC often require ongoing medical care to treat their condition and manage their symptoms. As UC is commonly diagnosed at a young age,[1] it can negatively affect a person's work life during their most productive years as people may be forced to take time off from work or reduce working hours due to symptoms of the condition [7, 8] Collectively, the indirect (societal) and direct (healthcare) costs associated with UC represent a significant economic burden to people, the National Health Service (NHS), and society.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
A diagnosis of UC is often made based on a combination of several factors. This includes clinical assessments (observation of the signs and symptoms of UC), laboratory testing (commonly of a stool or blood sample) and visual inspection of the gastrointestinal tract

(involving imaging such as an endoscopy, where a small camera is inserted to visualise the large bowel/rectum).[9] During imaging, a small sample of tissue can be removed from the bowel and tested to confirm a diagnosis of UC; this is called a biopsy.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for UC?

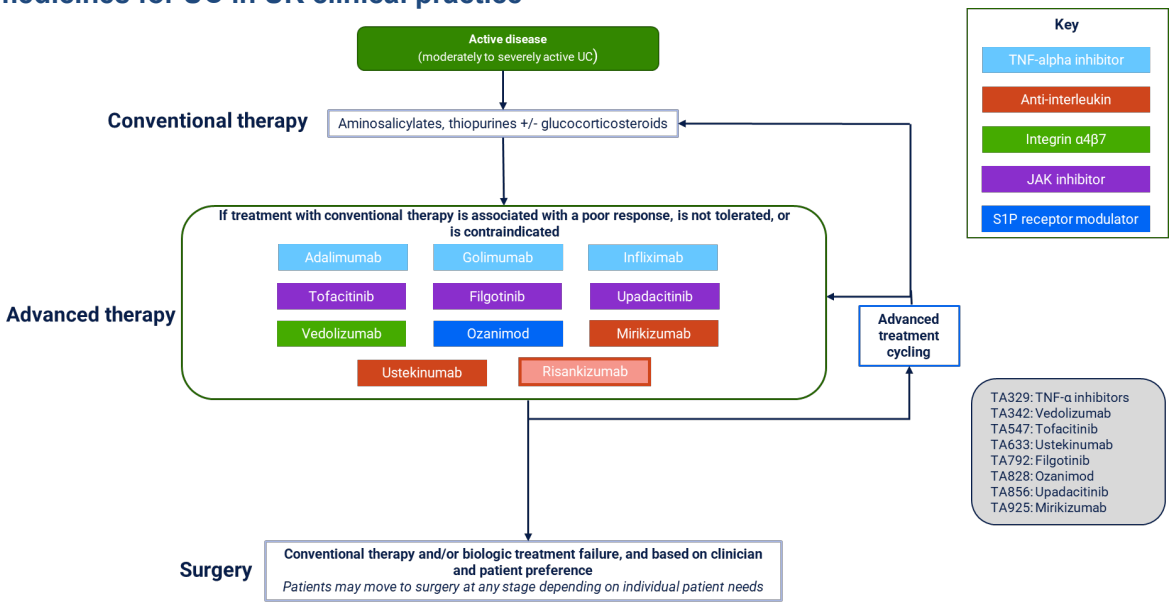
In England and Wales, the treatment and management of UC is guided by advice from NICE.[10] Generally, people with UC are treated in a stepwise manner where medication is changed when a person does not respond to, or stops responding to, their current treatment. The main aims of treatment in UC are to achieve and then maintain remission (where no symptoms remain) or response (where symptoms are still present but improved). In addition, a key aim of treatment in UC is to achieve and maintain healing of the lining of the large bowel which is observed via endoscopy. This is called 'mucosal healing' and is an increasingly important treatment goal in UC as it is associated with better long-term outcomes for people with UC including reduced need for hospitalisation for their condition and/or surgery (see below).[11]

The Mayo scoring system may be used by healthcare professionals to assess remission or response and to determine the severity of UC. Various factors, such as the frequency that a person needs to go to the toilet and rectal bleeding, are scored on a scale of 0–3 up to a maximum score of 12. Higher scores correspond to more severe disease.[12]

Initially, people with moderately to severely active UC are treated with therapies such as immunomodulators and corticosteroids, which are collectively referred to as 'conventional therapies'. These treatments alter the functioning of the immune system as a whole, rather than targeting the inflammation of UC specifically.[1, 13, 14] If treatment with conventional therapy is not suitable, or if treatment with conventional therapy is unable to control the condition and symptoms, people will go on to receive different treatments, called advanced therapies.[1, 13, 14] Advanced therapies act by working on specific targets within the immune system that are thought to contribute to the chronic and inappropriate inflammatory response observed in UC. By acting on these specific targets, treatment with advanced therapies helps to reduce inflammation within the large bowel and rectum, which leads to a reduction in bowel damage and a reduction in the associated debilitating symptoms.

As shown in Figure 1, there are several types of advanced therapy and people with UC may need to try a range of treatments to find one which works for them.

Figure 1: Anticipated availability of risankizumab compared with currently available medicines for UC in UK clinical practice



Limitations of current treatment options and unmet need

Despite several treatments being available for moderately to severely active UC, some people cannot tolerate certain treatments and in others, the treatments do not work well enough or the initial response to treatment gradually wears off over time and flare-ups return.

For individuals whose UC still remains uncontrolled after trying treatment with different advanced therapies, or for some individuals who elect to take it, surgery is a treatment option. This involves a colectomy (permanently removing the large bowel), and modifying the small intestine to pass waste products out of the individual's body via a stoma (waste bag) instead of via the large bowel.[13, 15] Approximately 20–30% of people will eventually require surgery.[16]

As such, there remains an unmet need for a new treatment option to be made available for people with moderately to severely active UC that works well and has a tolerable safety profile, and can help to reduce the number of people that experience long-term complications and may eventually require surgery.

Comparators to risankizumab

Whilst there are several treatments available for people with moderately to severely active UC, risankizumab is likely to be used as an alternative treatment option to ustekinumab, which is another advanced therapy that is recommended for use by NICE.[17] Risankizumab and ustekinumab both work by targeting interleukins in the body, which are key drivers of the inflammatory response in UC. Both treatments also have the same mode of administration.

This submission therefore compares risankizumab to ustekinumab only.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The impact of UC, as reported by people with UC

In 2021, a global survey of 2,100 people with UC was carried out. The key findings showed that for people with moderately to severely active UC, 84% of people felt UC was mentally exhausting and 65% of people felt that they spend more time in the bathroom than anywhere else (visiting the bathroom an average of 10 times a day on their worst days).[18] Additionally, the most important aspects of UC management were found to be the ability to perform daily activities (59%), avoidance of toilet accidents (55%) and the ability to control pain (53%).

Preference for treatment objectives

An individual preference study carried out in 2017 found that people with UC identified the most important treatment goals as improving quality of life (40.2%) and completely resolving symptoms (33.3%).[19] Furthermore, symptoms that individuals considered to be most important to control were abdominal pain (23.1%) and bowel movement urgency (17.1%). Finally, a survey of doctors and people with UC also found that improving quality of life and preventing disease progression were important goals for people with UC.[20]

Unmet need and the value of risankizumab

The above studies show that there is an unmet need for an effective treatment option in UC that is able to improve symptoms and has manageable side effects. The efficacy (how well it works) and safety (what side effects the treatment might have) of risankizumab, the new treatment being evaluated in this submission, were assessed in two large clinical trials called INSPIRE and COMMAND.

The results showing how well risankizumab works in people with UC are summarised below in Section 3d.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Risankizumab belongs to a class of medicines called monoclonal antibodies. Monoclonal antibodies are proteins that have been engineered to recognise and bind specifically to other proteins in the body. Risankizumab is a type of monoclonal antibody which specifically targets a protein called interleukin-23 (IL-23). IL-23 has a key role in driving the inflammation of the lining of the large bowel and rectum which causes the bowel damage and associated symptoms of UC. By inhibiting IL-23 (binding to IL-23 and blocking the actions of IL-23), risankizumab reduces inflammation, which leads to reduced symptoms and damage to the large bowel and rectum for people with UC.[21] Despite several treatments being available for UC, some people cannot tolerate certain treatments and in others, the treatments do not work well enough or the initial response to treatment gradually wears off over time and flare-ups return. As such, there remains an unmet need for a new treatment option to be made available for people with moderately to severely active UC that works well and has a tolerable safety profile.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Risankizumab is not intended to be used with any other treatment for UC.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
How is risankizumab taken? There are two phases in which risankizumab is taken: the induction phase, when individuals first start to receive it, and the maintenance phase, which is a longer-term phase to maintain disease control.

Induction phase: To begin to bring the flare-ups of UC under control, the first three doses of risankizumab are given intravenously (through a drip into a vein); each dose contains 1200 mg of risankizumab and is given every four weeks at Week 0, Week 4 and Week 8. After completion of the induction phase, if a doctor concludes there has been a good enough clinical response to the induction treatment, people will transition to receive maintenance dosing.

Maintenance phase: After completion of the induction phase, risankizumab is injected subcutaneously (under the skin) every 8 weeks to maintain disease control. This injection contains a dose of 180 mg or 360 mg. Your doctor will decide which dose is best for you. The injections are delivered via an on-body injection device, which can be placed on either the thigh or abdomen for the duration of the injection.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Table 1 summarises the two key clinical trials which have studied people with moderately to severely active UC being treated with risankizumab. These clinical trials are called INSPIRE and COMMAND. INSPIRE assessed treatment with risankizumab in the induction phase and COMMAND assessed treatment with risankizumab in the maintenance phase.

The two trials are Phase III randomised, double-blind, placebo-controlled, multicentre studies which are made up of sub-studies. Both the trials and sub-studies are explained in more detail below.

Table 1. Trials investigating risankizumab

Clinical trial name and number	**INSPIRE** NCT03398148	**COMMAND** NCT03398135
Location	Asia-Pacific, Europe, North America, South Africa, South America	Asia-Pacific, Europe, North America, South Africa, South America
Number of individuals included	1,558	1,242
Trial completion date	May 2023	May 2024 (estimate)
Key inclusion criteria	The trial included individuals that: • Aged 18–80 years of age (inclusive) or age 16–18 years of age where permissible • Had a confirmed diagnosis of UC for at least 3 months prior to baseline • Had active UC with an Adapted Mayo score of 5 to 9 points and an endoscopic subscore of 2 to 3 • Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies or tofacitinib	The trial included individuals that: • Had completed INSPIRE • Had achieved a clinical response, defined as a decrease from baseline of induction study of Adapted Mayo score ≥2 points and ≥30%, plus a decrease in RBS≥1 or an absolute RBS≤1
Key exclusion criteria	The trial excluded individuals that were: • Had been diagnosed with Crohn's disease, IBD-unclassified or a history of radiation colitis or ischemic colitis	The trial excluded: • if high grade colonic dysplasia or colon cancer were discovered at the endoscopy performed at the final visit of INSPIRE

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Key results for the INSPIRE (induction) study

The key outcome of the INSPIRE induction trial was the proportion of people who achieved clinical remission after 12 weeks of treatment with risankizumab compared to placebo.[22] Clinical remission was assessed based on an adapted version of the Mayo scoring system. The results found that more than three times as many people receiving risankizumab achieved clinical remission (a tough to achieve treatment goal where people experience only low levels of disease activity) at Week 12 than those receiving placebo. Improvement was also seen in the proportion of people who achieved clinical response (a substantial improvement in their symptoms) for people receiving risankizumab compared to placebo.[22] Statistical tests showed that these results were statistically significant (which means that they are very unlikely to have happened due to chance, and much more likely to have happened due to receiving treatment with risankizumab) and indicate that risankizumab was more effective than placebo at enabling people to achieve clinical remission and clinical response.[22] These results were broadly consistent regardless of whether people had previously received other advanced therapies before enrolment to the INSPIRE trial.[22]

Key results for the COMMAND (maintenance) study

People who achieved a clinical response to risankizumab in the INSPIRE trial went on to receive maintenance therapy in the COMMAND trial. There were two maintenance doses investigated: 180 mg and 360 mg.[23] The key outcome of the COMMAND trial was the proportion of people who achieved clinical remission after 52 weeks in people who responded to 12 weeks of risankizumab induction dosing in the INSPIRE trial. Similar to the results observed in the INSPIRE trial, the results of the COMMAND trial showed a greater proportion of people achieved clinical remission if they were treated with risankizumab 180 mg or risankizumab 360 mg, compared with placebo, and this result was statistically significant.[23]

Indirect evidence for risankizumab in UC

As discussed in Section 2c, people with moderately to severely active UC in the UK currently have access to other advanced therapy options, with treatment decisions made based on factors such as how well they have responded to other treatments in the past, and whether there are any medical reasons that would make them unsuitable to receive certain treatment options.

As described above, it is anticipated that risankizumab will be used as an alternative treatment option to ustekinumab, which also targets interleukins in the body.

This submission therefore compares risankizumab to ustekinumab only. However, no clinical trials have been conducted that directly compare both risankizumab and ustekinumab. The key risankizumab trials described above, INSPIRE and COMMAND, directly compared risankizumab to placebo only. Therefore, a statistical analysis called an indirect treatment comparison was done to compare risankizumab to ustekinumab ‘indirectly’. This is a common approach in the evaluations of new treatments. This statistical analysis is explained in further detail in Document B, Section B.3.9.

Risankizumab compared to ustekinumab

Overall, compared to ustekinumab, the indirect treatment comparison (also called a network meta-analysis or NMA) showed that risankizumab was similarly effective in the achievement and maintenance of clinical response and clinical remission, and is a well-tolerated treatment option. These analyses are associated with some limitations since the results are estimations only. In addition, factors such as differences between the populations recruited to the

risankizumab and ustekinumab trials being indirectly compared are likely to introduce a degree of uncertainty in the estimates produced.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Risankizumab is associated with improvements in quality of life measures

The INSPIRE and COMMAND trials measured how people's quality of life changed after taking risankizumab or placebo. Quality of life was measured using questionnaires at Week 12 of the INSPIRE trial and at Week 52 of the COMMAND trial. The questionnaires used were called the Inflammatory Bowel Disease Questionnaire (IBDQ), the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) and the European Quality of Life 5-Dimension 5 Level (ED-5D-5L). The questionnaires asked individuals about different aspects of their daily life and asked them to quantify on various scales the extent to which UC impairs these aspects of daily living. In both the INSPIRE and COMMAND trials, people receiving risankizumab showed statistically significant improvements compared with placebo on the IBDQ and FACIT-Fatigue scales (which means that they are very unlikely to have happened due to chance, and much more likely to have happened due to receiving treatment with risankizumab).

Risankizumab is associated with improvements in key symptoms

At Week 12 of the INSPIRE study, people receiving risankizumab showed statistically significant improvements compared with placebo in bowel urgency, abdominal pain, hospitalisation, bowel movements at night, tenesmus (frequent urge to go to the toilet without being able to go), faecal incontinence and interrupted sleep due to UC.[22]

Similarly, at Week 52 of the COMMAND study, people receiving risankizumab showed statistically significant improvements compared with placebo in bowel urgency and nocturnal bowel movements and tenesmus for both doses.[23] Additionally, the 180 mg dose of risankizumab showed statistically significant improvements compared with placebo for abdominal pain and interrupted sleep due to UC.[23]

As described in Section 2a, the symptoms described above are particularly burdensome to people with UC.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine can be associated with side effects and the same medicine can produce different reactions in different people. In both INSPIRE and COMMAND, risankizumab was generally well tolerated. No new side effects were discovered for risankizumab compared to the known side effects for risankizumab when it is used to treat other conditions.

Side effects were recorded in INSPIRE and COMMAND if they were experienced by greater than or equal to 5% of the people in the trial. In the INSPIRE induction trial, the most frequently observed side effects experienced by people receiving risankizumab were COVID-19, anaemia (low red blood cells) and arthralgia (joint stiffness). However, the proportion of people who experienced side effects in the INSPIRE trial was higher for people receiving placebo than people receiving risankizumab. Fewer than 1 in 100 people discontinued treatment with risankizumab due to side effects in the INSPIRE trial.

In the COMMAND maintenance trial, the most frequently observed side effects experienced by people receiving risankizumab were COVID-19, worsening of UC and nasopharyngitis (common cold). Similarly to the INSPIRE trial, the proportion of people who experienced side effects in the COMMAND trial was higher for people receiving placebo than people receiving risankizumab. Fewer than 3 in 100 people discontinued treatment with risankizumab due to side effects in the COMMAND trial.

Beyond the side effects observed in the INSPIRE and COMMAND trials, people should tell their doctor, pharmacist or nurse if they experience any of the following side effects:[24]

Very common: may affect more than 1 in 10 people

- upper respiratory infections with symptoms such as sore throat and stuffy nose

Common: may affect up to 1 in 10 people

- feeling tired
- fungal skin infection
- injection site reactions (such as redness or pain)
- itching
- headache
- rash

Uncommon: may affect up to 1 in 100 people

- small raised red bumps on the skin
- hives (urticaria)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There is a need for more treatments for people with UC

Currently, some people with UC receive treatments that do not work well enough and therefore continue to experience debilitating symptoms and continued inflammation and bowel damage. The need for an effective treatment is increased in people who cannot tolerate current treatment options for medical reasons, and for whom current treatment is not effective enough.

Risankizumab is effective for treating moderate to severe UC

In the INSPIRE and COMMAND trials, risankizumab was shown to have higher efficacy compared with placebo. Importantly, bowel urgency, abdominal pain and tenesmus were all improved with risankizumab treatment compared to placebo. These are symptoms that are among the most burdensome to people with UC. Risankizumab was also associated with improvements in endoscopic endpoints, including mucosal healing; these are key goals of treatment and give people with UC the best chance of achieving long-term control of the condition.

Additionally, the COMMAND trial showed people treated with risankizumab were more likely to maintain disease control without the use of corticosteroids than people treated with placebo. This is important because although corticosteroids can help to control a flare-up of UC, they are not effective in maintaining control of the condition long term. In addition, if used long term, corticosteroids can also be associated with predictable and potentially serious side effects, such as serious infection, diabetes, weight gain, high blood pressure and osteoporosis (thinning of the bones). An important goal in the treatment for people with UC is therefore to reduce steroid exposure.

Risankizumab is administered using an auto injector device

Maintenance treatment with risankizumab can be self-administered using an on-body device. This is a benefit to people with UC as it means that it can be administered at home.

Overall, risankizumab represents a new treatment option that can be made available for both individuals and clinicians as an alternative treatment for people with moderately to severely active UC.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?

- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Risankizumab is generally well-tolerated and is an effective treatment in UC. However, like all existing treatments in UC, risankizumab does not work for everyone and some people might not experience any improvement in their symptoms.

Additionally, like all existing treatments for UC, some people may experience side effects while taking risankizumab. However, the side effects associated with risankizumab are infrequent and are generally considered manageable; these have been summarised in Section 3g.

Beyond these points, there are no additional key disadvantages with treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Introduction to the economic model built for this submission

A cost-comparison model was developed for risankizumab with the aim of comparing the costs associated with treatment when using this treatment, compared with using ustekinumab. It was designed to reflect the usual way that UC is treated with either risankizumab or ustekinumab within the NHS.

Ustekinumab was considered the principal comparator for the model as it is recommended for use in the same population for which risankizumab is being positioned. In addition, both ustekinumab and risankizumab target interleukins, and both treatments are administered in the same way (intravenously during the induction period and then subcutaneously during maintenance therapy). For these reasons, it is anticipated that risankizumab would be

considered by doctors as an alternative treatment to ustekinumab in the proposed treatment population.

Based on the results from the indirect treatment comparison (see response to section 3e), the efficacy of risankizumab was assumed to be similar to ustekinumab. The costs associated with treatment using ustekinumab were therefore compared with the costs of using risankizumab to determine whether risankizumab would be a cost-effective treatment.

Clinical trial outcomes used in the model

Given the assumption of similar efficacy between risankizumab and ustekinumab, a cost-comparison model was developed for this submission. As such, no clinical outcomes were considered within the model, only costs.

How the costs of treatment differ between risankizumab and ustekinumab

The following costs were included within the cost-comparison model:

- Cost of the medicine (drug acquisition)
- Cost of giving the treatment to people (drug administration)

Risankizumab will be provided to the NHS at a confidential discounted price which has been considered in the results because it is known to AbbVie. It should be noted that a confidential discount may apply to ustekinumab as well, but this cannot be included in the analysis because it is unknown to AbbVie.

Cost-comparison results

When assuming similar efficacy for risankizumab and ustekinumab, the cost-comparison model predicts risankizumab (at its discounted price) to cost less than ustekinumab (at its full price). This means that the introduction of risankizumab to clinical practice may represent a cost saving.

Uncertainty

There was uncertainty within the model around how long people might stay on treatment or what dose of treatment people might receive in clinical practice. However, when these model inputs were varied in the model, it was found that varying them did not change the overall conclusion.

Conclusion

Overall, the results of the economic analysis predicted risankizumab to be a good use of NHS resources as an additional treatment option for people with moderately to severely active UC.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a ‘step change’ in treatment and/ or effectiveness compared with current treatments. Are there any

QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
As described above, risankizumab provides both doctors and patients with a new treatment option for people who cannot tolerate current treatment options for medical reasons, and for whom current treatment is not effective enough. In particular, risankizumab is new treatment option with a long half-life (the time it takes for the amount of a drug's active substance in your body to reduce by half). This means that once administered, risankizumab stays in the body for a long time. Compared with other treatments, the effects of risankizumab may continue for longer than other treatments. Finally, as described above, maintenance treatment with risankizumab can be self-administered using an on-body device. This is a benefit to people with UC as it means that it can be administered at home, reducing the need for people with UC to have to attend hospital appointments for treatment. The on-body device is also easier for people to use than other treatments that have to be injected under the skin as the dose of risankizumab can be delivered at the push of a button.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no equality issues that are anticipated for the use of risankizumab in UC.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on ulcerative colitis:

- Crohn's and Colitis UK (https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis?parent=4107&page=1&tags=&category=&sort=)

- IBDrelief (https://www.ibdrelief.com/learn)

Further information on NICE and the role of individuals:

- Public Involvement at NICE: Public involvement | NICE and the public | NICE Communities | About | NICE

- NICE's guides and templates for patient involvement in HTAs: Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf

- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/

- INAHTA: http://www.inahta.org/

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Term	Definition
Arthralgia	Joint stiffness
Clinical remission	A period of relative disease improvement, specifically defined using the Mayo scoring system as: • Stool frequency subscore = 0 or 1, with ≥1-point decrease from baseline • Rectal bleeding subscore = 0 • Endoscopic subscore = 0 or 1 (excluding friability)
Clinical response	Where a person shows a response to a drug, specifically defined as: • ≥2-point and ≥30% decrease in the modified Mayo score from baseline • Rectal bleeding subscore = 0 or 1, or ≥1-point decrease from baseline

Double blind	Where neither the individual or investigator know which drug is given to which person
Flare-up	Where disease symptoms worsen or return after periods of improvement
Genetic mutations	Our genes pick up mistakes that happen when cells divide. These mistakes are called genetic mutations or mutations. It is usual for cells to repair faults in their genes or for the faults to be removed by the body. Cancer happens when cells with genetic mutations are not repaired or removed from the body and instead multiply out of control
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases
Interleukins	A type of protein that plays a key role in the immune system
Inflammation	The result of the immune response to injury of tissues including redness, swelling and loss of function
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to people in a particular country.
Monoclonal antibody	A type of protein that is made in the laboratory and can bind to certain targets in the body
Mucosal healing	A reduction in damage, inflammation, ulcers, and blood observed in the gastrointestinal tract
NICE (The National Institute for Health and Care Excellence)	The body in England that decides whether to approve new medicines for funding on the NHS based on whether they can be demonstrated to be value for money
Placebo-controlled	When the study drug is compared to a drug that has no therapeutic effect, using this drug as a control
Protein	These are structures inside all cells of our body that are important for many activities including growth, repair and signalling
Randomised trial	A trial where a drug is compared to one or more comparators, which can include a placebo, and people are randomly allocated to one treatment group
Relapse	The return of a disease or the signs and symptoms of a disease after a period of improvement
Remission	Period of relative disease inactivity
Tenesmus	A frequent urge to go to the toilet without being able to go

4c) References

1. Crohn's and colitis UK. Ulcerative colitis. Available at https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/understanding-crohns-and-colitis/ulcerative-colitis [accessed 28th June 2023].
2. National Health Service (NHS). Overview Ulcerative colitis. Available at https://www.nhs.uk/conditions/ulcerative-colitis/ [accessed 13th September 2023].
3. King D, Reulen RC, Thomas T, et al. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. Aliment Pharmacol Ther 2020;51:922-934.
4. Pasvol TJ, Horsfall L, Bloom S, et al. Incidence and prevalence of inflammatory bowel disease in UK primary care: a population-based cohort study. BMJ Open 2020;10:e036584.

5. Devlen J, Beusterien K, Yen L, et al. The burden of inflammatory bowel disease: a patient-reported qualitative analysis and development of a conceptual model. Inflamm Bowel Dis 2014;20:545-552.
6. Larsson K, Lööf L, Nordin K. Stress, coping and support needs of patients with ulcerative colitis or Crohn's disease: a qualitative descriptive study. J Clin Nurs 2017;26:648-657.
7. Lönnfors S, Vermeire S, Greco M, et al. IBD and health-related quality of life -- discovering the true impact. J Crohns Colitis 2014;8:1281-6.
8. Sammut J, Scerri J, Xuereb RB. The lived experience of adults with ulcerative colitis. J Clin Nurs 2015;24:2659-67.
9. National Health Service (NHS). Diagnosis: Ulcerative colitis. Available at https://www.nhs.uk/conditions/ulcerative-colitis/diagnosis/ [accessed 14th September 2023].
10. National Institute for Health and Care Excellence (NICE). NG130. Ulcerative colitis: management. Available at https://www.nice.org.uk/guidance/ng130/resources/ulcerative-colitis-management-pdf-66141712632517 [accessed 3rd July 2023].
11. Barreiro-de Acosta M, Vallejo N, de la Iglesia D, et al. Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 vs 1): A Longitudinal Cohort Study. Journal of Crohn's and Colitis 2015;10:13-19.
12. Pabla BS, Schwartz DA. Assessing Severity of Disease in Patients with Ulcerative Colitis. Gastroenterol Clin North Am 2020;49:671-688.
13. National Health Service (NHS). Treatment: Ulcerative colitis. Available at https://www.nhs.uk/conditions/ulcerative-colitis/treatment/ [accessed 14th September 2023].
14. Guts UK. Ulcerative Colitis. Avalible at https://gutscharity.org.uk/advice-and-information/conditions/ulcerative-colitis/#section-4 [accessed 14th September 2023].
15. Crohn's and Collitis UK. Surgery for Ulcerative Colitis. Available at https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/surgery-and-complications/surgery-for-ulcerative-colitis [accessed 18th September 2023].
16. Kühn F, Klar E. Surgical Principles in the Treatment of Ulcerative Colitis. Viszeralmedizin 2015;31:246 - 250.
17. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active ulcerative colitis [TA633] Technology appraisal guidance. .
18. Dubinsky MC, Watanabe K, Molander P, et al. Ulcerative Colitis Narrative Global Survey Findings: The Impact of Living With Ulcerative Colitis—Patients' and Physicians' View. Inflammatory Bowel Diseases 2021;27:1747-1755.
19. Casellas F, Herrera-de Guise C, Robles V, et al. Patient preferences for inflammatory bowel disease treatment objectives. Digestive and Liver Disease 2017;49:152-156.
20. Rubin DT, Sninsky C, Siegmund B, et al. International Perspectives on Management of Inflammatory Bowel Disease: Opinion Differences and Similarities Between Patients and Physicians From the IBD GAPPS Survey. Inflamm Bowel Dis 2021;27:1942-1953.
21. Crohn's and Collitis UK. Medicines on the horizon. Available at https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/treatments/medicines-on-the-horizon#:~:text=Risankizumab%20is%20approved%20in%20the,enough%20to%20other%20biologic%20medicines [accessed 18th September 2023].
22. AbbVie. Data on file. INSPIRE CSR.
23. AbbVie. Data on file. COMMAND CSR.
24. Electronic Medicines Compendium. Skyrizi 150 mg solution for injection in pre-filled pen - Patient Information Leaflet. 2021. Available at https://www.medicines.org.uk/emc/product/12625/pil [accessed June 2022].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Risankizumab for people with previously treated moderately to severely active ulcerative colitis [ID6209]

Clarification questions

December 2023

File name	Version	Contains confidential information	Date
ID6209_Risankizumab in UC_ Clarification Question Responses_Redacted	Final	Yes	7th December 2023

Section A: Clarification on effectiveness data

Systematic review

A1. Table 19 (Appendices) reports your assessment of the RoB 2 tool for studies and not for outcomes or results. RoB 2 should be applied at minimum for each key outcome separately because risks of bias may different between these (particularly between efficacy and safety outcomes). Please provide RoB 2 assessments by outcome for the studies included in the network meta-analysis.

The ROB 2 assessment was not conducted for each outcome separately as it was not anticipated that the risk of bias would be substantially different across different outcomes. Given the low overall risk of bias of all RCTs included in the NMA, the same assessment is expected for all outcomes. This approach is aligned with the approach taken for the assessment of RCTs included in previous NMAs for ulcerative colitis (UC) and with previous NICE appraisals of moderately to severely active UC where quality assessments were completed at a study level and not outcome level.[2-4] Therefore, a RoB 2 assessment for each RCT by outcomes has not been provided.

It should also be noted that the completion of the RoB 2 was provided as complimentary to the quality assessment of each RCT, despite the RoB 2 assessment not being a requirement in the NICE user guide for company evidence submission.[1]

Clinical effectiveness

A2. Priority Question: The network meta-analyses presented cover four outcomes from the NICE scope. Please provide network meta-analysis results on all outcomes listed in the NICE scope for which there are data.

The NMAs conducted for this submission included a number of efficacy outcomes (clinical remission, clinical response, endoscopic improvement) and safety outcomes (serious adverse events [SAEs] and serious infections), in line with previous NICE appraisals in UC.[4, 5]

Clinical remission, clinical response and endoscopic improvement were the most consistently reported outcomes across the RCTs included in the NMA and are also considered the most relevant efficacy outcomes in UC, based on the British Society of Gastroenterologist guidelines and clinical expert opinion.[6, 7] For safety, both SAEs and serious infections were assessed; the incidence of serious infections represents one of the most important safety outcomes in UC and the inclusion of this outcome within the NMA also aligns with previous NICE appraisals in UC.[4, 5]

The four outcomes listed in the NICE final scope for risankizumab in UC that were not included in the NMA are corticosteroid-free remission, rate of hospitalisation, rate of surgical intervention and health-related quality of life. NMAs were not conducted for these outcomes for several reasons.

Firstly, for rate of hospitalisation and rate of surgical intervention, event rates are low across the included RCTs and therefore any NMA conducted based on these data would be associated with substantial uncertainty in the results. A summary of UC-related hospitalisations, UC-related surgeries, corticosteroid-free remission and HRQoL outcomes for the RCTs included in the NMA are presented in Table 8 and Table 9 of **Appendix A** for the induction and maintenance phases, respectively.

Secondly, for some of these outcomes, comparator data were not available from all relevant RCTs to enable inclusion in the NMA. Table 8 and Table 9 of **Appendix A** show a number of missing data (reported as 'NR' [not reported]) and therefore this lack of outcome data for some of the RCTs mean that any NMA analyses conducted for these outcomes would be limited.

Finally, for corticosteroid-free remission, the varying outcome definitions across the RCTs included in the NMA makes a meaningful comparison of this outcome unfeasible (see Table 1 below for corticosteroid-free remission definitions across the RCTs included in the NMA).

The approach taken for the inclusion of outcomes in the NMA is in line with several other NICE appraisals in UC.[4, 5, 8] In the NICE appraisals of mirikizumab (TA925), ozanimod (TA828) and upadacitinib (TA856), rates of hospitalisation, rates of surgical intervention, corticosteroid-free remission and health-related quality of life were listed in the NICE final scope but not included in the NMAs conducted for each appraisal.[4, 5, 8]

Given the data limitations to conduct adequate comparisons of these outcomes, no further NMA analyses have been conducted for this response.

Table 1: Comparison between definitions for corticosteroid-free remission across RCTs included in the NMA

Intervention	Trial	Corticosteroid-free remission definition	Method of assessment (central/local read)
Risankizumab	**COMMAND (NCT03398135)**	Clinical remission (stool frequency sub score ≤1, and not greater than baseline; rectal bleeding sub score = 0; endoscopic sub score ≤1 without the evidence of friability) with no corticosteroid use for 90 days	NR
Ustekinumab	**UNIFI (NCT02407236)**	Steroid-free definition was not reported. Remission is based on total Mayo score of ≤2 and no sub-score >1	Agreement between central and local
Vedolizumab	**GEMINI 1 (NCT00783718)**	Glucocorticoid-free among patients receiving oral glucocorticoids at baseline	NR
	VISIBLE 1 (NCT02611830)	Discontinuation of oral corticosteroids, followed by clinical remission at week 52, assessed in patients using oral corticosteroids at baseline	Central
Mirikizumab	**LUCENT-2 (NCT03524092)**	Corticosteroid-free remission is defined as clinical remission at week 40, symptomatic remission at week 28, and no corticosteroid use for ⩾12 weeks prior to week 40	Central

Abbreviations: NR: Not reported.

A3. Priority Question: Results from INSPIRE Substudy 1 are not presented. This was a Phase 2b study, within which Risankizumab 1800 mg was compared with placebo in the same types of patients at the same time points and followed up for the same amount of time for the same outcomes. This would seem to provide similarly relevant evidence of efficacy and safety to the subsequent Phase 3 Substudy 2. Please provide results for these patients or explain, with justification, the rationale for their exclusion from the evidence base (including whether this was solely because of the different administration periods of 3 vs 2 hours).

The primary efficacy analysis of INSPIRE was conducted in INSPIRE sub-study 2 and therefore INSPIRE sub-study 2 represents the principal data informing the efficacy and safety of induction treatment with risankizumab in this submission. The data used in the induction NMA for risankizumab were also obtained from INSPIRE sub-study 2.

Results from INSPIRE sub-study 1 were not initially presented within the submission as they do not inform the primary efficacy analysis of INSPIRE. INSPIRE sub-study 1 was a Phase IIb dose-ranging study and therefore only a limited numbers of patients were recruited per arm. A summary of the trial methodology and baseline characteristics for INSPIRE sub-study 1 were included in Appendix J of the Company submission (CS).

The Company would also like to highlight that risankizumab 1800 mg is not the dose for which the Company is seeking license for in induction treatment and therefore may not be as pertinent as risankizumab 1200 mg in this submission. Efficacy and safety results in INSPIRE sub-study 1 for the 1200 mg IV dose of risankizumab compared to placebo are consistent with those observed in INSPIRE sub-study 2. For completeness, results for the 1200 mg IV dose of risankizumab compared to placebo in INSPIRE sub-study 1 are provided in **Appendix B** of this response document.

A4. The network meta-analysis results are presented in Tables 33 to 46 (and Appendix D.2.6). How the numbers in the tables should be interpreted is not explained. We believe that the presented odds ratios should be interpreted as follows: (odds of event on column-defining treatment)/(odds of event on row-defining treatment). This means that: for efficacy outcomes, bold numbers >1 favour Risankizumab; and for safety outcomes, bold numbers <1 favour Risankizumab. Please confirm our interpretation is correct.

The Company can confirm that the EAG's interpretation of the odds ratios presented as part of the NMA results is correct; an odds ratio of 1.0 means no difference between arms, an odds ratio less than 1.0 means that the event is less likely in the risankizumab arm than the comparator and an odds ratio of more than 1.0 means that the event is more likely in the risankizumab arm than the comparator. Therefore, for efficacy outcomes, results in bold that are >1 favour risankizumab and for safety outcomes, results in bold that are <1 favour risankizumab. However, the credible intervals of analyses should also be considered when interpreting the results as when these cross one, any observed difference is not statistically significant.

A5. In Appendix Table 9 (of baseline characteristics for maintenance phase studies), there is no entry for LUCENT-2. Please provide these baseline data or explain their absence.

The Company apologises for the omission of these data in the original submission; please find the baseline characteristics for the LUCENT-2 study in Table 2.

Table 2: Baseline patients characteristics of the LUCENT-2 study (maintenance)

Study	Treatment arm	N	Age (years; mean)	Age (years; SE)	Male (%)	Weight (kg; mean)	Weight (kg; SE)	Disease duration (years; mean)	Disease duration (years; SE)	Extensive colitis or pancolitis (%)	Total Mayo score (mean)	Total Mayo score (SE)	Adapt. Mayo score (mean)	Adapt. Mayo score (SE)	CRP (mean)	CRP (SE)	Concurrent immuno-modulators (%)	Concurrent steroids (%)
LUCENT-2	MIR200	389	43.4	0.7	55.0%	NA	NA	6.9	0.4	32.9%	NA	NA	NA	NA	3.8	0.3	20.1%	34.7%
LUCENT-2	PBO	192	41.2	0.9	54.2%	NA	NA	6.7	0.4	30.7%	NA	NA	NA	NA	3.0	0.4	20.3%	35.4%

Abbreviations: IR: inadequate response; PBO: placebo; SE: standard error.

A6. Thank you for sharing the clinical study reports (CSRs). To help us judge the risk-of-bias assessments, we have some questions that are not easy for us to answer from these CSRs and we would be grateful if you could help with summary responses (ideally) or directions on where to look in the CSRs.

(a) How many patients in INSPIRE and COMMAND provided actual data for the efficacy and safety outcomes and how many had outcomes imputed?

Data were imputed either due to being missing, due to intercurrent event handling, or due to both reasons. Data imputation also varied by variable type i.e., categorical and continuous. As an example, actual and imputed data for the primary efficacy outcome of clinical remission per Adapted Mayo score for INSPIRE at Week 12 and COMMAND at Week 52 are provided below in Table 3 and Table 4, respectively.

For safety outcomes, no imputation was conducted, and all data presented were the actual data.

Details of the pre-specified methods can be found in the statistical analysis plan (SAP) within the CSRs (Appendix 16.1__9 for both the INSPIRE and COMMAND CSRs) which were provided within the reference pack alongside the CS.

Table 3: Actual and imputed data in clinical remission per Adapted Mayo score at Week 12; INSPIRE sub-study 2, ITT2

	Placebo IV (N=325) n (%)	Risankizumab 1200 mg IV (N=650) n (%)
Actual	[redacted]	[redacted]
Imputed (due to missing or intercurrent event handling)	[redacted]	[redacted]
Missing due to logistic restrictions	[redacted]	[redacted]
Missing due to other	[redacted]	[redacted]

Footnotes: ITT2 includes all randomised patients who received at least one dose of study drug during Induction Period 1 from INSPIRE sub-study 2. Clinical remission per Adapted Mayo score is defined as stool frequency subscore (SFS) <= 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and endoscopic subscore <= 1 without the evidence of friability.
Abbreviations: IV: intravenous.

Table 4: Actual and imputed data in clinical remission per Adapted Mayo score at Week 52; COMMAND sub-study 1, ITT1RN_A

	Placebo IV (N=183) n (%)	Risankizumab 180 mg SC (N=179) n (%)	Risankizumab 360 mg SC (N=186) n (%)
Actual	[redacted]	[redacted]	[redacted]
Imputed (due to missing or intercurrent event handling)	[redacted]	[redacted]	[redacted]
Missing due to logistic restrictions	[redacted]	[redacted]	[redacted]
Missing due to other	[redacted]	[redacted]	[redacted]

Footnotes: ITT1RN_A population includes all randomised patients who received at least one dose of study drug in COMMAND sub-study 1 after receiving IV risankizumab (either 600 mg, 1200 mg or 1800 mg) for only one period of 12 weeks in the induction study INSPIRE. Clinical remission per Adapted Mayo score is defined as stool frequency subscore (SFS) <= 1, and not greater than baseline, rectal bleeding subscore (RBS) = 0, and

endoscopic subscore <= 1 without the evidence of friability.
Abbreviations: SC: subcutaneous.

(b) How were the imputations done? We don't understand what is meant by "non-responder imputation while incorporating multiple imputation", since simple imputation of non-response seems to be rather a different approach from multiple imputation. Also, we would like details of the multiple imputation model.

In INSPIRE and COMMAND, the NRI-MI (Non-Responder Imputation while incorporating Multiple Imputation) approach to data analysis categorised any patient who did not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exception was that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic or due to geo-political conflict in Ukraine or surrounding area were handled by Multiple Imputation (MI). In addition, on or after the date of a UC-related corticosteroid intercurrent event or the occurrence of a UC-related surgery, patients were counted as non-responders.

The imputation of missing data was done as follows: Markov Chain Monte Carlo (MCMC) was first applied to augment data into a monotonic missing pattern, where applicable, and PROC MI was used to generate 30 datasets using the regression method. The variables included in the imputation model were: treatment arm, stratification factors (for example, in INSPIRE sub-study 2, they were: Advanced Therapies-IR status [yes vs no], baseline corticosteroid use [yes vs. no], baseline Adapted Mayo score [≤ 7 vs. > 7]), baseline measurement, and if applicable, postbaseline measurements at each visit up to the end of the analysis period).

Full details of the data imputation methods conducted across INPSIRE and COMMAND can be found in the statistical analysis plan (SAP) within the CSRs (Appendix 16.1__9 for both the INSPIRE and COMMAND CSRs) which were provided within the reference pack alongside the CS.

(c) What sensitivity analyses were undertaken based on alternative assumptions for imputing missing outcome data?

Tipping point analyses were conducted as sensitivity analyses for the primary endpoint in both INSPIRE and COMMAND. As observed (AO) data was used as a supplementary analysis; results of these analyses can be found in Table 14.2_2.3_B of the INSPIRE CSR and Table 14.2_2.3.1 of the COMMAND CSR.[9, 10] Full details of sensitivity analyses can be found in the SAPs, which are within the CSRs (Appendix 16.1__9 for both the INSPIRE and COMMAND CSRs) and were provided in the reference pack alongside the CS.

(d) Could you please clarify how serious adverse effects were defined and how the data on these were collected?

Within both the INSPIRE and COMMAND trials, investigators monitored each patient for clinical or laboratory evidence of AEs throughout the study. If identified, the study site investigator

entered SAE data into an electronic data capture system provided by the company, this was to be done within 24 hours of the site being made aware of the SAE. If an AE met any of the following criteria, it was to be reported as a SAE:

- **Death of subject:** an event that results in the death of a subject.
- **Life-threatening:** an event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
- **Hospitalisation or prolongation of hospitalisation:** an event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
- **Congenital anomaly:** an anomaly detected at or after birth, or any anomaly that results in foetal loss.
- **Persistent or significant disability/incapacity:** an event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle).
- **Important medical event requiring medical or surgical intervention to prevent serious outcome:** an important medical event that may not be immediately life-threatening or result in death or hospitalisation, but based on medical judgment may jeopardise the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalisation, prolongation of hospitalisation, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Section B: Clarification on cost-effectiveness data

Model comparators

B1. Priority Question: After consulting with clinical advisors, we understand that Vedolizumab is used in clinical practice after failure of anti-TNF alpha inhibitor drugs, and Ustekinumab is used further in the pathway after trying Vedolizumab. Both Ustekinumab and Vedolizumab have been used as comparators in the recent NICE appraisal for Mirikizumab (TA925).

(a) Please can the company provide clarity on the positioning of Risankizumab? Specifically, whether the company is positioning Risankizumab after failure of anti-TNF alpha inhibitor drugs, which

would mean Vedolizumab is the most appropriate comparator. Or whether the company is positioning Risankizumab after failure of Vedolizumab, in which case Ustekinumab is an appropriate comparator, but the positioning would need to be reflected in the population for the budget impact analysis.

Within this submission, risankizumab is positioned as a treatment for patients with moderately to severely active UC in whom tumour necrosis factor (TNF)-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough. This is in line with the population recommended by NICE for ustekinumab (TA633)[11].

The relevance of ustekinumab as the appropriate comparator to risankizumab in this indication was supported by UK clinical expert opinion, which indicated that based on mechanism of action, risankizumab represents an alternative treatment to ustekinumab. Risankizumab and ustekinumab have a related mechanism of action; both target interleukins (IL) and both inhibit IL-23, the key signalling molecules that drive the chronic inflammation associated with UC. Vedolizumab has a different mechanism of action and instead binds to α4β7 integrin, targeting immune cell migration into the gut. Therefore, it is understood that risankizumab is more likely to be used as an alternative treatment to ustekinumab in UK clinical practice rather than vedolizumab.

Based on the rationale provided above and the clinical expert opinion that risankizumab would be considered as an alternative treatment to ustekinumab, the Company maintain that ustekinumab is considered the most relevant comparator in this appraisal. Nevertheless, a cost-comparison analysis of risankizumab and vedolizumab is detailed below in Question B1b for completeness.

(b) If positioning after failure of anti-TNF alpha inhibitors, can the company provide a cost-comparison analysis using Vedolizumab as a comparator.

As discussed in the response to part a) of this question, the Company maintain that ustekinumab represents the most relevant comparator in this appraisal. Nevertheless, for completeness, results of a cost-comparison analysis of risankizumab and vedolizumab are detailed below with the associated model inputs and assumptions detailed in Appendix B.

Results for the cost-comparison analysis of risankizumab (at PAS price) versus vedolizumab (at list price) are presented in Table 5. Over the model time horizon of 10 years, risankizumab (at PAS price) was associated with cost savings versus vedolizumab (at list price) of [redacted] per person.

It should be noted that the net price of vedolizumab is confidential, which should be taken into account when interpreting the results of this analysis. However, the expectation is that when the net price for vedolizumab is considered, risankizumab remains a cost-saving option for patients with moderately to severely active UC.

Table 5: Results of scenario analysis including vedolizumab (risankizumab PAS price; vedolizumab list price)

Treatment	Induction			Maintenance			Overall total costs[a]
	Drug acquisition costs	Drug administration costs	Total induction costs	Drug acquisition costs	Drug administration costs	Total maintenance costs	
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	£6,150	£406	£6,556	£149,753	£5,607	£155,360	£161,916
Incremental costs per patient (for risankizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Overall total costs over a 10 year time horizon.
Abbreviations: PAS: patient access scheme.

Escalation of dosage

B2. Priority Question: The company assumes both drugs have similar adverse events and mechanisms of action, but that 92.5% of patients having Ustekinumab require dose escalation while only 30% of patients on Risankizumab require escalation. Could the company explain why this is so different between the drugs and provide evidence for the assumption of different escalation rates? Our clinical experts advised that the decision to escalate any drug occurs after 2 flares in a year or a very severe first flare. If different escalation rates are assumed, is the company implying different treatment or side effects?

The proportion of patients assumed to receive escalated doses of risankizumab and ustekinumab in the base case cost-comparison analysis were based on the NICE evaluation for risankizumab in Crohn's disease (TA888) in which 30% of patients receiving risankizumab were assumed to require dose escalation and 92.5% of patients receiving ustekinumab were assumed to require dose escalation.[13] The assumption made in TA888 was taken from a UK advisory board during which six clinical experts were asked to estimate the proportion of moderate-to-severe CD patients that required dose escalation during the maintenance phase of biologic treatment in clinical practice. The median of the responses received was used to inform the values used within the appraisal. These assumptions and their relevance to UC were validated at a UK advisory board held in September 2023 with four clinical experts and two economic experts, in which the experts noted that the majority of patients receiving ustekinumab would be on the escalated dose immediately after induction within the maintenance phase.

Additional expert clinical opinion obtained as part of this appraisal further confirmed that almost all patients receiving ustekinumab for moderately to severely active UC would be on the escalated dose immediately after induction. A recent real-world evidence study conducted in the UK supports this, reporting that out of 110 patients with UC that were treated with ustekinumab, only six were maintained on Q12W dosing schedule with the remaining patients escalated to Q8W or Q4W schedules during maintenance therapy.[14] The clinical experts also noted that patients receiving ustekinumab would typically receive the escalated dose at the end of the induction period whereas for patients receiving risankizumab, the majority of patients would likely start with the 180 mg dose in the maintenance phase and then escalate to the 360 mg dose when there is a disease flare.

Although the base case cost-comparison analysis applied different proportions of patients receiving the escalated dose of risankizumab and ustekinumab respectively, it is not assumed that the escalated dose of either treatment is associated with different efficacy or safety compared with the standard dose. This is supported by the results of the NMA (presented in Section B.3.9 of the CS) which demonstrate that efficacy and safety results were comparable between the standard and escalated doses of ustekinumab and risankizumab across the vast majority of outcomes assessed. These results support the core assumption of the cost-comparison model that the different technologies have similar health benefits, both in terms of efficacy and safety.

B3. Priority Question: The model assumes that patients escalate immediately after the initiation period. Our clinical experts have advised that it would take two flares in a year for the dose to be escalated. Could the company:

(a) provide evidence on the time to escalation for all drugs

Time to dose escalation data for risankizumab are not available from INSPIRE and COMMAND or reported for ustekinumab in the published data. As such, insights relating to the time to dose escalation for both risankizumab and ustekinumab have been derived from UK clinical expert opinion and real-world dose escalation experience.

Feedback from UK clinical experts indicated that most patients receiving ustekinumab would typically receive the escalated dose at the end of the induction period whereas for patients receiving risankizumab, the majority of patients would likely start with the 180 mg dose in the maintenance phase and then escalate to the 360 mg dose when there is a disease flare. Given the real-world use of risankizumab in this indication in UK clinical practice is relatively limited to date, it is expected that evidence on time to dose escalation will become further established over time.

(b) adjust the model so that escalation is phased in over the first maintenance year, rather than all patients escalate immediately after the initiation period

The assumption that patients on either risankizumab or ustekinumab escalate to a higher dose immediately after the induction period was made within the base case cost-comparison model based on UK clinical expert feedback (see response to Question B3a) in the absence of data on time to escalation from either INSPIRE or COMMAND or the ustekinumab trials. This assumption is also in line with previous NICE appraisals in which a percentage of patients were assumed to receive an escalated maintenance dose immediately following induction.[4, 5, 11]

Given detailed data on time to dose escalation are not available, the Company maintain that this assumption is appropriate. For completeness however, results are presented below for a scenario analysis in which a phased escalation approach has been adopted within the model (Table 6).

The phased dose escalation has been implemented such that the dose escalation applied to calculations in the 1st maintenance year is half of the “full” escalation value. For example, for risankizumab, calculations for maintenance costs in year 1 use a dose escalation of 15%, then use the full dose escalation value (i.e. 30%) for cost calculations in all additional years of the model.

Results from this scenario analysis show that risankizumab (at PAS price) was associated with cost savings versus ustekinumab (at list price) of [redacted] per person. It should be noted that the net price of ustekinumab is confidential, which should be taken into account when interpreting the results of this analysis.

Table 6: Results of scenario analysis incorporating phased dose escalation in the maintenance phase (risankizumab PAS price; ustekinumab list price)

Treatment	Induction			Maintenance			Overall total costs[a]
	Drug acquisition costs	Drug administration costs	Total induction costs	Drug acquisition costs	Drug administration costs	Total maintenance costs	
Base case							
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	£6,676	£135	£6,811	£135,019	£0	£135,019	£141,830
Incremental costs per patient (for risankizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analysis incorporating phased dose escalation							
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	£6,676	£135	£6,811	£133,033	£0	£133,033	£139,844
Incremental costs per patient (for risankizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall total costs over a 10-year time horizon.
Abbreviations: PAS: patient access scheme.

B4. If patients in the maintenance phase escalate to 360mg Risankizumab:

(a) How are their side effects/adverse events likely to change?

Based on results from COMMAND (presented in Section B.3.10.2 of Document B), rates of AEs and SAEs were similar between the 180 mg and 360 mg doses of risankizumab. Overall, [redacted] ([redacted]) of patients in the risankizumab 180 mg arm and [redacted] ([redacted]) in the risankizumab 360 mg arm experienced a treatment-emergent AE. The same number of patients experienced an SAE in each arm ([redacted]), representing 5.2% and 5.1% in the 180 mg and 360 mg arms, respectively.

Within the NMA (presented in B.3.9.8 of Document B), the comparison of SAEs between the 180 mg and 360 mg risankizumab arms of COMMAND further support similar rates of SAEs, with an odds ratio of [redacted] for the 180 mg dose versus the 360 mg dose. The odds ratio for each risankizumab dose compared to placebo was also similar: [redacted] for the 180 mg dose and [redacted] for the 360 mg dose. Slight differences were observed in the NMA comparison of risankizumab doses in terms of serious infections, with an odds ratio of [redacted] for the 180 mg dose versus the 360 mg dose. However, the number of serious infections was very low in both arms ([redacted] in the 180 mg arm and [redacted] in the 360 mg arm) and the credible interval [redacted], meaning that the rates of serious infections can be considered comparable.

Additional expert clinical opinion obtained as part of this appraisal further confirmed this and indicated that increased AEs are typically not seen when moving patients from a standard dose to an escalated dose for UC biologic therapies and there is not typically an observed relationship between dose and AEs.

(b) If they experience more side effects at the escalated dose, is it likely that they move back to the standard 180mg dose but take it more frequently? How much more frequently? Or would they discontinue?

As highlighted in the response to Question B4a, rates of AEs and SAEs were similar between the 180mg and 360mg maintenance doses of risankizumab in COMMAND. Rates of discontinuation due to AEs were also low for both risankizumab doses in COMMAND and were similar between doses, [redacted] and [redacted] for the 180 mg and 360 mg arms, respectively.

Feedback from UK clinical experts is that it would be unlikely for patients to de-escalate from the 360 mg dose to the 180 mg dose of risankizumab in the maintenance phase due to AEs. Where this might happen, the frequency of the 180 mg dose would not be increased beyond Q8W as this would not be in line with the SmPC for risankizumab in this indication.[15] Regardless of whether patients are receiving 180 mg Q8W or 360 Q8W of risankizumab, the costs associated with treatment are the same.

B5. Priority Question: Please provide more information on how the KOL feedback was elicited to obtain the proportion of Ustekinumab on standard dose. Who was consulted? How was the response elicited (interview, advisory

board etc.)? And how was the Ustekinumab 7.5% standard dose proportion estimated?

The proportion of patients assumed to receive the standard dose of ustekinumab was 7.5%. This was calculated based on the assumption that 92.5% of patients receiving ustekinumab would be on the escalated dose, based on clinical expert opinion (7.5% = 100% – 92.5%). Please see the response provided to Question B2 for detail on how this clinical expert opinion was obtained.

B6. The dosing schedule sheet shows that maintenance of the drug is delivered on 12w intervals. Is that linked to anything in the model? The text refers to 8w intervals. Would it be plausible in routine clinical practice for clinicians to escalate the use of Risankizumab by giving patients more frequent doses instead of increasing dose from 180mg to 360mg?

It is important to note that maintenance doses of risankizumab are delivered at Week 12 (following induction dosing) and then every eight weeks thereafter, not in 12 week intervals as suggested in the question. As the recommended maintenance dose frequency specified in the SmPC for risankizumab is every 8 weeks, increasing the frequency of the 180 mg or the 360 mg dose would not be in line with the frequency specified in the label.[15]

Dosing within the model is in line with the dosing schedules detailed in the SmPCs for risankizumab and ustekinumab.[15, 16] Risankizumab is escalated through increasing the dose from 180 mg to 360 mg. Ustekinumab is escalated through increasing the frequency of administration from every 12 weeks (Q12W) to every 8 weeks(Q8W).

Other model questions

B7. The company assumes that adverse events are similar based on very uncertain evidence from the meta-analysis (wide confidence intervals crossing the null). Given this uncertainty, could the company include the costs of adverse events in the model (at least as a sensitivity analysis)?

The costs associated with the treatment of serious infections have been incorporated into the cost-comparison model as a scenario analysis, with results presented in Table 7 below. Rates for serious infections were derived from the predicted absolute rates of serious infections from the fixed effects NMAs for induction and maintenance, respectively. Serious infections are the only AEs considered, in line with previous cost-effectiveness models for moderately to severely active UC.[4, 5, 11]

Results from this scenario analysis were very similar to the base case and show that risankizumab (at PAS price) was associated with cost savings versus ustekinumab (at list price) of [redacted] per person. It should be noted that the net price of ustekinumab is confidential, which should be taken into account when interpreting the results of this analysis.

Table 7: Results of scenario analysis including costs of serious infections (risankizumab PAS price; ustekinumab list price)

Treatment	Induction				Maintenance				Overall total costs[a]
	Drug acquisition costs	Drug administration costs	Serious infection costs	Total induction costs	Drug acquisition costs	Drug administration costs	Serious infection costs	Total maintenance costs	
Base case									
Risankizumab	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	NA	[redacted]	[redacted]
Ustekinumab	£6,676	£135	NA	£6,811	£135,019	£0	NA	£135,019	£141,830
Incremental costs per patient (for risankizumab)	[redacted]	[redacted]	**NA**	[redacted]	[redacted]	[redacted]	**NA**	[redacted]	[redacted]
Scenario analysis including the costs of serious infections									
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	£6,676	£135	£7	£6,818	£135,019	£0	£59	£135,079	£141,896
Incremental costs per patient (for risankizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Overall total costs over a 10 year time horizon.
Abbreviations: PAS: patient access scheme.

B8. Priority Question: The model assumes that all patients remain on treatment for 10 years, however, patients may discontinue early if they do not respond to treatment, or later at routine medical reviews if the treatment stops working so well. Can the company incorporate treatment discontinuation into the model?

Treatment discontinuation has not been included within the base case cost-comparison model due to the inherent assumption that the efficacy and safety of risankizumab and ustekinumab are equal. Clinical expert opinion sought by the Company supports the assumption of equal discontinuation rates between risankizumab and ustekinumab as efficacy and safety is not expected to differ between the treatments. As the rate of treatment discontinuation is assumed to remain equivalent between risankizumab and ustekinumab, and the costs of subsequent treatments would be assumed to be the same, discontinuation was not included so as not to add any unnecessary complexity into the model. This is in line with previous NICE cost-comparison appraisals in which treatment discontinuation was not incorporated into the model.[17]

Furthermore, according to clinical expert opinion, when patients discontinue treatment with risankizumab or ustekinumab, they are likely to go on to receive further, multiple lines of treatment, as highlighted by clinical expert opinion sought by the Company. Incorporating subsequent treatments would introduce additional complexity to the model and it would not be possible to determine the sequence accurately.

It is acknowledged that not all patients may continue treatment with either risankizumab or ustekinumab for a full 10 years; nevertheless it is expected that patients may stay on treatment for at least 5–6 years, and the impact of this shorter treatment duration is expected to have a minimal impact on results.

Treatment discontinuation has therefore not been incorporated within the model for the reasons stated above.

B9. Could the company discount costs in the model (at the 3.5% NICE recommended discount rate)?

As per the NICE user guide for the cost-comparison company evidence submission template, discounting is not normally required in cost-comparison models.[18] As such, discounting has not been included within the model and results for the base case cost-comparison analysis including discounting have not been provided.

Section C: Textual clarification and additional points

Missing Information

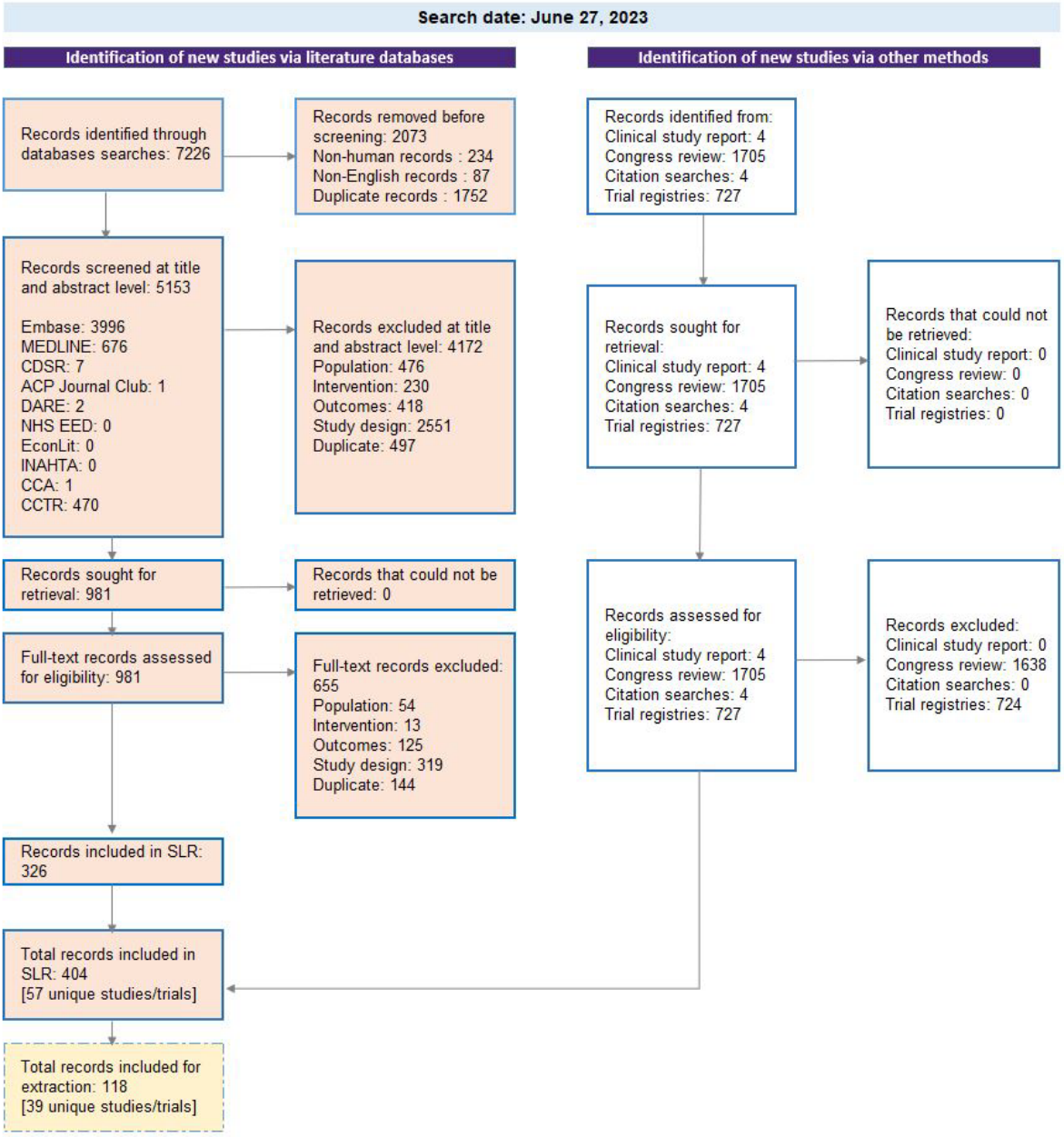
C1. The ‘PRISMA’ flowchart you present is not taken from the PRISMA website and it is not an appropriate format given the variety of searches that you have

undertaken. Please complete this version: http://prisma-statement.org/documents/PRISMA_2020_flow_diagram_new_SRs_v2.docx

We are unable to validate your study identification process based on current reporting. We can see the numbers arising from your database searches, but not the numbers of studies identified through the searches of trials registers, the numbers of HTA reports and company submissions based on web searching, the number of abstracts or posters identified through the conference searching, and how studies or reports identified from checking systematic reviews were processed.

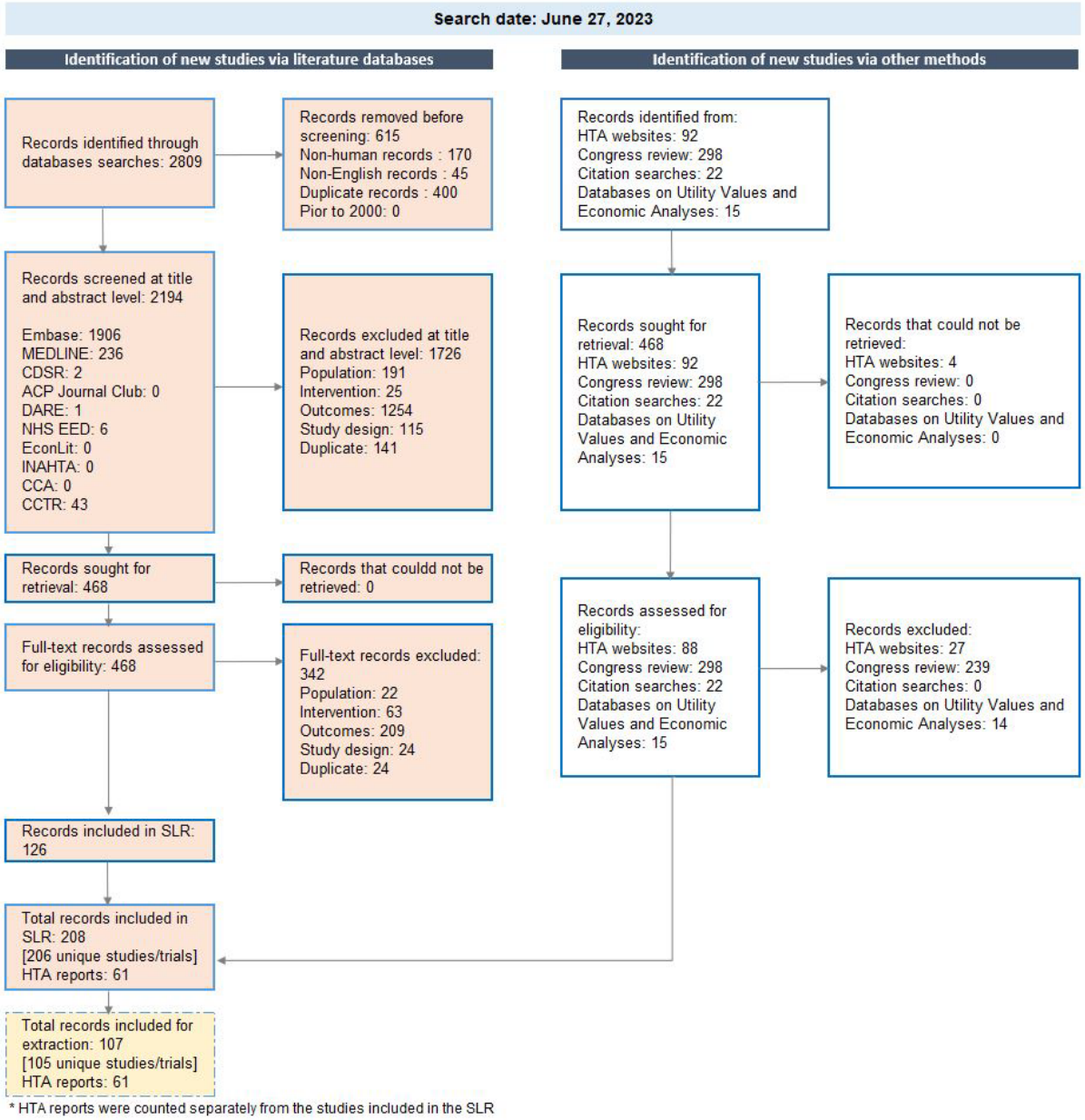
Please see updated PRISMA diagrams for the clinical SLR and cost and healthcare resource use SLRs in Figure 1 and Figure 2, respectively.

Figure 1: Updated PRISMA diagram for the clinical SLR



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

Figure 2: Updated PRISMA diagram for the cost and healthcare resource use SLR



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

C2. We would expect to see a protocol for your systematic review, ideally one which has been prospectively registered on a register such as PROSPERO.

(a) Please can you provide a link to your registered protocol OR provide us with a copy of the protocol?

(b) If you did not prospectively register a protocol, please can you explain why?

The protocol for the clinical and economic SLRs were registered prospectively on PROSPERO. This registered protocol has been provided in the reference pack and can be found at

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021278578.[19]

C3. Please can we clarify Lines 40-46 of your search syntax. Our understanding is that you date limited (Line 43) to reduce the number of items retrieved so that you could undertake a server-side de-duplication within the limits allowed by Ovid, please could you confirm?

- **Line 40 35 not 39 (7226)**
- **Line 41 limit 40 to English (7139)**
- **Line 42 limit 41 to human (6905)**
- **Line 43 limit 42 to yr="2020 -Current" (2636)**
- **Line 44 remove duplicates from 43 (1807)**
- **Line 45 42 not 43 (4269)**
- **Line 46 remove duplicates from 45 (3346)**

Please find further details on Lines 40–46 of the search strategy below:

- Line 40 removed studies with irrelevant study designs, studies on animals and case reports
- Line 41 limited the results to records published in English
- Line 42 limited the results to records involving human participants
- Lines 43 – 47 deduplicated the searches. Since the Ovid platform cannot deduplicate searches with over 6000 hits, the records were split into two groups with manageable hit numbers, that were deduplicated separately and then combined at the end. Please see detailed explanations of each line item below:
    - Line 43: searches were split into two groups, based on the year of publication (after 2020 and before 2020) for the purpose of de-duplication
    - Line 44: records published after 2020 were deduplicated
    - Line 45: identifies records published before 2020
    - Line 46: records published before 2020 were deduplicated
    - Line 47: combines overall unique records identified (both before and after 2020).

Appendix A: Summary of rate of hospitalisation, rate of surgical intervention, corticosteroid-free remission and HRQoL outcomes for RCTs included in the NMA

Table 8: Summary of rate of hospitalisation, rate of surgical intervention, corticosteroid-free remission and HRQoL outcomes in the induction phase for RCTs included in the NMA

Endpoint	Occurrence of UC-related hospitalisations n (%)	Occurrence of UC-related surgeries n (%)	Corticosteroid-free remission	HRQoL: IBDQ score
Risankizumab: INSPIRE, Week 12				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab: UNIFI, Week 8				
Placebo	14 (4.4)	2 (0.6)	NR	143.5
Ustekinumab 130 mg IV	2 (0.6)	0 (0)	NR	159.2
Ustekinumab 6 mg/kg IV	5 (1.6)	0 (0)	NR	161.9
Vedolizumab: GEMINI 1, Week 6				
Placebo	NR	NR	NR	NR
Vedolizumab 300 mg IV	NR	NR	NR	NR
Vedolizumab: NCT02039505, Week 10				
Placebo	NR	NR	NR	NR
Vedolizumab 300 mg IV	NR	NR	NR	NR
Vedolizumab: VISIBLE 1, Week 6				
Vedolizumab 300 mg IV	NR	NR	NR	NR
Mirikizumab: LUCENT-1, Week 12				
Placebo	NR	NR	NR	38.41
Mirikizumab 300 mg IV	NR	NR	NR	25.21

Abbreviations : IBDQ : Irritable Bowel Disease Questionnaire; IV : intravenous; UC : ulcerative colitis.

Table 9: Summary of rate of hospitalisation, rate of surgical intervention, corticosteroid-free remission and HRQoL outcomes in the maintenance phase for RCTs included in the NMA

Endpoint	Occurrence of UC-related hospitalisations n (%)	Occurrence of UC-related surgeries n (%)	Corticosteroid-free remission	HRQoL: IBDQ score
Risankizumab: COMMAND, Week 52				
Placebo	[redacted]	[redacted]	46 (25)	[redacted]
Risankizumab 180 mg SC	[redacted]	[redacted]	71 (40)	[redacted]
Risankizumab 360 mg SC	[redacted]	[redacted]	69 (37)	[redacted]
Ustekinumab: UNIFI, Week 52				
Placebo	10 (5.7)	3 (1.7)	41 (23.4)	159.3
Ustekinumab 90 mg SC Q8W	3 (1.7)	1 (0.6)	74 (42)	178.2
Ustekinumab 90 mg SC Q12W	4 (2.3)	1 (0.6)	65 (37.8)	172.3
Vedolizumab: GEMINI 1, Week 52				
Placebo	NR	NR	72 (10)	NR
Vedolizumab 300 mg IV Q4W	NR	NR	73 (33)	NR
Vedolizumab 300 mg IV Q8W	NR	NR	70 (22)	NR
Vedolizumab: NCT02039505, Week 60				
Placebo	NR	NR	3 (20)	NR
Vedolizumab 300 mg IV	NR	NR	6 (46.2)	NR
Vedolizumab: VISIBLE 1, Week 52				
Placebo	NR	NR	2 (8.3)	135.2
Vedolizumab 108 mg SC	NR	NR	13 (28.9)	180.7
Vedolizumab 300 mg IV	NR	NR	6 (28.6)	170.7
Mirikizumab: LUCENT-1, Week 52				
Placebo	2 (1)	NR	39 (22)	24.51

Mirikizumab 200 mg SC	0 (0)	NR	164 (45)	49.75

Abbreviations: SC: subcutaneous; UC: ulcerative colitis.

Appendix B: INSPIRE sub-study 1 results

Results for the licensed 1200 mg IV dose of risankizumab compared to placebo in INSPIRE sub-study 1 are presented below.

Clinical remission per Adapted Mayo score at Week 12 (INSPIRE sub-study 1)

In INSPIRE sub-study 1 at Week 12, patients who received risankizumab 1200 mg IV achieved higher rates of clinical remission per Adapted Mayo score at Week 12 compared to patients who received placebo, achieving a nominal p value <0.05 (Table 10).

Table 10: Proportion of patients achieving clinical remission per Adapted Mayo score at Week 12; INSPIRE sub-study 1; ITT1A, NRI

Treatment	N	Responder	Response rate difference compared to placebo	
		n (%)	Adjusted difference[a,b]	P value[b]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Risk difference = (risankizumab – Placebo). [b] Based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline corticosteroid use (yes, no) and baseline adapted mayo score (≤ 7, > 7). ITT1A includes all randomised patients who received at least one dose of study drug during Induction Period 1 from sub-study 1. Clinical remission per Adapted Mayo Score was defined as SFS ≤ 1, and not greater than baseline, RBS of 0, and endoscopic subscore ≤ 1.

Abbreviations: CMH: Cochran-Mantel-Haenszel; IV: intravenous; NRI: Non-Responder Imputation; OL: open-label; RBS: rectal bleeding sub-score; SFS: stool frequency sub-score.
Source: AbbVie. Data on File. INSPIRE CSR.[9]

Secondary outcomes (INSPIRE sub-study 1)

Risankizumab 1200 mg IV demonstrated improvements compared to placebo across all secondary endpoints evaluating symptomatic, endoscopic improvement, endoscopic-histologic and patients-reported quality of life outcomes (Table 11).

Table 11: Summary of secondary endpoints; INSPIRE sub-study 1, ITT1A

Treatment	N	Responder	Response rate difference compared to placebo		
		n (%)	Adjusted difference[a,b]	90% CI[b]	P value[b]
Endoscopic improvement at Week 12[c], NRI					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response per Adapted Mayo score at Week 12[d], NRI					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response per partial Adapted Mayo score at Week 4[e], NRI					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab 1200 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic remission at Week 12[f] NRI					

Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				
Hospitalisations through Week 12 (all cause)					
Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				
HEMR at Week 12[h], NRI					
Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				
UC-SQ overall symptom score at Week 12, OC (within group LS mean)					
Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				
IBDQ total at Week 12, OC					
Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				
SF-36 physical component summary at Week 12, OC					
Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				
FACIT-Fatigue Total at Week 12, OC (within group LS mean)					
Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				
UC-related Surgeries through Week 12					
Placebo	[redacted]				
Risankizumab 1200 mg IV	[redacted]				

Footnotes: [a] Risk difference = (risankizumab – Placebo). [b] Based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline corticosteroid use (yes, no) and baseline adapted mayo score (<= 7, > 7). [c] Endoscopic improvement was defined as endoscopy sub score of 0 or 1. [d] Clinical response per Adapted Mayo sore was defined as decrease from baseline in adapted mayo score ≥2 points and ≥ 30%, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. [e] Clinical response per Adapted Mayo score was defined as decrease from baseline in adapted mayo score ≥1 point and ≥ 30%, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. [f] Endoscopic remission was defined as endoscopy sub score of 0. [g] P value for comparisons between treatment arms and placebo arm using chi-square test or Fisher's exact test. [h] Histologic Endoscopic Mucosal Remission was defined as endoscopy sub score of 0 and Geboes score < 2.0. + P-value ≤ 0.1; * P-value ≤ 0.05; ** P-value ≤ 0.01; *** P-value ≤ 0.001.

Abbreviations: CI: confidence interval; CMH: Cochran-Mantel-Haenszel; ; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HEMR: histological-endoscopic mucosal remission; IBDQ: Inflammatory Bowel Disease Questionnaire; IV: intravenous; NRI: Non-Responder Imputation; OL: open-label; RBS: rectal bleeding sub-score; SF-36: Short Form (36) Health Survey; SFS: stool frequency sub-score; UC: ulcerative colitis; UC-SQ: Ulcerative Colitis-Symptom Questionnaire

Source: AbbVie. Data on File. INSPIRE CSR.[9]

Adverse reactions (INSPIRE sub-study 1)

During the double-blind period of Induction Period 1 INSPIRE sub-study 1, the proportion of patients with adverse events (AEs), severe AEs, and SAEs which led to study drug discontinuation in the risankizumab 1200 mg IV arm were low (<6.0%) and numerically lower compared to the placebo arm (Table 12). No deaths were reported in INSPIRE sub-study 1.

Table 12: Overview of TEAEs and all deaths; INSPIRE sub-study 1, SAS1A and SAS1B

	Placebo IV (N=59) (PY=15.5)		Risankizumab 1200 mg IV (N=61) (PY=15.1)	
	n (%)	(E/100 PY)	n (%)	(E/100 PY)
Patients with any treatment-emergent:				
AE	[redacted]	[redacted]	[redacted]	[redacted]
AE with reasonable possibility of being drug-related[a]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]
Any COVID-19 related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
All deaths[b]	[redacted]	[redacted]	[redacted]	[redacted]
Any COVID-19 related death	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] As assessed by investigator. [b] Includes non treatment-emergent deaths. Patients are counted once in each row, regardless of the number of events they may have had.
Abbreviations: AE: adverse event; E/100 PY: events per 100 patient-years; IV: intravenous; PY: patient years; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Source: AbbVie. Data on File. INSPIRE CSR.[9]

Appendix C: Model inputs and assumptions for comparison to vedolizumab

The model inputs and assumptions were aligned with those used in the company base case cost-comparison analysis. The total drug acquisition costs for the induction and maintenance phases are presented in Table 13 and Table 14, respectively. The number of administrations and total administration costs for both risankizumab and vedolizumab are presented in Table 15.

The assumption that 50% of patients taking vedolizumab would be taking SC and 50% would be taking IV is based on clinical expert opinion that not all patients are suitable for SC.

Table 13: Drug acquisition costs for the induction phase (risankizumab PAS price; vedolizumab list price)

	Induction			
Treatment	**No. of units used during induction**	**Unit size**	**Unit price (£)**	**Total induction cost (£)**
Risankizumab	3	600 mg	[redacted]	[redacted]
Vedolizumab IV	3	300 mg	£2,050.00	£6,150.00
Vedolizumab SC	3	108 mg	£512.50	

Abbreviations: PAS: patient access scheme.

Table 14: Drug acquisition costs for the maintenance phase (risankizumab PAS price; vedolizumab list price)

Treatment	**Maintenance phase dosage**	**Unit size**	**Unit price (£)**	**Total Year 1 maintenance cost (£)**	**Total Year 2+ maintenance cost (£)**
Risankizumab	Standard: 180 mg Q8W (70%) Escalated: 360 mg Q8W (30%)	180 mg 360 mg	[redacted]	[redacted]	[redacted]
Vedolizumab IV	Standard: 300 mg Q8W (70%) Escalated: 300 mg Q4W (30%)	300 mg	£2,050.00	£11,838.75	£15,323.75
Vedolizumab SC	Standard: 108 mg Q2W	108 mg	£512.50		

Footnote: A 5050 split of IV/SC was assumed for vedolizumab.
Abbreviations: Q8W: every 8 weeks; QD: once daily; SC: subcutaneous.

Table 15: Drug administrations for risankizumab and vedolizumab during the induction and maintenance phase

Treatment	**Induction**	**Maintenance (Year 1)**	**Maintenance (Year 2+)**

	Number of administrations	Total administration costs	Number of administrations (per year)	Total administration costs	Number of administrations (per year)	Total administration costs
Risankizumab	3.00	£406.07	5.00	£0.00	6.50	£0.00
Vedolizumab	3.00	£406.07	12.90	£460.21	17.23	£571.87

Footnote: A 50/50 split of IV/SC was assumed for vedolizumab.
Abbreviations: IV: intravenous; SC: subcutaneous.

References

1. National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition). Process and methods. Published: 26 September 2012. Available at: https://www.nice.org.uk/process/pmg4/resources/methods-for-the-development-of-nice-public-health-guidance-third-edition-pdf-2007967445701 (Accessed April 2022), 2012.
2. Bonovas S, Lytras T, Nikolopoulos G, et al. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther 2018;47:454-465.
3. National Institute for Health and Care Excellence. Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]. Available at https://www.nice.org.uk/guidance/indevelopment/gid-ta10872 [accessed 16th October 2023].
4. National Institute for Health and Care Excellence. Ozanimod for treating moderately to severely active ulcerative colitis. TA828. Available at https://www.nice.org.uk/guidance/ta828 [accessed 3rd July 2023].
5. National Institute for Health and Care Excellence. Upadacitinib for treating moderately to severly active ulcerative colitis. TA856. Available at https://www.nice.org.uk/guidance/TA856 [accessed 3rd July 2023].
6. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1-s106.
7. Hibi T, Ishibashi T, Ikenoue Y, et al. Ulcerative Colitis: Disease Burden, Impact on Daily Life, and Reluctance to Consult Medical Professionals: Results from a Japanese Internet Survey. Inflamm Intest Dis 2020;5:27-35.
8. National Institute for Health and Care Excellence (NICE). Mirikizumab for treating moderately to severly active ulcerative colitis. Technology appraisal guidance [TA925] Available at: https://www.nice.org.uk/guidance/TA925 [last accessed 25th October 2023].
9. AbbVie. Data on file. INSPIRE CSR.
10. AbbVie. Data on file. COMMAND CSR.
11. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active ulcerative colitis [TA633] Technology appraisal guidance. London, UK: National Institute for Health and Care Excellence. 2020. Available at https://www.nice.org.uk/guidance/TA633 [accessed 16th October 2023].
12. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active ulcerative colitis. TA342. Available from: https://www.nice.org.uk/guidance/ta342/resources/vedolizumab-for-treating-moderately-to-severely-active-ulcerative-colitis-pdf-82602604482757 (Accessed April 2022).
13. National Institute for Health and Care Excellence (NICE). Risankizumab for previously treated moderately to severly active Crohn's disease (TA888). Available at https://www.nice.org.uk/guidance/TA888/history [last accessed 23rd October 2023].
14. Honap S, Al-Hillawi L, Baillie S, et al. Ustekinumab for the treatment of moderate to severe ulcerative colitis: a multicentre UK cohort study. Frontline Gastroenterol 2022;13:517-523.
15. Medicines and Healthcare products Regulatory Agency. Risankizumab. Available at https://products.mhra.gov.uk/search/?search=risankizumab&page=1 [accessed 13 October 2023]
16. European Medicines Agency (EMA). Summary of product characteristics (SmPC). Stelara (ustekinumab) Available at https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf [last accessed 26th October 2023].
17. National Institute for Health and Care Excellence. Upadacitinib for treating moderately to severly active Crohn's disease. TA905. Available at https://www.nice.org.uk/guidance/TA905 [accessed 5th December 2023].
18. National Institute for Health and Care Excellence (NICE). User guide for company evidence submission template. Fast track cost-comparison case. Available at https://www.nice.org.uk/process/pmg32/resources/user-guide-for-the-cost-comparison-company-evidence-submission-template-pdf-72286772526277 [accessed 28 June 2023].
19. AbbVie Data on File. Protocol Version 3: Systematic literature reviews on the efficacy and safety, health-related quality of life, and economic outcomes of therapies for ulcerative colitis. .

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Risankizumab for previously treated moderately to severely active ulcerative colitis in people aged 16 and over [ID6209]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Crohn's & Colitis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's & Colitis UK is the UK's leading charity for everyone affected by Crohn's and Colitis. We're working to improve diagnosis and treatment, and to fund research into a cure; to raise awareness and to give people hope, comfort, and confidence to live freer, fuller lives. We want: • To drive world-class research that improves lives today and brings us closer to a world free from Crohn's and Colitis tomorrow • Everyone to understand Crohn's and Colitis • To support and empower everyone to manage their conditions • To drive high-quality and sustainable clinical care • Early and accurate diagnosis for all. Founded as a patients' association in 1979, we now have over 48,000 members across the UK. Our members include people living with the conditions, their families and friends, health professionals and others who support our work. We have 50 Local Networks which arrange educational meetings, generate publicity and organise fundraising. Funding is through membership subscriptions and a wide range of fundraising activities, including events, grants, legacies and corporate partnerships. Full details are available in our annual accounts Crohn's & Colitis UK's annual reports and accounts (crohnsandColitis.org.uk)
4b. Has the organisation received any funding from the company bringing the treatment to NICE for	Yes, we received £10,000 from AbbVie at the end of last year towards our Early Diagnosis work. This year (2023 and in to 2024) they have pledged £10,000 towards our core funding costs (ie organisational core costs). The contract has been signed but we are just awaiting the funds to be banked.

evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; and • research - our own and that of external organisations.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The symptoms of Ulcerative Colitis, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships.[1] [2] *"Life with UC has been difficult, as I was constantly ill over a period of years, I had my relationship break down. I have been lucky that my previous line manager at work had a daughter of his own who suffered from UC, so any hospital stays weren't a problem and he allowed me to work from home on particularly bad days."* **Quote from a person living with Ulcerative Colitis.** Given that disease severity is wide-ranging, and while each person has their own individual experience, we would like to take this opportunity to describe the impact and experience of the specific cohort of patients with moderate to severe Ulcerative Colitis that this guidance is targeting. This cohort is likely to comprise of patients with Ulcerative Colitis who experience more severe flares, weight loss, fever and constitutional symptoms, and whose disease has not responded to or are unable to tolerate other treatments, and/or can benefit from this treatment in particular. Truelove and Witts define severe Ulcerative Colitis as six or more stools a day plus at least one of the features of systemic upset (marked with an *): visible blood; pyrexia*; pulse rate greater than 90 BPM*; erythrocyte sedimentation rate (mm/hour) * and anaemia.[3] The Mayo Score defines severe Colitis as more than five stools a day, blood passed without stool, obvious blood with stools in most cases and severe disease (spontaneous bleeding, ulceration).[4] For this subgroup of patients with moderate to severe Ulcerative Colitis, the condition is more than challenging, but frequently overwhelming and detrimentally life-altering, as described below: *"I had 3 blood transfusions, multiple steroids, sleepless drained nights, cannula paracetamol, Iron deficiency, stomach ulcers and multiple drugs and many blood tests, not being able to eat and losing a*

	huge amount of weight over 2 and a half stone in just 2 weeks wasn't expected out the blue in my life." **Quote from a person living with Ulcerative Colitis.** **Mortality** There are risks and mortality associated with untreated and uncontrolled disease. NICE Guideline on Ulcerative Colitis states: 'Ulcerative Colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled'.[5] This is echoed by BSG Guidelines that state that 'acute severe Colitis is a potentially life-threatening condition'.[6] Acute severe Colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy).[7] Between 15-25% of patients with Ulcerative Colitis will need to be hospitalised due to an acute severe flare-up at some stage. Often this will be the first presentation of their disease.[8] When a flare occurs in acute severe Colitis, deterioration can occur rapidly. Patients will require close monitoring and review by appropriate specialists. It's also vitally important to make decisions quickly to avoid severe complications. The very real risks associated with acute severe Colitis include:

[1] Crohn's and Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards
[2] IBD UK (2019) IBD Standards
[3] NICE (2019) NICE Guideline on Ulcerative Colitis: Management (NG130) https://www.nice.org.uk/guidance/ng130/chapter/Recommendations
[4] Dignass, A,. Second European evidence-based consensus on the diagnosis and management of Ulcerative Colitis Part 1: Definitions and diagnosis. Journal of Crohn's and Colitis Vol 6. Issue 10 https://www.sciencedirect.com/science/article/pii/S1873994612004047#t0020
[5] NICE (2019) Guideline on Ulcerative Colitis: Management: Overview | Ulcerative Colitis: management | Guidance | NICE
[6] The British Society of Gastroenterology (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://gut.bmj.com/content/60/5/571.long
[7] Ibid
[8] Ibid

- Life-threatening haemorrhage
- Toxic megacolon - can occur in up to 1 in 40 people with Colitis[9]
- Perforation of the bowel[10]

Additional complications of chronic, uncontrolled, active Ulcerative Colitis also include:

- Osteoporosis and vitamin D deficiency. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity[11]
- Anaemia[12].
- Increased risk of cancer[13]

Impact on emotional and mental health

Emotional wellbeing can be significantly affected by difficulty in coping with personal lives and feelings of anger, embarrassment, frustration, sadness and fears of needing surgery or developing cancer.[14] Stigma and lack of wider understanding of the condition exacerbate the impact.

Anxiety and depression are higher in people with IBD, with mood disorders at least in part a consequence of the IBD itself and its medical treatment (e.g., corticosteroid therapy), surgery, including specifically colectomy and stoma formation.[15] Additionally, most reports indicate that stress may be involved in triggering relapse.

"*The last 9 months have been really quite horrible for me dealing with my UC and I went through a really low point in my life, feeling very anxious and depressed. I took 5 months off work and only*

[9] Parray, F. Q. et al. (2012). Ulcerative Colitis: a challenge to surgeons. Int. J. Prev. Med. 3, 749–63.
[10] IBDUK (2019) IBD Standards 2019: Homepage | IBD UK
[11] Mowat C, Cole A, Windsor A et al. (2011) Guidelines for the management of inflammatory bowel disease in adults. Gut, 60, 571-607.
[12] Crohn's and Colitis Foundation.(2020) Anaemia. https://www.crohnscolitisfoundation.org/sites/default/files/2020-03/anemia.pdf
[13] The British Society of Gastroenterology (2019) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html
[14] Cosnes J, et al., (2011). Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology, 140 (6), 1785-94.
[15] Graff L. A. et al., (2009). Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflamm Bowel Dis, 15 (7), 1105-18.

	recently started a new job. My UC really affected my social life and confidence especially with getting out of the house and carrying out simple tasks." **Quote from a person living with Ulcerative Colitis.** "*The isolation I have felt has been overwhelming. I can't take my children to the park, for a walk or play date or any of the other simple things that I used to take for granted. I do not have any kind of social life myself as it is simply not possible for me to go out when I may need to open my bowels with no warning."* **Quote from a person living with Ulcerative Colitis.** *"When I am unwell, the constant anaemia makes everyday life feel like wading through treacle, the pain can be crippling. The very real concern of faecal incontinence gives me physical symptoms of stress as well as affecting me emotionally and mentally."* **Quote from a person living with Ulcerative Colitis.** The experience of caring for someone with IBD can be especially difficult given that it is to some degree an invisible condition and due to the unpredictable nature of the symptoms, which many also find extremely uncomfortable to talk about, and the effects of treatment. For parents of young people, there are challenges around providing support, while enabling independence and seeing lives and aspiration affected by the son or daughter's condition. "*He was struggling to maintain a healthy weight, was constantly feeling sick, rushing to the toilet and in pain and missing a great deal of his work at a stage in his career that was very important to him. He was unable to continue his sport and his social life was negligible*." **Quote from the parent of a person living with Ulcerative Colitis.** **Social functioning** Social functioning can be impaired - leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. *"During the majority of my time living with UC and the ever-changing drugs, I had no quality of life. I was off sick from work for 8 months. I was unable to drive my children to or from school or make them their breakfast as this was the time, usually until about midday, that I could not leave the toilet. There*

	was no fun time with my 3 wonderful children or my husband, I was always in bed, in pain or on the toilet. We did not cuddle or play, because if any of them touched my tummy, it would be so sore. This period of illness really affected my confidence. My friends gave up coming around as I was so poorly. My quality of work really dropped. I continuously made mistakes because of the side effects from all the drugs." **Quote from a person living with Ulcerative Colitis.** Research shows that young people aged 16-25 with IBD who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. There is a clear associated "productivity loss" by health state, whereby the lowest score for health state (Visual Analogue Score 0-2.5) corresponds with a 71% productivity loss.[16]

Current treatment of the condition in the NHS

[16] Gay M et al. (2011) Crohn's, Colitis and Employment – from Career Aspirations to Reality. Crohn's and Colitis UK.

7. What do patients or carers think of current treatments and care available on the NHS?	There is unmet need amongst people with moderate to severe Ulcerative Colitis. Patients express dissatisfaction with many of the current treatment options. Many experience lack of response (primary or secondary) and/or adverse reactions. The effects of steroids are extremely unpleasant and long-term safety profile of other treatments, including biologics, are of some concern. "*When I am unwell, I struggle with extreme tiredness and extended periods in the bathroom which makes my working life very difficult. I work in construction so spend a lot of time away from toilets. Vedolizumab, when I first started, it was my wonder drug. It was difficult spending so much time in hospital but worth it to be completely symptom free. I was in remission for nearly 4 months.* *I was then given Golimumab which was a lot more convenient, and I liked having the control of self-administering. This however never gave me remission and my CRP worsened over the period I was taking it. I am now being offered Tofacitinib but have been told this is my final option*." **Quote from a person living with Ulcerative Colitis.** "*I have suffered with UC for 13 years. It's always been moderate to severe. I have tried all drugs including all biologics. All failed after a while. The best was Infliximab, I had my first ever remission for 2 years. However, it came to an end in Aug 2017. I had 18 months of pain and blood, countless hospital admissions, yet I was still pushed to try yet another biologic, Vedolizumab then Golimumab. None of it worked. 6 weeks later I had an emergency op and my colon was removed. My recovery is slow as I was ill for quite some time before and I'm building up my stamina now."* **Quote from a person living with Ulcerative Colitis.** *"My 'moon face' from the constant use of prednisolone was depressing and because of my ill health my hair became really thin. Prednisolone also affected my mood. I was so angry and unhappy. This also kept me awake at night, so I took sleeping pills."* **Quote from a person living with Ulcerative Colitis.** **Surgery** For many patients with Ulcerative Colitis, 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. *"Surgery would have been a massive emotional and psychological barrier for our son at this stage in his life*." Quote from a person living with Ulcerative Colitis. *"Personally, I'm not prepared for the drastic surgery of having my colon removed*." Quote from a person living with Ulcerative Colitis. 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. *"I had severe Pan Ulcerative Colitis. I started my journey with an emergency admission in a very poor state (…). I spent 2 weeks in hospital while they tried to stop the frequency and bleeding, I came out on steroids, cyclosporine and Asacol. I was better for a little while but soon became very ill again and was off work. I was put on azathioprine but could not tolerate this, so I was switched to mercaptopurine. This put me in remission for 3 years, when this no longer worked I was put on Simponi. The initial double dose showed some promising results, but the single dose didn't keep me in remission. Following this I* ***became dependent on steroids.*** ***My life was terrible quality. I missed out on opportunities at work, very rarely went anywhere and people*** *would comment on my features from the steroids, and they said I looked a strange green-yellow colour.* *Finally, I had enough of being ill and hospital admissions and blood transfusions and requested surgery to remove my colon. My consultant told me if I was in any other country, they'd have taken it out much sooner. The surgeon said it disintegrated as he was taking it out it was in such a bad state. I now have a j-pouch and*

	while life is a lot better it isn't the cure that was promised, and it impacts on my life considerably." Quote from a person living with Ulcerative Colitis. Surgery has significant associated long- and short-term risks which include: - general anaesthetic complications - infections - adhesions - pouchitis - pouch leakage - abscesses - fistulae - small bowel obstruction - post-operative bleeding - sexual dysfunction - delayed wound healing - nerve damage.[17,18] Additionally, a meta-analysis has shown 'an approximate threefold increase (from 15% to 48%) in the risk of infertility in women with Ulcerative Colitis as a result of ileal pouch anal anastomosis (IPAA).[19] Johnson et al. reported the infertility rate in females who had pelvic pouch surgery was significantly higher compared to females who were managed medically (38.1 % compared with 13.3 %; $p < 0.001$).[20] We would also urge the Committee to consider the persistent quality of life issues that impact multiple domains, including psychological and sexual functioning. A 2015 study found 81% experienced problems in at least one of the following areas: depression, work productivity, restrictions in diet, body image, and sexual function. In the same study, amongst moderate to severe Ulcerative Colitis patients, post-colectomy, 27% of men and 28% of women reported that their sexual life was worse now than before surgery.[21]

[17] IbidFF

[18] Brown, C. et al., (2015). Long-term outcomes of colectomy surgery among patients with Ulcerative Colitis. *Springerplus,* 4, 573.
[19] Waljee A, et al., (2006). Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in Ulcerative Colitis. Gut, 55 (11), 1575–1580.
[20] Johnson P, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, Cohen Z, McLeod R. Female infertility after ileal pouch-anal anastomosis for Ulcerative Colitis. Dis Colon Rectum. 2004 Jul;47(7):1119-26. doi: 10.1007/s10350-004-0570-7.
[21] Brown, C. et al., (2015). Long-term outcomes of colectomy surgery among patients with Ulcerative Colitis. *Springerplus,* 4, 573.

8. Is there an unmet need for patients with this condition?	The range of options available for treating Ulcerative Colitis 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. There are significant short and long-term side effects with corticosteroids, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis. Their use is also limited to induction of remission. "I was steroid dependent and all conventional UC therapies failed – including anti TNF (Infliximab). Long term steroid use resulted in osteoporosis at age 28. I was housebound for many years due to UC and was unable to work. Quality of life was zero." Quote from a person living with Ulcerative Colitis. Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them. In the majority of patients who do respond, the benefits take three to six months to appear. Significant risks of thiopurines including non-Hodgkin's lymphoma (as high as 4-5-fold compared with unexposed IBD patients and further increased when used in combination with anti-TNFs). Other side effects include early hypersensitivity reactions such as fever and pancreatitis, bone marrow suppression and hepatotoxicity requiring frequent lab monitoring during treatment. Anti-TNFs are increasingly being used earlier in the treatment pathway and can have a significant and positive effect on quality of life for patients. However, up to 40% of patients treated with anti-TNF therapy do not respond to induction therapy. In the approximately one-third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time. Overall, there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with Ulcerative Colitis to resume their lives and restore their quality of life.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients most likely to benefit from this drug are those for whom currently available therapies are ineffective, contraindicative or they develop an intolerance. In this group, it is likely that individuals, without further choice, will return to treatment/s which have already been established to be inadequate. This may include highly undesirable long-term steroid use or unproven unconventional therapy. It is also likely that patients in this group who exhaust all other treatment options would be forced to have a colectomy, either elective or as an emergency. *"I am well aware that these drugs have a very significant cost but without them, the last 12 years would have been very different for me. Even with them I have had to have 2 lots of surgery to remove scarred bowel but without them I think I would have had to have more extensive surgery and possibly not even be here to send this email. I am also well aware that I am on my last chance here with current available drugs having taken everything the NHS has to offer; if the vedo stops working then I have nowhere else to go with medication. New drugs and options for medication will be vital for my health going forward."* **Person with IBD, in which drug treatments have not been effective.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Prescription costs faced people living with long-term and chronic conditions, including Ulcerative Colitis, in England, are shown to contribute to economic disadvantage, which can impact adherence and lead to complications and increased cancer risks and cost to the NHS. However, the disadvantage is not specific to Risankizumab, and the value of an additional treatment option may will remain beneficial as it will reduce the risk of loss of response.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who have had little or no success with currently available medical treatment options, and wish to avoid or delay surgery, are likely to benefit. This would include young people wishing to complete studies and those for whom surgery would be considered unacceptable due to cultural or religious factors.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For certain religious groups, the impact of active disease and the effects of surgery may interfere with religious practices and cause distress, which could be alleviated by an additional medical therapeutic option. Although not specific to Risankizumab, prescription costs may also be a factor associated with lower income.

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is significant unmet need for people with moderate to severe Ulcerative Colitis. Current treatments remain far from optimal for patients, a substantial number of whom experience a lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety. • Risankizumab offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making).

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Cost Comparison

[ID6209] Risankizumab for previously treated moderately to severely active ulcerative colitis in people aged 16 and over

- **Would risankizumab be used at the same point in the patient pathway as ustekinumab in the NHS (i.e. following a TNF inhibitor)?**
- Yes – pretty much exactly ie after failure of anti-TNF (or potentially another first line advanced therapy). Also after multiple advanced therapies have failed. Likely to be very limited first line use in patients in whom TNF is not suitable – this is the same profile as for ustekinumab.
-
- **Is risankizumab more likely to displace ustekinumab than vedolizumab?**
- Yes – the similarities in mechanism of action as well as the position in the treatment pathway make risankizumab a more logical replacement for ustekinumab than for vedolizumab (the latter also being approved first-line, which risankizumab is not and therefore will not displace vedolizumab in this setting). In addition, the patient profile of ustekinumab-treated patients is likely to include a reasonable proportion of patients with extra-intestinal manifestations in whom vedolizumab is unlikely to be chosen but who would be suitable for treatment with risankizumab instead.

Efficacy

- **Are all of the efficacy outcomes relevant (clinical response, clinical remission, endoscopic improvement). Are any more important than others?**
- Yes. All are relevant and important in their own ways. I think it is difficult to assign ranks of importance as it depends (in part) from whose perspective one is asking the question. For example, as a clinical trialist, I am probably most impressed by the hardest endpoints – eg mucosal improvement – as evidence of efficacy and likelihood of altering long-term outcomes. Alternatively, as a doctor who cares about how my patients feel, then clearly clinical remission is relevant. Even long-term clinical response is important as this may be the best we can hope for in some patients with very difficult disease

- NMA suggests that risankizumab has similar efficacy to ustekinumab, albeit with wide credible intervals. Does that align with your clinical experience/expectation?
- Yes. The experience of p40 inhibition vs p19 inhibition in several inflammatory conditions suggests that the latter is as good as or better than the former. Thus, overall, acknowledging the weaknesses of NMA, I think it is entirely believable that risankizumab is at least as effective as ustekinumab.
- NMA suggests there may be meaningful treatment effect differences between risankizumab and vedolizumab. Does that align with your clinical experience/expectation?
- Probably not, although clearly my clinical experience of risankizumab in UC is very limited. I would be very wary of over-interpretation of NMA in this context; the vedolizumab Gemini 1 study recruited between 2008-12. Adalimumab was only licensed for UC in 2012. Therefore, the vedolizumab trial included only anti-TNF failed patients most of whom will only have been exposed to infliximab alone. This is a totally different cohort of patients to the risankizumab trial cohort many of whom will have been exposed not only to anti-TNF but also to other biologics (including vedolizumab) and JAK inhibitors.
- In addition, the 'placebo' response in the maintenance arm of rerandomized responder studies of p19 and p40 agents is always high due to the 'hangover' effect of these drugs. This is a consistent finding across several trials in IBD and challenges the ability to interpret the maintenance arm of NMAs. For context, the clinical remission rate in the 'placebo' arm in the maintenance trial of pisankizumab was 10 percentage points higher than in the vedolizumab trial (approx. 25%vs15%)

Model assumptions

- In the company's model, all patients on induction treatment continue to maintenance treatment, and there is no treatment discontinuation during the maintenance phase. This is based on the assumption that the discontinuation rates for ustekinumab and risankizumab will be equal, and have therefore been omitted for simplicity. **Is the assumption of equal discontinuation rates reasonable?**
- Yes – I think so – both drugs are well tolerated and neither suffesr from significant immunogenicity.
- The EAG assumes 35.7% of patients having risankizumab or ustekinumab would not continue to the maintenance phase (based on risankizumab trial data). Is this rate reasonable?

- Not on translation to clinical practice. There are two main reasons 1) the definition of lack of response to induction therapies in clinical trials is an arbitrary, agency-driven endpoint that is much stricter than what we use in clinical practice. As an example, if a patient has complete symptomatic remission at the end of induction, but has even a tiny patch of active inflammation that reaches Mayo 2, or has a single ulcer despite vast mucosal improvement, then this patient is deemed a non-responder. This is not that uncommon in real life (although most clinicians don't scope at week 8-12 so it isn't necessarily well understood). Equally, we will tend to continue treatment if patients are feeling better without necessarily reaching trial-defined definitions of clinical response.
- 2) Patients in clinical trials are a significantly more refractory cohort than real-life patients.
- Overall, therefore, I would say this figure is greatly higher than real-life practice. As a real-life example, in a multicentre UK cohort of ustekinumab-treated patients with UC (96% of whom were biologic failures), only 4 of 110 patients stopped due to primary non-response. I cite this simply to show the difference of real world and clinical trial data (Honap et al Forntline Gastroenterology 2022)
- **The EAG assumes an annual discontinuation rate in the maintenance phase of 8.7% (based on ustekinumab data) and a rate of 1.9% in a scenario analysis (based on risankizumab data). Which is most plausible?**
- I would say somewhere in between. 1.9% definitely feels low but 8.7% feels high – does this come from LTE from a clinical trial as, again, I would say these figures don't represent real life. I would quote that sort of figure for more immunogenic drugs like anti-TNF.
- **Is it reasonable to assume dose escalation for 92.5% of ustekinumab patients and 30% for risankizumab patients?**
- For ustekinumab – yes. Nearly all patients are on q8 treatment. For risankizumab, I really can't say as there is no real-world experience - sorry

I hope the above is helpful and I am sorry I couldn't attend the meeting live.

External Assessment Group Report

Risankizumab for people with previously treated moderately to severely active ulcerative colitis

Produced by: Bristol Technology Assessment Group, University of Bristol

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Rider on responsibility for report
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.

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Contributions of authors
Julian Higgins, Chris Cooper, Melissa Benavente, and Eva Li critiqued the clinical effectiveness evidence reported. Elsa Marques, Joe Carroll, and Nicky Welton critiqued the cost-comparison analysis. Chris Cooper and Eva Li critiqued the systematic review informing the clinical comparison and the review of costs. Chris Cooper critiqued the searches informing this submission. All authors were involved in drafting and commenting on the final report.

Confidential data (CON) are highlighted in blue throughout the report.

Abbreviations

Abbreviation	Definition
AE	adverse effect
BNF	British National Formulary
CCA	cost comparison analysis/ cost comparison approach
cPAS	confidential Patient Access Scheme
CSR	clinical study report
EAG	Evidence Assessment Group (Bristol TAG)
IV	intravenous injection
JAK	janus kinase
MTA	multiple technology appraisal
NMA	network meta-analysis
OR	odds ratio
PAS	Patient Access Scheme
ROBIS	risk of bias in systematic reviews tool
SAE	serious adverse effect
SC	subcutaneous injection
SmPC	Summary of Product Characteristics
TNF	tumour necrosis factor
UC	ulcerative colitis
vs	versus

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1 EXECUTIVE SUMMARY

AbbVie (the company) seek to make a case that their drug, risankizumab, is similarly effective and cheaper than ustekinumab for people with moderately or severely active ulcerative colitis in whom anti TNF alpha drugs are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

The company proposes that:

1. ustekinumab is a reasonable comparator for risankizumab based on current UK clinical practice.
2. risankizumab is similarly effective and as safe as ustekinumab; and
3. risankizumab, whilst initially [redacted] expensive in the induction phase compared with ustekinumab, is a [redacted] treatment across a 10-year time horizon. As patients are assumed to receive both treatments for 10-years, the [redacted] made when comparing with ustekinumab in the maintenance phase [redacted] the incremental cost of risankizumab in the induction phase.

The EAG is broadly in agreement that a cost comparison analysis is appropriate, having reviewed the company's submitted evidence and received advice from our clinical advisors.

The summary of EAG's key issues:

- In the absence of head-to-head trials comparing risankizumab to ustekinumab, the company present an NMA to make the case for clinical similarity. The NMA has been well conducted but the results do not provide evidence of similar clinical effect due to the wide 95% credible intervals around some results, indicating considerable uncertainty in the relative efficacy and safety of the two treatments. Given the lack of definitive evidence on non-inferiority, it is not possible to rule out there being differences in treatment outcomes and side effects.

- The evidence provided is short-term and inferences cannot necessarily be extrapolated for the 10-year period of analysis.

- The company's model is very simplistic and ignores important factors that would decrease or overturn the cost-differential between the two drugs. For example, it does not include discontinuation for either risankizumab or ustekinumab. In the clinical trials, patients only continued to maintenance therapy if they responded to treatment. Serious adverse events can also lead to discontinuation, as evidenced by the clinical study report for the INSPIRE and COMMAND studies. The EAG also considers that given that patients receive treatment over a period of 10-years, it is important to discount future costs and is in line with the NICE guidance for EAGs on cost comparison appraisals.

- The EAG's clinical advisors suggested that vedolizumab would be a reasonable additional comparator alongside ustekinumab. In a cost-comparison analysis for mirikizumab in TA925, a new drug recently approved for use in the same patient group, mirikizumab was also compared with both ustekinumab and vedolizumab. The EAG explored a comparison with vedolizumab in a scenario analysis.

2 BACKGROUND

This report provides a critique of the evidence submitted by the company (Abbvie) in support of risankizumab for moderate to severely active ulcerative colitis (UC) for whom anti-TNF alpha drugs are deemed unsuitable or where prior biological treatment is not tolerated or not working well enough. It considers the company's evidence submission and executable model received on 06/11/2023. It also considers the company's response to a request for clarification from the EAG received on 7/12/2023 and additional results including an updated economic model received on the 19/12/2023.

The company considers that a cost-comparison approach (CCA) is appropriate as they claim that risankizumab has similar effectiveness and is cheaper than ustekinumab for treating patients with moderately to severely active UC, in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.

The company seek to position risankizumab as a second line treatment for patients with moderately to severely active UC, after failure of anti-TNF alpha drugs. In that sense, risankizumab is being positioned as a direct competitor to vedolizumab, ustekinumab, mirikizumab, and JAK inhibitor drugs. The company proposes that ustekinumab is a reasonable comparator for risankizumab based on similarity of mechanism of action, current UK clinical practice.

Risankizumab is a fully humanised monoclonal antibody designed to attach to the p19 subunit of Interleukin-23, blocking the release of inflammatory proteins.[1-3] Risankizumab has a similar mechanism of action to mirikizumab and to ustekinumab. The EAG's clinical advisors state that clinical decision-making is multifactorial, and patients may try more than one treatment within a class if they had an initial response on a drug in that class.

Risankizumab is also used in moderate-to-severe plaque psoriasis, active psoriatic arthritis, and moderate-to-severe Crohn's disease. [1]

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The company's definition of the decision problem aligns with the final NICE scope (Table 1). Our clinical advisors confirm that the population is representative of UK clinical practice.

3.1 Appropriateness of the comparator

In a CCA, the company is permitted to pick a single comparator technology from the NICE scope provided that it aligns with NICE recommend treatments and has a substantial market share.[4] The company have chosen ustekinumab. The EAG agrees that this can be considered an appropriate comparator. The EAG considers the following drugs could also have been considered as appropriate comparators:

Vedolizumab: approved in NICE Guidance in TA342 (June 2015). Clinical advisors to the EAG agrees it is commonly used for this patient population. The company argues that vedolizumab has a different mechanism of action from risankizumab and would not be displaced by rizankizumab in clinical practice.[5] Although the EAG accepts that vedolizumab has a different mechanism of action, this is not a reason to exclude it as a comparator. Clinical advisors to the EAG advised that clinical decision-making is multifactorial and vedolizumab would be an option for patients they would treat with risankizumab or ustekinumab, and therefore it is a relevant comparator.

Mirikizumab: NICE recently approved in TA925 (October 2023) for use in the same population.[6] The company notes that mirikizumab has a similar mechanism of action to risankizumab. Mirikizumab is not yet established in UK clinical practice, and therefore not a relevant comparator for this CCA, but is likely to become a relevant comparator in the future.

JAK inhibitors: Another class of drugs positioned as second line after failure of anti-TNF alpha drugs and are potential comparators for patients who are not pregnant or trying to get pregnant.

The number and types of available treatment options in UC is growing and more options are available. For example, etrasimod is a newer drug with a different mechanism of action and currently undergoing NICE appraisal (expected publication in February 2024). Clinical advice to the EAG suggests that there is considerable scope to select treatments based on centre, clinician, or patient preferences, and that mechanism of action is not a reason to exclude a treatment as an option.

3.2 Market share

Based on its clinical advice and the 2019 market research data from Janssen (TA633),[7] the EAG notes that vedolizumab is the most frequently used biologic for treating UC after failure of anti-TNF alpha drugs. Evidence submitted by the company in their budget impact analysis estimates that the market share of vedolizumab (subcutaneous [SC] + intravenous [IV] delivery) is [redacted] and ustekinumab [redacted]

NICE guidance for submission under a CCA states that the company's choice of comparator does not need to have the biggest market share, nor the cheapest or most effective option,[4] and so ustekinumab is an appropriate comparator on that basis. However, the market share data illustrate the position of vedolizumab as a potential additional comparator alongside ustekinumab. Mirikizumab cost comparison appraisal in TA925 also compared mirikizumab against ustekinumab and vedolizumab.[6]

Table 1: Summary of Decision Problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or 1 or more biologic therapies.	Adults with moderately to severely active UC in whom anti TNF alpha drugs are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough.	The target population for risankizumab in this submission is in line with the anticipated use of risankizumab in UK clinical practice and with the patient population in which ustekinumab is recommended by NICE in TA633. This positioning represents a subpopulation of the anticipated licensed indication and the population specified in the NICE final scope for this evaluation.	After consulting clinical advisors, the EAG agrees that the populations are similar.
Intervention	Risankizumab	As per scope	NA	The intervention matches the NICE scope.
Comparator(s)	• anti TNF-alpha drugs (such as infliximab, adalimumab or golimumab) • JAK inhibitors (such as tofacitinib, filgotinib or upadacitinib) • ustekinumab • vedolizumab • ozanimod • etrasimod (subject to ongoing NICE evaluation) • mirikizumab (subject to ongoing NICE evaluation).	Ustekinumab	The company claims that ustekinumab is the only relevant comparator to risankizumab for the following reasons: • Ustekinumab represents established UK clinical practice in the proposed target population. • Both ustekinumab and risankizumab have a similar mechanism of action of targeting interleukin-23 inhibitors. They also have a similar route of administration; IV in the induction phase and SC in the maintenance phase. • Evidence on a series of network meta-analyses submitted by the company claims comparable efficacy and safety (see section 3.9 in the company submission)	The EAG agrees that ustekinumab is a relevant comparator in this population with established clinical practice and market share. The EAG considers other comparators positioned as second line after anti-TNF alpha drugs with established clinical practice, such as vedolizumab, could

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			The company claims all other comparators in the scope are not relevant for the following reasons: • Mirikizumab has a similar mechanism of action but not yet established UK clinical practice . • Etrasimod has not yet been appraised by NICE in this indication. • All other comparators have a different mechanism of action and therefore not comparable to risankizumab in this indication.	have also been considered relevant comparators, regardless of mechanism of action. See section 3.1.
Outcomes	The outcome measures to be considered include: • rate of and duration of response, relapse and remission • corticosteroid-free remission • rate of endoscopic improvement • rate of hospitalisation • rate of surgical intervention • mortality • adverse effects of treatment • health-related quality of life.	• proportion of patients with clinical response and remission (assessed by the Adapted Mayo score) at Week 12 and Week 52 • proportion of patients with corticosteroid-free remission through Week 52 • proportion of patients with endoscopic improvement (assessed by the endoscopy subscore) at Week 12 and Week 52 • proportion of patients with UC-related hospitalisation through Week 12 and Week 52 • occurrence of UC-related surgeries through Week 12 and Week 52 • mortality • adverse effects of treatment	Further outcomes of clinical importance are also included in this submission, including but not limited to: • proportion of patients with no bowel urgency at Week 12 and Week 52 • proportion of patients with no abdominal pain at Week 12 and Week 52 • proportion of patients with no nocturnal bowel movements at Week 12 and Week 52 • proportion of patients with no tenesmus at Week 12 and Week 52 • change from baseline in number of faecal incontinence episodes at Week 12 and Week 52 • change from baseline in number of days per week with sleep interrupted due to UC at Week 12 and Week 52	The outcomes align with the NICE scope other than surgical intervention which is an outcome in the cost but not the clinical review. The company reports results for these outcomes for the placebo-controlled trials of risankizumab. For the comparison of risankizumab versus ustekinumab, the company reports a subset of the outcomes (clinical response, clinical

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		• health-related quality of life (assessed using EQ-5D-5L, WPAI-UC, SF-36, FACIT-Fatigue, PGIS and IBDQ)		remission, endoscopic improvement, serious adverse events and serious infections). The core outcomes driving the model are all present.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	• CCA with a 10-year time horizon from an NHS perspective	The company claims similar clinical health benefits and safety of risankizumab compared with ustekinumab and is cost saving, and therefore carried out a CCA.	The EAG agree that the CCA is appropriate and so reporting of incremental costs per QALY is not required. The EAG agrees with the time horizon and perspective on costs.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	If the evidence allows the following subgroups will be considered: • people who have been previously treated with 1 or more biologic therapies • people who have been previously treated with a JAK inhibitor • people who have not received a prior biologic therapy or a JAK inhibitor.	Clinical efficacy data for risankizumab from the pivotal INSPIRE and COMMAND trials have been presented within this submission for the following subgroups: • Advanced therapy-inadequate responder (IR), defined as patients who have had an intolerance or inadequate response to advanced therapy – see Section B.3.7. • Non-advanced therapy-IR, defined as patients who have had an inadequate response or intolerance to conventional therapy. This population also included	Non given for the CCA	There were no available data to carry out subgroup analysis suggested in the scope in the cost- comparison analyses by the EAG.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		patients who had previously received biologic therapy or tofacitinib but had stopped therapy based on reasons other than inadequate response or intolerance – see Section B.3.3.1. • No subgroups analyses were considered by the company in the cost comparison analysis		
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No special considerations related to equity or equality were included	None given	The EAG agrees no special equity or equality issues need to be raised.

4 SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

Our critique follows NICE guidance for a 'light touch' review of the evidence.[4]

4.1 Critique of the trials of the technology of interest

The company describe their two trials, INSPIRE (for the induction phase) and COMMAND (for the maintenance phase). INSPIRE and COMMAND are Phase III, double-blind, placebo-controlled trials evaluating the efficacy and safety of risankizumab in adults with moderately to severely active UC. We assessed the risk of bias to be low in INSPIRE and low for safety results from COMMAND but had some concerns about risk of bias in efficacy results in COMMAND due to imputation of missing data (see Appendix C).

INSPIRE consists of two sub-studies, a Phase II dose-finding trial (sub-study 1) and a Phase III trial (sub-study 2). The company submission presented results from sub-study 2 only, which randomised 977 participants in a 2:1 ratio into a comparison of risankizumab 1200mg IV (weeks 0, 4, 8) with placebo for 12 weeks. INSPIRE sub-study 2 provides convincing evidence that risankizumab is an efficacious treatment in the induction phase for the outcomes examined (including clinical remission, clinical response and endoscopic improvement: see Company Submission, Document B, Tables 23 and 24). In response to a request for clarification from the EAG (clarification response, question A3), the company provided results from sub-study 1. This included a randomised comparison between 1200 mg IV risankizumab and placebo in a similar population as sub-study 2. Results from sub-study 1 were broadly consistent with those of sub-study 2.

COMMAND consists of three sub-studies, the first of which (sub-study 1) is a randomised trial and is appropriately selected by the company as the relevant evidence about the maintenance phase. Sub-study 1 randomised 548 participants in a 1:1:1 ratio to receive 180 mg SC risankizumab, 360 mg SC risankizumab or SC placebo for 52 weeks. COMMAND sub-study 1 provides convincing evidence that risankizumab is an efficacious treatment in the maintenance phase for the outcomes examined (including clinical remission and endoscopic improvement: see Company Submission, Document B, Tables 25 and 26).

4.2 Critique of the systematic review

The systematic review sought trials of treatments for moderately to severely active UC. In the first instance they used this to identify evidence directly comparing risankizumab and ustekinumab. It identified no such studies. We critiqued the systematic review using the ROBIS tool [8] (reported in full in Appendix A). The review was at low risk of bias. The EAG searches were also unable to find any studies directly comparing risankizumab with ustekinumab.

4.3 Critique of the network meta-analyses (NMA)

The company performed a network meta-analysis (NMA), based on the same systematic review of randomised trials referred to in Section 4.2. They included trials of the following four treatments with placebo controls:

- Risankizumab

- Ustekinumab
- Vedolizumab
- Mirikizumab

The EAG agrees with the rationale for the NMA, based on the lack of evidence directly comparing risankizumab with ustekinumab.

The company present results for two populations: the overall population and a bio-exposed population (defined as "patients with moderately to severely active UC who have received one or more prior biologic therapies and had an inadequate response or intolerance; and those who stopped prior biologic therapy for reasons other than inadequate response or intolerance"). These populations are consistent with the NICE scope.
The company examined a subset of the outcomes listed in the NICE scope, and did not include corticosteroid-free remission, rate of hospitalisation, rate of surgical intervention or health-related quality of life. In response to a request for clarification from the EAG (clarification response, question A2), the company explained that omission of these outcomes was due to low numbers of events, lack of data, and variation in outcome definitions across trials. The EAG is content with this explanation.

The company critiqued all studies included in the NMA (including INSPIRE and COMMAND) for risk of bias using the University of York Centre for Reviews and Dissemination checklist and RoB 2.[9, 10] RoB 2 assessments were undertaken for the trials as a whole rather than separately for results for different outcomes. This is not how RoB 2 should be implemented.

We repeated the RoB 2 assessments separately for efficacy and safety outcomes of all studies included in the NMA and generally agree with the company's assessment (Appendix C). In most aspects we regard the trials to be at low risk of bias. However, we had concerns about missing data since some trials had large or unreported proportions of missing outcome data, particularly during the maintenance phase. Where reported, the proportions of participants with missing data tended to be different between treatment arms, with greater proportions missing in the placebo groups. Missing data were generally imputed (specifically as non-responders for the efficacy outcomes), which would be likely to bias the results in favour of the active intervention. There is insufficient information about missing data on safety outcomes for us to predict the impact of missing data on these outcomes. However, for the company's trials, for which we have detailed information, the safety analyses appear to have included almost all participants, so were judged to be at low risk of bias. If similar approaches had been used for the other trials, our concerns for safety outcomes would be alleviated.

We critiqued the NMA using a preliminary version of the ROB NMA tool, a tool to assess risk of bias in NMAs [11] and found it to be at low risk of bias (Appendix B). There were two minor areas of concern. First, interventions were excluded from the NMA because they had different mechanisms of action, a reason we do not support. However, we think this is unlikely to have introduced bias into the comparisons among the interventions that were included because previous NMAs have not identified head-to-head comparison among the drugs, although it may have resulted in reduced precision. Second, as discussed above, we had concerns about bias due to missing outcome data in several of the trials, particularly for

the maintenance phase. However, it is possible that these biases had minimal impact on the NMA, because, if there was a similar amount of bias in favour of the active intervention in each trial, these could be 'cancelled out' in the indirect comparisons made as part of the NMA.

4.3.1.1 Results of the NMA

We focus here on the primary clinical outcomes (remission, response, endoscopic improvement), and safety outcomes (serious infections and serious AEs) from the NICE scope.

The company focus on comparison of risankizumab with ustekinumab. We summarise the evidence for clinical similarity of these treatments first, before addressing an alternative comparison based on the company's NMA, risankizumab vs vedolizumab (which the EAG explores as a scenario analysis in Section 6.3.8 of this report).

4.3.1.1.1 Risankizumab vs ustekinumab

Table 2 summarises results from the NMA for the induction phase for all outcomes analysed and both clinical populations. Some of the NMAs produce similar point estimates (specifically for clinical response in the overall population and endoscopic improvement for the bio-exposed population). However, our principal observation from the NMAs is that the credible intervals are wide for almost all outcomes, with all but one 95% credible interval including either a doubling or a halving (or both) of the odds of the event. This indicates uncertainty in the relative efficacy and safety of risankizumab and ustekinumab.

Table 2: Induction phase – NMA results for risankizumab vs ustekinumab.
Odds ratios (ORs) with 95% credible intervals. ORs > 1 favour risankizumab for efficacy outcomes and favour ustekinumab for safety outcomes.

Population	Efficacy		Safety	
	Clinical response	**Endoscopic improvement**	**Serious infections**	**Serious adverse events**
Induction (overall)	[redacted]	[redacted]	[redacted]	[redacted]
Induction (bio-exposed)	[redacted]	[redacted]	Not reported	Not reported

In the maintenance phase, comparisons are made between different doses of risankizumab and schedules for ustekinumab (Table 3 and Table 4). Point estimates for the efficacy outcomes are broadly near 1 (the point of clinical equivalence between risankizumab and ustekinumab), but again the credible intervals are wide for all outcomes, indicating uncertainty in the relative efficacy and safety of the two treatments. Credible intervals for most of the safety outcomes are very wide (encompassing a quartering or quadrupling of the odds of the event).

Table 3: Maintenance phase – NMA results for risankizumab vs ustekinumab (overall population).

ORs with 95% credible intervals. ORs > 1 favour risankizumab (R) for efficacy outcomes and favour ustekinumab (U) for safety outcomes.

	Efficacy			Safety	
	Clinical remission	Clinical response	Endoscopic improvement	Serious infections	Serious adverse events
R 180mg vs U 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R 180 mg vs U 90 mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R 360mg vs U 90 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R 360 mg vs U 90 mg Q12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Maintenance phase – NMA results for risankizumab vs ustekinumab (bio-exposed population).

ORs with 95% credible intervals. ORs > 1 favour risankizumab (R) for efficacy outcomes and favour ustekinumab (U) for safety outcomes.

	Efficacy		
	Clinical remission	Clinical response	Endoscopic improvement
R 180mg vs U 90 mg Q8W	[redacted]	[redacted]	[redacted]
R 180 mg vs U 90 mg Q12W	[redacted]	[redacted]	[redacted]
R 360mg vs U 90 mg Q8W	[redacted]	[redacted]	[redacted]
R 360 mg vs U 90 mg Q12	[redacted]	[redacted]	[redacted]

4.3.1.1.2 Risankizumab vs vedolizumab

As outlined in section 3.1, we consider that vedolizumab could have been used as an alternative comparator, based on its use in UK clinical practice and market share. Using the company's NMA, we summarise the results of comparisons of risankizumab with vedolizumab in Table 5, Table 6 and Table 7. In response to the EAGs clarification questions, the company now report a cost comparison analysis comparing risankizumab with vedolizumab (see section 6).

Table 5 summarises the results in the induction phase, comparing risankizumab with vedolizumab. The point estimates for efficacy favour risankizumab, and 95% credible intervals are such that the evidence for this superiority is reasonably strong. There is also evidence that fewer serious adverse events are associated with risankizumab than with vedolizumab. Results for serious infections are very uncertain.

Table 5: Induction phase – NMA results for risankizumab vs vedolizumab.
ORs with 95% credible intervals. ORs > 1 favour risankizumab for efficacy outcomes and favour vedolizumab for safety outcomes.

	Efficacy		Safety	
	Clinical response	Endoscopic improvement	Serious infections	Serious adverse events
Induction (overall population)	[redacted]	[redacted]	[redacted]	[redacted]
Induction (bio-exposed population)	[redacted]	[redacted]	Not reported	Not reported

In the maintenance phase, comparisons are made between different doses of risankizumab and schedules for vedolizumab (Table 6 and Table 7). There is evidence, both for the overall population and the bio-exposed population, of greater efficacy of vedolizumab compared with risankizumab during the longer maintenance phase, although some of the credible intervals include 1. Results for the safety outcomes are much more uncertain, and do not provide evidence either way as to which drug has lower rates of serious infection or serious adverse events.

Table 6: Maintenance phase – NMA results for risankizumab vs vedolizumab (overall population).
ORs with 95% credible intervals. ORs > 1 favour risankizumab (R) for efficacy outcomes and favour vedolizumab (V) for safety outcomes.

	Efficacy			Safety	
	Clinical remission	**Clinical response**	**Endoscopic improvement**	**Serious infections**	**Serious adverse events**
R 180mg vs V 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R 180 mg vs V 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R 360mg vs V 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

R 360 mg vs V 300 mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Maintenance phase – NMA results for risankizumab vs vedolizumab (bio-exposed population).

ORs with 95% credible intervals. ORs > 1 favour risankizumab (R) for efficacy outcomes and favour vedolizumab (V) for safety outcomes.

	Efficacy		
	Clinical remission	**Clinical response**	**Endoscopic improvement**
R 180mg vs V 300 mg Q4W	[redacted]	[redacted]	[redacted]
R 180 mg vs V 300 mg Q8W	[redacted]	[redacted]	[redacted]
R 360mg vs V 300 mg Q4W	[redacted]	[redacted]	[redacted]
R 360 mg vs V 300 mg Q8W	[redacted]	[redacted]	[redacted]

4.4 Summary

The EAG supports the company's proposal that this appraisal is suitable for the CCA. The choice of ustekinumab as the comparator was reasonable, but vedolizumab could also have been considered an appropriate comparator. The main caveat to this is that the evidence presented in the company's submission was not of clinical equivalence. There were no head-to-head trials comparing risankizumab to ustekinumab, and the company presented an NMA to make the case for clinical similarity. Although the NMA was well conducted, the results have wide 95% credible intervals, indicating considerable uncertainty in the relative efficacy and safety of the two treatments. Given the lack of definitive evidence on non-inferiority, it is not possible to rule out there being differences in treatment outcomes and side effects. Nonetheless, the EAG regards it as unusual in general for trials to provide firm evidence of treatment equivalence.

After consultation with clinical advisors, and consultation of market share data submitted by the company, the EAG believes that vedolizumab is also an important comparator with substantial market share in clinical use for second line treatment after anti-TNF alpha drugs. Both vedolizumab and ustekinumab were also considered comparators in the recent cost comparison analysis for mirikizumab for UC in TA925 .[6]

5 SUMMARY OF THE EAG'S CRITIQUE OF COST COMPARISON EVIDENCE SUBMITTED

The company developed a CCA of risankizumab compared with ustekinumab over a 10-year time horizon, under the assumption of clinical equivalence between risankizumab and ustekinumab.

5.1 Critique of literature review

The company conducted a systematic literature review of the cost and resource use data in moderate to severely active ulcerative colitis. This was critiqued using the ROBIS tool.[12] The review was at low risk of bias. No costs in the cost comparison analysis were identified from the resource-use systematic review. The EAG agrees with this finding.

5.2 Critique of the Company's model

5.2.1 The model structure

The company's model is developed in Excel to calculate costs for risankizumab and ustekinumab over a 10-year time horizon. Patients incur costs during a short-term induction phase, followed by a long-term maintenance phase. The model is more simplistic than previous cost-comparisons in the clinical area (e.g., TA925[6]). For example, it only considers treatment acquisition and administration costs, but no other treatment-related or follow-up costs; assumes that all patients continue into the maintenance phase regardless of whether they respond to treatment in the induction phase; and it does not incorporate discontinuation of treatment at any time, or re-initiation rates.

The model incorporates the possibility of dose escalation for patients undergoing either treatment (section 5.2.5).

5.2.2 Time horizon

The company models the costs of risankizumab and ustekinumab over a 10-year time horizon. Clinical advice to the EAG found this time horizon to be appropriate. The company produces alternative scenarios of 5, 15, and 20 years. The results are sensitive to the time horizon. This is because risankizumab is [redacted] than ustekinumab in the induction phase, [redacted] in the maintenance phase; the longer the time horizon, the [redacted] risankizumab is compared with ustekinumab.

5.2.3 Treatment acquisition and administration costs

Treatment acquisition costs for ustekinumab were taken from drug list prices as published in the BNF. Risankizumab unit dose [redacted] is [redacted] than ustekinumab unit dose (130mg or 90mg) at drug list prices.

Treatment administration costs were included for treatments administered intravenously (IV). Risankizumab and ustekinumab treatments delivered by subcutaneous (SC) injection were assumed to be delivered by patients and incur no additional administration costs. Different administration costs were calculated for both risankizumab and ustekinumab in the first year due to the differing dosing schedules of the IV treatments in the induction period.

The company used appropriate NHS reference costs for a gastroenterology service to cost an IV administration. The model includes healthcare resource costs related to the administration of the drugs compared, however due to the similar administration schedules, there were no large differences in administration costs between the two drugs. Treatments and administration costs are relatively small compared with drug acquisition costs.

The EAG agrees with the treatment and acquisition costs provided in the model.

5.2.4 Equivalency of treatment effects, adverse events, and side effects

The company's model assumes all treatment effects, adverse events, and side effects, are similar for risankizumab and ustekinumab throughout the period of analysis and therefore excludes them from the model. Following a request made at the clarification question stage, the company provided a scenario analysis including the cost of treating serious adverse events (sepsis, pneumonia, urinary tract infection, respiratory infection, and bronchitis) within the model. The company bases their argument for equivalency on the fact that the two drugs have the same mechanism of action and the results from their NMAs (section 4.2.3).

The EAG argues that:

a) The clinical effectiveness of the two drugs appears broadly similar but the NMA results are uncertain, so the results are also consistent with risankizumab being more or less effective and safe than ustekinumab (section 4.3).

b) Evidence submitted on similarity of treatment effects, adverse events, and side effects is immature. All evidence is short-term (52 weeks), and these relative effects may not persist over the 10-year period of the analysis.

c) Similar mechanisms of action do not necessarily mean equal effectiveness and safety profiles. Clinical advisors to the EAG advised that patients who experience side effects with one drug will not necessarily experience those side effects with the other drug even if the mechanism of action is the same.

d) It is also unclear whether quality-of-life or discontinuation rates would differ between the two treatments. No comparative evidence is provided on these important outcomes for both drugs.

5.2.5 Dose escalation

The proportion of patients requiring dose escalation in the ustekinumab group is the major driver of the increased costs for ustekinumab compared with risankizumab in the maintenance phase, and this is not explored in sensitivity analyses in the company's model. Dose escalation for patients receiving ustekinumab is achieved through increased frequency, with 90mg doses (standard dose) given at 8-week intervals instead of 12-week intervals. Dose escalation for patients receiving risankizumab instead occurs by increasing the dose from 180mg to 360mg, but still at 8-week intervals.

[redacted].

Patients are assumed to be escalated immediately after the induction phase. The model assumes that 92.5% of patients receiving ustekinumab are escalated, whereas only 30% of patients receiving risankizumab are escalated. Previous TAs in this area [6, 7] have assumed a 30% escalation rate based on the rates seen for anti-TNF alpha drugs. However, the company assumes a higher escalation rate for ustekinumab based on clinical expert opinion and the assumptions made in the risankizumab TA for Crohn's disease.[13]

The EAG clinical advisors agree that the proportion of patients receiving the escalated dose of ustekinumab is much higher than 30%, and that 92.5% is a reasonable estimate.

The EAG notes that the assumption of different escalation rates contradicts the company's argument that efficacy and safety is similar for both drugs. Clinical advisors to the EAG suggested that the proportion of patients requiring escalation with risankizumab is likely to be higher than 30% in clinical practice, particularly in those more treatment resistant patients (after failing other second line drugs such as vedolizumab or JAK inhibitors, where risankizumab may be used).

Clinical advisors to the EAG agree that those patients requiring escalation would be escalated right after the induction phase, for those more treatment resistant populations (after failure of other second line drugs). However, for patients with less treatment history (e.g., biologic naïve patients), these would be escalated after two flares in one year, or a very serious first flare.

5.2.6 Subgroups

The company have not provided analyses by any patient subgroups, as the model assumes equal efficacy between all treatments. However, there may still be different discontinuation rates and dose-escalation rates in population subgroups which could influence the cost comparison results. Applying discontinuation rates, even if equally across the intervention and comparison groups affects the results [redacted].

5.2.7 Sensitivity and scenario analyses

The model included four scenario analyses. Three exploring alternative time horizons to the company's 10-year base case. A fourth scenario explored changes in the proportion of patients who receive the escalated dose of risankizumab in the maintenance phase. This fourth scenario has [redacted]. No scenarios were presented for the proportion of patients who receive the escalated dose of ustekinumab. After clarification questions from the EAG, the company provided an additional scenario comparing risankizumab with vedolizumab, a scenario including adverse event costs ([redacted] compared with company base case [redacted]) and a scenario including phased dose escalation ([redacted] compared with company base case [redacted]).

5.2.8 Model validation

The construct validity of the cost comparison model depends on a number of strong assumptions. Health effects are excluded from the analysis as it assumes equivalence

between risankizumab and the ustekinumab in treatment effectiveness, adverse events, and patient quality-of-life (utilities) over the 10-year period of the analysis. It also assumes equivalent outcomes after any subsequent treatment following risankizumab and ustekinumab.

Although simplistic, the model calculations are logical and inputs costs have been well considered. The EAGs validity checks of the model calculations did not find any issues. However, the model fails to address some key factors that impact the costs in the analysis.

5.3 Key factors not included in the model

The model does not include various factors that may be relevant in comparing costs between risankizumab and ustekinumab. Even when rates of effects, side effects, adverse events, discontinuation, and discounting are the same for both groups, because of the differential in costs and cost-savings accrued over time in this model, including them will impact the results.

5.3.1 Discounting

The company's model does not apply discounting in the base case or as a scenario analysis. Because patients will require continuous treatment with these drugs for the entire period of analysis, and the relative costs of risankizumab are time sensitive (with [redacted] costs during the induction phase, but [redacted] costs during the maintenance phase), the EAG considers that discounting costs at the recommended 3.5% rate is appropriate and relevant and asked for this in clarification questions. The company justified their choice for not discounting as being in line with the NICE user guide for the cost-comparison company evidence submission template.

5.3.2 Discontinuation

The company's model does not include patients discontinuing treatment, as in other models in this area (e.g., CCA in TA925 of mirikizumab for the same UC population.[6]

In the company's trials, patients only continued into the maintenance phase (COMMAND trial) if they achieved a response to treatment in the induction phase (INSPIRE trial; Company Submission, Document B, Table 8). As such, 35.7% (Company Submission, Document B, Table 6) from the induction phase did not continue to maintenance treatment.

Discontinuation of treatment can also occur during the maintenance phase, as a result of treatment related adverse events, achieving deep remission, or death, and this is not included in the company's model.

There is no long-term evidence for the use of risankizumab in this population. Clinical advisors to the EAG have suggested that during the maintenance phase 20-30% of their patients on ustekinumab would discontinue or switch treatments around the 5-year medical review. Recently published evidence on four year follow-up of UC patients on the maintenance phase of ustekinumab report 29.4% of patients in the escalated dose and 29.8% of patients in the standard dose discontinue ustekinumab over four years.[14]

A limitation of the model is that it does not allow for different treatment discontinuation rates to be applied to each of the drugs compared. The model also does not include the costs of subsequent treatments after the discontinuation of risankizumab and ustekinumab. After consultation with clinical advisors, the EAG agrees that patients discontinuing risankizumab and ustekinumab would likely have similar subsequent treatment options.

5.3.3 Dose Escalation

The company assumes that dose escalation for risankizumab is from 180mg to 360mg and that the higher dose would be given at the same frequency as for the lower dose, as per the SmPC. Given there is [redacted], changes in the proportion of patients receiving standard or escalated doses [redacted] the cost of risankizumab. Our clinical advisors have noted that it is possible that in clinical practice, patients may be treated more frequently, every 6 or 4 weeks for example, when dose effects wane quicker than 8-weekly.

5.3.4 Adverse events and side effects

A limitation of the model is that adverse event rates or side effects, are assumed similar over the period and excluded from the model. While the EAG agrees that adverse events and side effects may be broadly comparable between groups, the estimates from the NMA for adverse events were very uncertain, and there is no evidence on long-term adverse event rates. After consultation with our clinical advisors, the EAG learned that patients may require a re-initiation period or a booster after an adverse event or flare. Given that the cost of risankizumab induction dose is [redacted] than ustekinumab induction doses, the cost-comparison results may be sensitive to assumptions about adverse events that could lead to re-initiation (or even discontinuation as above), even if the rates are similar between the two drugs.

5.3.5 Comparator

Given that vedolizumab is the most used treatment after failure of anti-TNF alpha drugs in this population, the EAG considers it could also be an appropriate comparator (see Section 3.1). In response to the EAG clarification questions' request the company provided a scenario analysis comparing risankizumab with vedolizumab, but reiterated their position that ustekinumab is their preferred comparator in their base case. The EAG reports the company's results for these analyses in Table 9.

5.3.6 Subgroups

The NICE final scope suggests analyses by the following subgroups:

a) people who have been previously treated with 1 or more biologic therapies
b) people who have been previously treated with a JAK inhibitor
c) people who have not received a prior biologic therapy or a JAK inhibitor.

The company have not included any subgroup analyses in their cost-comparison analysis, which assumes that the equivalence of risankizumab and ustekinumab holds across subgroups, and also that other factors, such as escalation and discontinuation do not depend on subgroup.

Given the positioning of risankizumab after anti-TNF alpha drugs, for patients in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough, all patients would either have been exposed to at least one biologic therapy or are not suitable for anti-TNF alpha drugs. Clinical advisors to the EAG suggested that treatment effects and adverse events would differ when risankizumab was offered to (i) patients straight after anti-TNF alpha drugs stopped working (or even in the absence of these), a more "treatment naïve" patient group, and (ii) those receiving risankizumab after failure of other comparators, such as vedolizumab and ustekinumab, a more "treatment resistant" patient group .

5.4 Summary

When comparing against the ustekinumab BNF prices, the acquisition costs for risankizumab are [redacted] than ustekinumab in the induction period, [redacted] ustekinumab in the maintenance phase, resulting in a [redacted] over a 5, 10 and 15 year time horizons. The results of the company's and EAG's analysis using cPAS prices for comparator drugs are reported in the confidential appendix to this report.

6 COMPANY AND EAG COST COMPARISON RESULTS

All results in this section incorporate the PAS price for risankizumab, and the list prices for comparators.

6.1 Company base case

Risankizumab saves on average [redacted] per patient over the 10-year period in the company base case (Table 8), when comparing risankizumab's cPAS price with ustekinumab at BNF list prices. The company's base case assumes 30% and 92.5% of patients in escalated dosages in risankizumab and ustekinumab respectively, no discontinuation, and no discounting.

Table 8: Company base case results using ustekinumab's list price and risankizumab cPAS price

Treatment	Induction costs	Maintenance costs	Total costs	Incremental costs for Risankizumab vs comparator
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	£6,811	£135,019	£141,830	[redacted]

6.2 Company scenarios

In sensitivity analyses to the time-horizon, risankizumab is [redacted] the longer the time-horizon, assuming risankizumab cPAS prices compared with ustekinumab's BNF list prices (Table 9). This is because risankizumab is [redacted] than ustekinumab in the

maintenance period. When comparing with 50% escalated patients on risankizumab, keeping the proportion of escalated patients in ustekinumab at 92.5%, there is [redacted]

In the scenario comparing with vedolizumab at BNF list prices, provided after EAG clarification questions (clarification question B1), in the company's additional scenario comparing with vedolizumab, risankizumab saves [redacted] over 10-years (Table 10).

Table 9: Company scenario analyses using ustekinumab's list price and risankizumab cPAS price

Scenario	Treatment	Induction costs	Maintenance costs	Total costs	Incremental costs for risankizumab vs comparator	Difference from the company's base case incremental cost
Company base case (10-year time horizon)	Risankizumab	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£135,019	£141,830	[redacted]	
1 - Time horizon (5 years)	Risankizumab	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£66,986	£73,797	[redacted]	[redacted]
2 - Time horizon (15 years)	Risankizumab	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£203,053	£209,863	[redacted]	[redacted]
3 - Time horizon (20 years)	Risankizumab	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£271,086	£277,896	[redacted]	[redacted]
4 – Escalated on risankizumab (50%)	Risankizumab	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£135,019	£141,830	[redacted]	[redacted]

Table 10: Company additional scenario with vedolizumab using vedolizumab's list price and risankizumab cPAS price

Treatment	Induction costs	Maintenance costs	Total costs	Incremental costs for risankizumab vs comparator
Risankizumab	[redacted]	[redacted]	[redacted]	N/A
Vedolizumab	£6,556	£155,360	£161,916	[redacted]

6.3 EAG base case and preferred assumptions

The EAG base case attempts to address some of the key factors not included in the company's model which would have an impact on the cost results. These are described below.

6.3.1 Discounting

As discussed in Section 5.3.1, the EAG considers a 3.5% discount appropriate.

6.3.2 Discontinuation

The EAG included the effect of discontinuation following induction due to lack of response of 35.7% of patients based on the company's trial data (see Section 5.3.2), and a discontinuation rate during the maintenance phase of 8.7389% based on 4-year follow-up data for ustekinumab (see section 5.3.2). Afif and colleagues [14] reported 4-year discontinuation rates for patients in the ustekinumab maintenance phase in standard and escalated doses. The EAG computed the 4-year discontinuation weighted average, 29.5%, assuming 92.5% of patients are in the escalated dose, which reflects a compounded annual discontinuation rate of 8.7389%.

The company reports in Table 13, p135 of the CSR document that over the first year, 1.6% of patients in the standard maintenance dose and 2.6% of patients in the escalated dose of risankizumab experience adverse events that lead to discontinuation. As these data are more immature than the published 4-year follow-up for ustekinumab, the EAG used it as a sensitivity analysis only and applied a weighted average of 1.9% annual discontinuation in both groups (assuming 30% escalated).

While the EAG suspects that these discontinuation rates may differ between the two treatments, given the lack of evidence in the risankizumab population and the lack of flexibility in the company's model to apply different rates, the EAG applied the same discontinuation rates to both treatments.

6.3.3 Escalation

After consultation with clinical advisors, the EAG assumes in sensitivity analyses that 10% and 20% of patients in risankizumab would require escalation to more frequent doses of 6-week intervals (Q6w) (see Section 5.3.4).

6.3.4 Adverse events

The EAG did not have adequate long-term evidence on serious adverse events that would require hospitalization, discontinuation, or reinitiation of treatment, and therefore we have not included this in our model .

6.3.5 Comparator

The EAG performs a cost-comparison analysis against vedolizumab, as well as ustekinumab (see Sections 3.1 and 5.3.5). Note however, that the NMA results (see Section 4.3.1.1.2) demonstrate that there may be meaningful treatment effect differences between risankizumab and vedolizumab in terms of effectiveness and safety, so that a cost

comparison analysis would not be appropriate. The results should be interpreted with this proviso.

There are a number of possible vedolizumab dosing schedules offered to patients. The NICE recommendations for vedolizumab SC dosing are: "Maintenance 108mg every 2 weeks, following at least 2 intravenous infusions; the first subcutaneous dose should be administered in place of the next scheduled intravenous dose."[15] Further information on the different dosing schedules of vedolizumab can be found in Appendix E.[16] In their vedolizumab scenario analysis, the company began subcutaneous vedolizumab treatment after three IV induction doses, which is an alternative dosing schedule within the NICE recommendations. The EAG provides two scenarios for SC vedolizumab maintenance use. The first beginning SC vedolizumab after two IV induction doses and the second beginning after three IV doses, as per the company's scenario.

6.3.6 Subgroups

The EAG did not have enough evidence to provide analyses by patient subgroups specified in the NICE scope (see Section 5.3.6).

6.3.7 Summary of the EAG base-case assumptions

The EAG base case assumes:

- Discounting of all costs at 3.5%
- Treatment discontinuation in 35.7% of patients after induction due to non-response
- Patient annual discontinuation rate during maintenance phase of 8.7% due to adverse events or other effects

Table 11 presents the results from the EAG's base-case analysis, showing the effect of iteratively changing the assumptions from the company's base-case. Using the risankizumab cPAS price and ustekinumab list price, the EAG base case finds [redacted] over the 10-year period.

Table 11 EAG iterative base case table using ustekinumab's list price and risankizumab cPAS price

		Treatment	Induction costs	Maintenance costs	Total costs	Incremental costs for Risankizumab vs comparator
1	**Company base case**	**Risankizumab**	[redacted]	[redacted]	[redacted]	
		Ustekinumab	£6,811	£135,019	£141,830	[redacted]
2	**+ Discounting costs at 3.5%**	**Risankizumab**	[redacted]	[redacted]	[redacted]	
		Ustekinumab	£6,811	£116,075	£122,886	[redacted]
3	**+ Discontinuation due to non-response after induction**	**Risankizumab**	[redacted]	[redacted]	[redacted]	
		Ustekinumab	£6,811	£74,288	£81,099	[redacted]
4	**+ Annual discontinuation**	**Risankizumab**	[redacted]	[redacted]	[redacted]	
		Ustekinumab	£6,811	£52,130	£58,941	[redacted]

	for other events (EAG base case)					

6.3.8 EAG scenario analysis

Table 12 reports the EAG's sensitivity analyses results. In these hypothetical sensitivity analyses the EAG assumes:

- 10% and 20% of patients in the risankizumab group require Q6w escalation
- Annual discontinuation rates of 1.9%
- Assuming both drugs escalate at 30% as in TA633 and TA925.[6, 7]

In the EAG's scenario analysis (Table 12), risankizumab is [redacted] when assuming that 10% and 20% of patients are escalated to Q6w, [redacted] than the EAG's base case if the annual discontinuation rate is 1.9%, and [redacted] in the hypothetical scenario of only 30% ustekinumab patients were assumed to require escalation as per TA633.

Table 12: EAG scenario analyses using ustekinumab's list price and risankizumab cPAS price

Scenario	Treatment	Induction costs	Maintenance costs	Total costs	Incremental costs for risankizumab vs comparator	Difference from the company's base case incremental cost
Company base case	**Risankizumab**	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£135,019	£141,830	[redacted]	
EAG base case	**Risankizumab**	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£52,130	£58,941	[redacted]	[redacted]
10% of Risankizumab patients escalating q6w	**Risankizumab**	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£52,130	£58,941	[redacted]	[redacted]
20% of Risankizumab patients escalating q6w	**Risankizumab**	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£52,130	£58,941	[redacted]	[redacted]
1.9% Annual discontinuation rate	**Risankizumab**	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£68,567	£75,378	[redacted]	[redacted]
30% dose escalation (both drugs)	**Risankizumab**	[redacted]	[redacted]	[redacted]		
	Ustekinumab	£6,811	£40,991	£47,802	[redacted]	[redacted]

The EAG also provides a cost-comparison with vedolizumab in Table 13 using two different SC maintenance dosing schedules. We used the EAG base-case assumptions and assumed a

weighted average of patients on vedolizumab IV and SC administrations. Both the company and the EAG assume 30% of patients are escalated on vedolizumab and risankizumab. Risankizumab is [redacted], compared with both vedolizumab's dosing schedules ([redacted] and [redacted] respectively), but [redacted] so than in the company's scenario.

Table 13: EAG vedolizumab scenario analyses using vedolizumab list prices and risankizumab cPAS prices

Scenario	Treatment	Induction costs	Maintenance costs	Total costs	Incremental costs for risankizumab vs comparator	Difference from the company's scenario incremental cost
Company's scenario with vedolizumab	**Risankizumab**	[redacted]	[redacted]	[redacted]		
	Vedolizumab	£6,556	£155,360	£161,916	[redacted]	
EAG base case	**Risankizumab**	[redacted]	[redacted]	[redacted]		
EAG comparison with vedolizumab using EAG's preferred dosing schedule	**Vedolizumab (weighted average of IV/SC population in maintenance)**	£4,371	£69,306	£73,677	[redacted]	[redacted]
EAG comparison with vedolizumab using the company's preferred dosing schedule	**Vedolizumab (weighted average of IV/SC population in maintenance)**	£6,556	£67,600	£74,156	[redacted]	[redacted]

[1]The EAG does not support an assumption of clinical equivalence between vedolizumab and risankizumab or ustekinumab without further evidence

6.4 Summary

The company's base case reports a saving of [redacted] per patient over the analysis period if risankizumab is used instead of ustekinumab. This is [redacted] in the EAG's base case, assuming ustekinumab's BNF list prices. The EAG notes that had it been possible to incorporate adverse events requiring re-initiation doses in the model, or different

discontinuation rates between groups, it is likely that the cost-differential be different and could be [redacted]. In sensitivity analysis, assuming 10% or 20% of patients would receive risankizumab doses more frequently than SmPC, the cost difference is [redacted] and [redacted] respectively. Assuming ustekinumab's escalation scenario at time of TA633 (30% patients escalated), [redacted][7] Risankizumab is cost-saving compared with all vedolizumab scenarios. However, equivalence between these two drugs is not established and a CCA is not appropriate for the comparison with vedolizumab. The vedolizumab model again does not allow for application of different assumptions (e.g., discontinuation, escalation, re-initiation rates) on the vedolizumab group.

7 EQUALITIES AND INNOVATION

No equalities or innovation arguments were proposed by the Company.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

The EAG's major concerns are:

- The evidence provided by the company does not demonstrate robust evidence of clinical equivalence of risankizumab and ustekinumab, due to the wide credible intervals around the estimated intervention effects.

- There is no evidence that any similarity between risankizumab and ustekinumab would continue over the 10-year period of the analysis.

- The cost comparison model omitted key factors that have an impact on the cost difference. It did not include discontinuation rates; it did not consider the potential need of re-initiation periods or boosters, or the need of more frequent dosing schedules. It also did not discount costs at 3.5% rate whereas the EAG considered discounting appropriate. Given that there are differences in costs between risankizumab and ustekinumab during the induction and maintenance phases, including these factors in the model, even if at the same rate between groups, [redacted]

- Vedolizumab is currently dominating the market (approximately 49% of the market share, compared with 29% for ustekinumab according to evidence provided by the company) and could be an additional comparator. There is some evidence that vedolizumab is superior to risankizumab for the maintenance phase at least, so the evidence does not demonstrate equivalence between these two drugs.

Given the large number of treatment options available for patients with moderate and severe UC, the EAG consider a future MTA evaluation including risankizumab, vedolizumab, ustekinumab, mirikizumab, and JAK inhibitors to be of value. This should include consideration of the positioning of these drugs in treatment sequence after anti-TNF alpha drugs.

9 REFERENCES

1. European Medicines Agency. *Skyrizi (risankizumab) EPAR*. 2023. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/skyrizi (Accessed Novemeber 2023).
2. Horst S. A Practical Guide to Use of Risankizumab. *The American journal of gastroenterology* 2023
3. Parigi TL, Iacucci M, Ghosh S. Blockade of IL-23: What is in the Pipeline? *Journal of Crohn's & colitis* 2022;**16**(Supplement_2)
4. National Institute for Health and Care Excellence (NICE). undated. Guidance for EAGs on cost comparison appraisals. (Accessed November 2023).
5. AbbVie. *Document B [Company Submission]: Risankizumab for people with previously treated moderately to severely active ulcerative colitis* 2023. (Accessed November 2023)
6. National Institute for Health and Care Excellence (NICE). *[TA925] Mirikizumab for treating moderately to severely active ulcerative colitis*. 2023. URL: https://www.nice.org.uk/guidance/ta925 (Accessed October 2023).
7. National Institute for Health and Care Excellence (NICE). *[TA633]: Ustekinumab for treating moderately to severely active ulcerative colitis (Commitee Papers)*. 2020. URL: https://www.nice.org.uk/guidance/ta633/evidence/final-appraisal-determination-committee-papers-pdf-8774360606 (Accessed November 2023).
8. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B*, et al.* ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *Journal of Clinical Epidemiology* 2016;**69**
9. Centre for Reviews and Dissemination. *CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination*. York: University of York; 2009.
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I*, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *British Medical Journal* 2019;**366**
11. Carole Lunny, Franklin Hu, Mona Akbarnejad, Kevin Lin, Lillian Chen, Ayah Kapani*, et al.* 2023. Piloting the Risk of Bias tool for Network Meta-analysis. URL: https://doi.org/10.17605/OSF.IO/D25WJ (Accessed November 2023).
12. AbbVie. *Document A [Company Submission]: Risankizumab for people with previously treated moderately to severely active ulcerative colitis* 2023. (Accessed November 2023)
13. National Institute for Health and Care Excellence (NICE). *[TA888]: Risankizumab for previously treated moderately to severely active Crohn's disease*. 2023. URL: https://www.nice.org.uk/guidance/ta888).
14. Afif W, Arasaradnam RP, Abreu MT, Danese S, Sandborn WJ, Miao Y*, et al.* Efficacy and Safety of Ustekinumab for Ulcerative Colitis Through 4 Years: Final Results of the UNIFI Long-term Maintenance Study. *The American journal of gastroenterology* 2023
15. British National Formulary (BNF). *Vedolizumab: Indications and dose*. 2023. URL: https://bnf.nice.org.uk/drugs/vedolizumab/#indications-and-dose (Accessed December 2023).
16. Takeda. *Entyvi dosing guide*. 2023. URL: https://www.entyviohcp.com/content/dam/takeda/imported/entyvio/pdfs/dosing-guide.pdf (Accessed December 2023).

APPENDIX A: RISK-OF-BIAS ASSESSMENT OF COMPANY'S SYSTEMATIC REVIEW OF CLINICAL EFFECT (ROBIS TOOL)

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y
1.2 Were the eligibility criteria appropriate for the scope?	Y
1.3 Were eligibility criteria unambiguous?	Y
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PY
Risk of bias judgement:	**Low**

Justification for judgement

- A brief protocol was registered on PROSPERO in advance of the review being conducted.
- Eligibility was restricted to studies reported in English language publications, leading to the possibility that relevant evidence reported in other languages would be excluded. Nonetheless, our investigations lead us to consider it unlikely that there are relevant studies reported in other languages.

Comments

Review eligibility criteria

Population

Adults (≥ 16 years old) with UC, regardless of prior biologics exposure or failure

Intervention

upadacitinib, risankizumab, vedolizumab, ustekinumab, adalimumab, infliximab, ozanimod, filgotinib, mirikizumab, golilumab, tofacitinib, etrasimod

Outcomes measures

Resource use and cost: Medication costs; Hospitalisation/Emergency room visits and costs; Outpatients visit and costs; Physician visits and costs; Laboratory costs; Diagnostic costs; Productivity loss costs (i.e., wage, % absence from work); Out-of-pocket expenses; Travel costs for patients and caregivers; Cost per remission; Cost per response; Cost per treatment success; Cost per LY; Cost per QALY; Cost per unit; Cost offsets; QALYs.

Study design

Retrospective/prospective cost analysis; Retrospective/prospective health care resource analysis; Cost-effectiveness analysis (CEA); Cost-utility analysis (CUA); Cost-minimization analysis (CMA); Cost-consequence analysis (CCA); Cost-benefit analysis (CBA); Budget impact analysis; Cost/economic burden of illness studies

Other restrictions

English language; Publication date 2000 to current

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y
2.2 Were methods additional to database searching used to identify relevant reports?	Y

2.3	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY
2.4	Were restrictions based on date, publication format, or language appropriate?	PY
2.5	Were efforts made to minimize error in selection of studies?	PY

Risk of bias judgement: Low

Justification for judgement

- The suboptimal reporting of the search impacts our ability to appraise what the company did. Limits on the search have been applied incorrectly in bibliographic databases and the approach to search syntax is incorrect in places and inconsistent throughout. Nonetheless, our investigations lead us to consider it unlikely that the searches have missed eligible studies.
- Study selection was undertaken independently by two researchers according to a clear inclusion criteria. A third researcher was available in the event of any disagreement.

Comments

Searches were undertaken in June 2023 in the following core database.

- Medline (Ovid);
- Embase (Ovid);
- NHS EED AND HTA; and
- Econlit.

The search reporting does not align with current standards or PRISMA reporting guidance. This impacts transparency and our ability to replicate the searches. Ideally the search strategies should have been provided for all the databases searched, and search results should have been reported for each database separately rather than combined across-databases.

The method of date limiting the searches to reduce N to allow for server-side deduplication is sub-optimal and it has the potential to mislead. As above, the searches should ideally have been run in individual databases and then combined for de-duplication. This would allow for clearer reporting of the study identification process.

There are typographical errors in the search syntax (e.g., Line 5, for Ustekinumab) and the company vary on their truncation of interventions which will impact retrieval.

The CS states the intervention terms were developed using subject headings, drug names, and brand or code names. However, the lists of eligible terms, codes and numbers, is not exhaustive.

The limit of searches to human only studies has been applied incorrectly, and the company have excluded letters (which may report eligible study data) from retrieval.

Searches were performed of trials registers, relevant conferences, and the websites of leading guidance agencies. Whilst the search terms were reported, the search syntax used for the trials registry resources are not reported as they were run, so we have not been able to validate their approach here against the registers.

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
3.1 Were efforts made to minimize error in data collection?	Y
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y
3.3 Were all relevant study results collected for use in the synthesis?	Y
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	N
3.5 Were efforts made to minimise error in risk of bias assessment?	N
Risk of bias judgement:	**Low**

Justification for judgement

- Data were extracted by one researcher and checked by another.
- Risk of Bias or study quality does not appear to have been appraised in this review,

Comments

Data collection methods: "Data from included records were extracted into a pre-defined Excel-based template by a single independent researcher and all results were 100% quality checked by a second independent researcher".

Whilst the data extraction process was appropriate, the data extraction tool (or a list of data extracted) was not reported.

The protocol indicates that studies would be appraised using the economic evaluations checklist from the Methods for the Development of the NICE public Health Guidance. Since no studies were included, this stage was not undertaken.

DOMAIN 4: SYNTHESIS AND FINDINGS	
4.1 Did the synthesis include all studies that it should?	Not applicable
4.2 Were all pre-defined analyses reported or departures explained?	Not applicable
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Not applicable
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Not applicable
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not applicable
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Not applicable
Risk of bias judgement:	**Not applicable**

Justification for judgement

The review did not include any costs from the review.

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

APPENDIX B: RISK-OF-BIAS ASSESSMENT OF NETWORK META-ANALYSIS (PRELIMINARY TOOL FROM LUNNY AND COLLEAGUES)

Item	Signalling statement	Judgement	Comments
Domain 1: Interventions and network geometry			
1.1	All interventions and their comparators included in the NMA are reasonable alternatives for the whole target population	True	Assessment guided by clinical advice in combination with trial inclusion criteria. These are all moderate-to-severe patients on induction/maintenance therapy .
1.2	No interventions were inappropriately excluded from the network	True	NICE guidance for EAGs states that the company are not expected to provide a full NMA to justify their choice of comparator.[4] The NMA focused on only four interventions from the NICE scope, including their own. This is justified as follows: "Further interventions were not included for a number of reasons, including that they have very different mechanisms of action, so as to not introduce additional heterogeneity into the network, and it is not anticipated that risankizumab would be considered an alternative treatment to these therapies". We do not agree that mechanism of action is a justifiable reason for exclusion (and would not introduce heterogeneity into the network in the usual sense of "heterogeneity"). Furthermore, risankizumab is positioned after failure of anti TNF alpha drugs at first-line, so the JAK inhibitors, ozanimod, and etrasimod (subject to ongoing NICE evaluation) are all 'potential' comparators. Nonetheless, we have no reason to be concerned that the omission of other interventions introduces a risk of bias, since they are unlikely to affect the comparisons between the four treatments included (previous network meta-analyses have not identified head-to-head comparisons among the drugs).
1.3	Interventions were appropriately grouped into nodes in the network	True	Different drugs, doses and schedules are separated into nodes.
1.4	All compared interventions were connected through a suitable chain of within study comparisons	True	In the induction network the studies are all compared with placebo, since there are no head-to-head trials with risankizumab.

Concerns regarding the domain-level network characteristics and geometry		**Low risk of bias**	

Domain 2: Effect modifiers			
2.1	Outcome definitions and timepoints were similar across direct comparisons in the network	Probably true	There is some variation in time points (6-12 weeks for induction and 40-52 for maintenance). Our clinical advice is that 8 weeks would normally be expected for the induction phase, but we regard 6 weeks as reasonable .The company submission comments on the issue as follows (Appendix, page 39): "*Consistent with TA633 [30] the NMA pooled outcomes reported over durations of 6 to 10 weeks for the induction phase and durations of 40 to 54 weeks for the maintenance phase, assuming that outcomes are comparable within these durations. Even with these relatively narrow duration ranges, the ERG still expressed concern of bias in favour of studies with a shorter maintenance phase and against studies with a shorter induction phase from this heterogeneity… However, this approach was accepted by the NICE Committees in previous UC submissions*". There is also variation in outcome definitions, which the company submission highlights. They argue that "*treatment effect sizes have been shown to be generally similar regardless of whether efficacy outcomes are defined by the Full Mayo score or Adapted Mayo score*" (Appendix, page 39)
2.2	Effect-modifying participant characteristics were similar across direct comparisons in the network	True	Appendix tables 8 and 9: no notable differences are apparent.
2.3	Effect-modifying study characteristics were similar across direct comparisons in the network	Probably true	We have not identified any variation in study-level characteristics.
2.4	If F/PF to 2.1, 2.2 or 2.3: The analysis appropriately addressed the differences in effect modifiers across the network	Not applicable	
Concerns regarding domain-level effect modifiers		**Low risk of bias**	

Domain 3: Statistical synthesis			
3.1	All eligible results were included in the analysis	True	We have no major concerns about non-reporting biases.
3.2	All pre-defined analyses, and only those analyses, were reported, or discrepancies were explained	True	The protocol lists the outcomes addressed in the NMA.
3.3	Biases in primary studies were minimal or addressed in the synthesis	Probably true	Risk of bias was generally low with concerns only about missing data. For efficacy outcomes, we considered any biases introduced by imputing missing data generally to favour the active interventions. Given that all trials in the NMA were placebo-controlled trials of active interventions, it is possible that these biases would to some extent be mitigated by the nature of the indirect comparisons. It is less clear what direction any biases might have operated for safety outcome due to a lack of information.
3.4	Appropriate methods were used to handle multi-arm studies	Probably true	The guidance they follow is robust and their reporting appears to align.
3.5	Appropriate assumptions were made about homogeneity or heterogeneity of effects within comparisons	True	A fixed-effects model was used on the basis that there is too little replication of comparisons to allow estimation of a heterogeneity variance for a random-effects analysis (unless very strong prior distributions are used). The model is therefore adequate for the data, but means the results are not robust to the presence of undetected between-study heterogeneity.
3.6	There was no evidence of conflict between direct and indirect estimates of the same effect	True	No potential sources of conflict because all drugs have been compared with placebo (a ‘star-shaped’ network).
3.7	If F/PF to 3.6: Conflicting results between direct and indirect evidence were adequately addressed	Not applicable	
3.8	If a Bayesian analysis was performed, the choice of prior distributions was appropriate	True	Standard uninformative prior distributions were used.

3.9	Sensitivity analyses demonstrated that findings were robust to the statistical model and estimation methods	Not applicable	No sensitivity analyses are apparent, although the methods used were accepted standards and there are not clearly debatable decisions made about the statistical methods.
Concerns regarding the NMA synthesis		**Low risk of bias**	

Overall risk of bias in the NMA	**Low risk of bias**

APPENDIX C: RISK-OF-BIAS ASSESSMENT OF INDIVIDUAL RANDOMIZED TRIALS (ROB 2 TOOL)

Risk of bias for efficacy (clinical remission)

Trial	Randomization process	Deviations from intended intervention	Missing outcome data	Assessment of outcome	Selection of reported result	Overall	Comments
INSPIRE (induction)	Low	Low	Low	Low	Low	**Low risk of bias**	No important concerns.
COMMAND (maintenance)	Low	Low	Some concerns	Low	Low	**Some concerns**	A large proportion of participants had missing data for clinical remission: 45 patients in the risankizumab 180 mg SC group (25.1%), 63 patients in the risankizumab 360 mg SC group (33.9%) and 78 patients in the placebo group (42.6%) had missing outcome data (information provided in response to a clarification question). We are unclear why the proportions are somewhat different between arms. These missing data were imputed either by assuming non-remission or using multiple imputation, which are unlikely to correct for bias.
GEMINI-1 (induction)	Low	Low	Some concerns	Low	Low	**Some concerns**	Missing outcome data for clinical remission were imputed as not having achieved remission. We can find no information on how many patients had missing outcome data.
GEMINI-1 (maintenance)	Low	Low	Some concerns	Low	Low	**Some concerns**	Missing outcome data for clinical remission were imputed as not having achieved remission. We can find no information on

							how many patients had missing outcome data.
LUCENT-1 (induction)	Low	Low	Low	Low	Low	**Low risk of bias**	The report does not provide numbers randomized to the two groups: there is a lack of information about 118 participants affected by a transcription error.
LUCENT-2 (maintenance)	Low	Low	Some concerns	Low	Low	**Some concerns**	Outcome data were missing for 53 patients in the mirikizumab group (14.5%) and 72 patients in the placebo group (40.2%). We are unclear why the proportions are somewhat different between arms. Outcomes for these patients were imputed.
NCT02039505 (induction)	Low	Low	Some concerns	Low	Low	**Some concerns**	It appears that 9 patients in the vedolizumab arm (5%%) and 4 patients in the placebo arm (5%%) discontinued so may have had their outcome imputed. These numbers are reasonably small and similar.
NCT02039505 (maintenance)	Low	Low	Some concerns	Low	Low	**Some concerns**	It appears that 11 patients in the vedolizumab arm (27%) and 24 patients in the placebo arm (57%) discontinued so may have had their outcomes imputed.
UNIFI (induction)	Low	Low	Low	Low	Low	**Low risk of bias**	No important concerns.
UNIFI (maintenance)	Low	Low	Low	Low	Low	**Low risk of bias**	No important concerns.
VISIBLE 1	Low	Low	Some concerns	Low	Low	**Some concerns**	All randomized participants appear to have been included in the analysis. However, the report also states that participants with missing data were imputed as not having achieved the outcome. Numbers who discontinued the study were 29 in the vedolizumab SC 108 mg arm (27%), 13 in the vedolizumab SC 300 mg arm (24%) and 35 in

							the placebo group (63%), which are high rates. It looks as if these may have had outcomes imputed, which would be unlikely to correct for bias.

Risk of bias for safety (serious adverse events)

Trial	Randomization process	Deviations from intended intervention	Missing outcome data	Assessment of outcome	Selection of reported result	Overall	Comments
INSPIRE (induction)	Low	Low	Low	Low	Low	**Low risk of bias**	No important concerns.
COMMAND (maintenance)	Low	Low	Low	Low	Low	**Low risk of bias**	No important concerns.
GEMINI-1 (induction)	Low	Low	Some concerns	Low	Low	**Some concerns**	We can find no information on how many patients had missing outcome data.
GEMINI-1 (maintenance)	Low	Low	Some concerns	Low	Low	**Some concerns**	We can find no information on how many patients had missing outcome data.
LUCENT-1 (induction)	Low	Low	Low	Low	Low	**Low risk of bias**	The report does not provide numbers randomized to the two groups.
LUCENT-2 (maintenance)	Low	Low	Some concerns	Low	Low	**Some concerns**	We can find no information on missing data for this outcome, although there was a large proportion of missing data for clinical remission (see above).
NCT02039505 (induction)	Low	Low	Low	Low	Low	**Low risk of bias**	The “Safety Analysis Set of the induction phase” is mentioned, but not defined, in the protocol, and it is unclear whether there were missing data on safety. It appears that 9 patients in the vedolizumab arm (5%%) and 4 patients in the placebo arm (5%%)

							discontinued so may have had their outcome imputed. These numbers are reasonably small and similar.
NCT02039505 (maintenance)	Low	Low	Some concerns	Low	Low	**Some concerns**	The "Safety Analysis Set of the maintenance phase" is mentioned, but not defined, in the protocol, and it is unclear whether there were missing data on safety. It appears that 11 patients in the vedolizumab arm (27%) and 24 patients in the placebo arm (57%) discontinued so may have had their outcomes imputed.
UNIFI (induction)	Low	Low	Low	Low	Low	**Low risk of bias**	No important concerns.
UNIFI (maintenance)	Low	Low	Low	Low	Low	**Low risk of bias**	No important concerns.
VISIBLE 1	Low	Low	Some concerns	Low	Low	**Some concerns**	All randomized participants appear to have been included in the analysis. It is unclear whether missing data were imputed for safety outcomes. Numbers who discontinued the study were 29 in the vedolizumab SC 108 mg arm (27%), 13 in the vedolizumab SC 300 mg arm (24%) and 35 in the placebo group (63%), which are high rates. It looks as if these may have had outcomes imputed, which would be unlikely to correct for bias.

APPENDIX D: RISK-OF-BIAS ASSESSMENT OF COMPANY'S SYSTEMATIC REVIEW OF COSTS (ROBIS TOOL)

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
1. Did the review adhere to pre-defined objectives and eligibility criteria?	Y
2. Were the eligibility criteria appropriate for the scope?	Y
3. Were eligibility criteria unambiguous?	Y
4. Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y
5. Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PY
Risk of bias judgement:	**Low**

Justification for judgement

- A brief protocol was registered on PROSPERO in advance of the review being conducted.
- Eligibility was restricted to studies reported in English language publications, leading to the possibility that relevant evidence reported in other languages would be excluded. Nonetheless, our investigations lead us to consider it unlikely that there are relevant studies reported in other languages.

Comments

Review eligibility criteria

Population

Adults (≥16 years old) with UC, regardless of prior biologics exposure or failure

Intervention

upadacitinib, risankizumab, vedolizumab, ustekinumab, adalimumab, infliximab, ozanimod, filgotinib, mirikizumab, golilumab, tofacitinib, etrasimod

Outcomes measures

Resource use and cost: Medication costs; Hospitalisation/Emergency room visits and costs; Outpatients visit and costs; Physician visits and costs; Laboratory costs; Diagnostic costs; Productivity loss costs (i.e., wage, % absence from work); Out-of-pocket expenses; Travel costs for patients and caregivers; Cost per remission; Cost per response; Cost per treatment success; Cost per LY; Cost per QALY; Cost per unit; Cost offsets; QALYs.

Study design

Retrospective/prospective cost analysis; Retrospective/prospective health care resource analysis; Cost-effectiveness analysis (CEA); Cost-utility analysis (CUA); Cost-minimization analysis (CMA); Cost-consequence analysis (CCA); Cost-benefit analysis (CBA); Budget impact analysis; Cost/economic burden of illness studies

Other restrictions

English language; Publication date 2000 to current

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y

2. Were methods additional to database searching used to identify relevant reports?	Y
3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY
4. Were restrictions based on date, publication format, or language appropriate?	PY
5. Were efforts made to minimize error in selection of studies?	PY
Risk of bias judgement:	**Low**

Justification for judgement

- The suboptimal reporting of the search impacts our ability to appraise what the company did. Limits on the search have been applied incorrectly in bibliographic databases and the approach to search syntax is incorrect in places and inconsistent throughout. Nonetheless, our investigations lead us to consider it unlikely that the searches have missed eligible studies.
- Study selection was undertaken independently by two researchers according to a clear inclusion criteria. A third researcher was available in the event of any disagreement.

Comments

Searches were undertaken in June 2023 in the following core database.

- Medline (Ovid);
- Embase (Ovid);
- NHS EED AND HTA; and
- Econlit.

The search reporting does not align with current standards or PRISMA reporting guidance. This impacts transparency and our ability to replicate the searches. Ideally the search strategies should have been provided for all the databases searched, and search results should have been reported for each database separately rather than combined across-databases.

The method of date limiting the searches to reduce N to allow for server-side deduplication is sub-optimal and it has the potential to mislead. As above, the searches should ideally have been run in individual databases and then combined for de-duplication. This would allow for clearer reporting of the study identification process.

There are typographical errors in the search syntax (e.g., Line 5, for Ustekinumab) and the company vary on their truncation of interventions which will impact retrieval.

The CS states the intervention terms were developed using subject headings, drug names, and brand or code names. However, the lists of eligible terms, codes and numbers, is not exhaustive.

The limit of searches to human only studies has been applied incorrectly, and the company have excluded letters (which may report eligible study data) from retrieval.

Searches were performed of trials registers, relevant conferences, and the websites of leading guidance agencies. Whilst the search terms were reported, the search syntax used for the trials registry resources are not reported as they were run, so we have not been able to validate their approach here against the registers.

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
1. Were efforts made to minimize error in data collection?	Y
2. Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y
3. Were all relevant study results collected for use in the synthesis?	Y

4.	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	N
5.	Were efforts made to minimise error in risk of bias assessment?	N
	Risk of bias judgement:	**Low**

Justification for judgement

- Data were extracted by one researcher and checked by another.
- Risk of Bias or study quality does not appear to have been appraised in this review,

Comments

Data collection methods: "Data from included records were extracted into a pre-defined Excel-based template by a single independent researcher and all results were 100% quality checked by a second independent researcher".

Whilst the data extraction process was appropriate, the data extraction tool (or a list of data extracted) was not reported.

The protocol indicates that studies would be appraised using the economic evaluations checklist from the Methods for the Development of the NICE public Health Guidance. Since no studies were included, this stage was not undertaken.

DOMAIN 4: SYNTHESIS AND FINDINGS		
1.	Did the synthesis include all studies that it should?	Not applicable
2.	Were all pre-defined analyses reported or departures explained?	Not applicable
3.	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Not applicable
4.	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Not applicable
5.	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not applicable
6.	Were biases in primary studies minimal or addressed in the synthesis?	Not applicable
	Risk of bias judgement:	**Not applicable**

Justification for judgement

The review did not include any costs from the review.

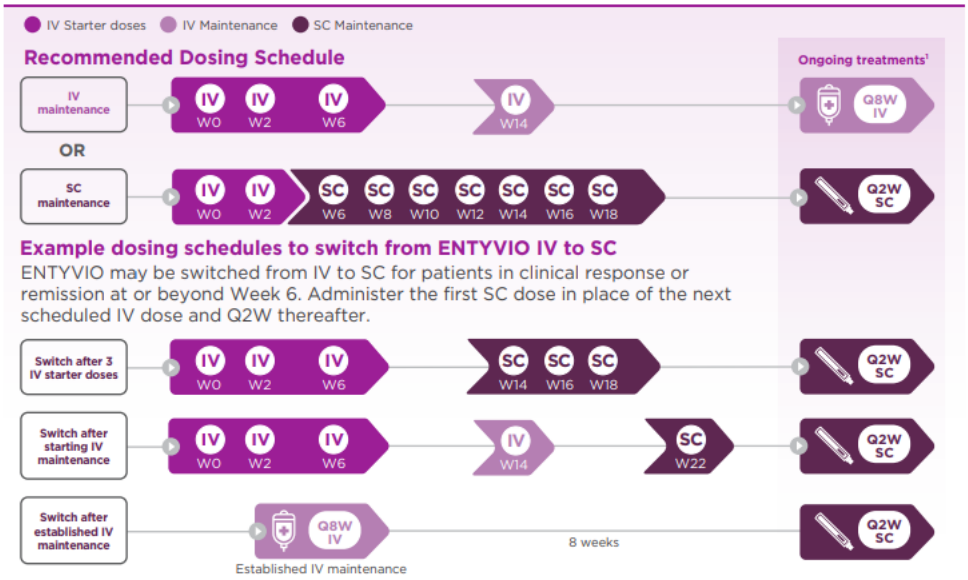
Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

APPENDIX E: RECOMMENDED VEDOLIZUMAB DOSING SCHEDULES

Information from the manufacturer of vedolizumab on the possible dosing schedules available for administering vedolizumab.[16]

FLEXIBILITY IN UC ADMINISTRATION OPTIONS[1]

- Recommended IV dosage: 300 mg infused by IV over approximately 30 minutes at Weeks 0, 2, and 6; then Q8W thereafter
- Following ENTYVIO IV doses at Weeks 0 and 2, ENTYVIO may be switched to SC at Week 6 with a recommended dosage of 108 mg administered Q2W
- ENTYVIO may be switched from IV to SC for patients in clinical response or remission beyond Week 6. Administer the first SC dose in place of the next scheduled IV dose and Q2W thereafter
- Discontinue ENTYVIO in patients who do not show evidence of therapeutic benefit by Week 14



Single Technology Appraisal

Risankizumab for previously treated moderately to severely active ulcerative colitis in people aged 16 and over [ID6209]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **1 February 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as ‘depersonalised data’ in pink.

Section 1: Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 7 Section 1: "The EAG also considers that given that patients receive treatment over a period of 10-years, it is **important to discount** future costs." Page 25 Section 5.3.1: "The company's model **does not apply discounting** in the base case or as a scenario analysis." Page 33 Section 8: "It also **did not discount costs** at 3.5% rate which the EAG finds appropriate."	Please amend as follows: Page 7 Section 1: "The EAG also considers that given that patients receive treatment over a period of 10-years, it is important to discount future costs**, however this is not normally required in a cost-comparison analysis as per the NICE user guide**." Page 25 Section 5.3.1: "The company's model does not apply discounting in the base case or as a scenario analysis, **as this is not normally required in a cost-comparison analysis as per the NICE user guide**." Page 33 Section 8: "It also did not discount costs at 3.5% rate which the EAG finds appropriate, as **this is not normally required in a cost-**	As per the NICE user guide for the cost-comparison company evidence submission template, discounting is not normally required in cost-comparison models.[1]	The NICE Guidance for EAGs on cost comparison appraisals document states: "Discounting of costs may not be required in a cost comparison analysis but can be applied if relevant". It is therefore within NICE recommended guidance to apply discounting if found relevant, which the EAG argues it is. These statements are therefore not a factual inaccuracy. We have edited to clarify as follows: In page 7 Section 1: "The EAG also considers that given that patients receive treatment over a period of 10-years, it is important to discount future costs and **is in line with the NICE guidance for EAGs on cost comparison appraisals.**" Page 25 Section 5.3.1.: "(...) the EAG considers that discounting costs at the recommended 3.5% rate is appropriate and relevant **and asked this in clarification questions. The company**

	comparison analysis as per the NICE user guide."		**justified their choice for not discounting as being in line with the NICE user guide for the cost-comparison company evidence submission template.**" Page 33 Section 8: "It also did not discount costs at 3.5% rate, **whereas the EAG considered discounting appropriate.**"
Page 7 Section 1: "The NMA has been well conducted but the results do not provide evidence of similar clinical effect due to the wide 95% credible intervals **around all results**, indicating **considerable** uncertainty in the relative efficacy and safety of the two treatments." Page 18 Section 4.3.1.1.1: "… our principal observation from the NMAs is that the credible	Please amend as follows: Page 7 Section 1: "The NMA has been well conducted but the results do not provide evidence of similar clinical effect due to the wide 95% credible intervals **around some results**, indicating ~~**considerable**~~ **potential** uncertainty in the relative efficacy and safety of the two treatments." Page 18 Section 4.3.1.1.1 "… our principal observation from the NMAs is that the credible intervals are wide for ~~**all**~~ **some** outcomes…"	The EAG use the terms 'wide' and 'very wide' to describe some of the credible intervals observed in the NMA; it is unclear whether a validated definition has been used for the use of 'wide' or 'very wide'. Without clarification of this definition, it is suggested that the use of 'very wide' is not factually accurate and should be removed. It is also not factually accurate to state that wide credible intervals were	We now provide interpretations of our use of the term "wide" ("95% credible interval including either a doubling or a halving (or both) of the odds of the event") and "very wide" ("encompassing a quartering or quadrupling of the odds of the event"). The former is intended to indicate that there is not strong evidence of *equivalence*. We maintain that in this respect credible intervals are wide for all outcomes. These definitions are now included in the report in page 18 Section 4.3.1.1.1.

intervals are wide for **all** outcomes…" Page 18 Section 4.3.1.1.1: "Credible intervals for the safety outcomes are **very** wide." Page 21 Section 4.4: Although the NMA was well conducted, **the** results have wide 95% credible intervals, indicating considerable uncertainty in the relative efficacy and safety of the two treatments. Page 33 Section 8: The evidence provided by the company does not demonstrate robust evidence of clinical equivalence of risankizumab and ustekinumab, due to the wide credible intervals around the estimated intervention effects.	Page 18 Section 4.3.1.1.1 "**Some of the** credible intervals for the safety outcomes are ~~**very**~~ wide." Page 21 Section 4.4: Although the NMA was well conducted, ~~**the**~~ **some** results have wide 95% credible intervals, indicating considerable uncertainty in the relative efficacy and safety of the two treatments. Page 33 Section 8: The evidence provided by the company does not demonstrate robust evidence of clinical equivalence of risankizumab and ustekinumab, due to the wide credible intervals around **some of** the estimated intervention effects.	seen around *all* results within the NMA. The text should accurately reflect this.	

Page 8 Section 2: “The company seek to position risankizumab as a **second line treatment** for patients with moderately to severely active UC, after failure of anti-TNF alpha drugs.” Page 21 Section 4.4: “…the EAG believes that vedolizumab is also an important comparator with substantial market share in clinical use for **second line treatment** after anti-TNF alpha drugs” Page 26 Section 5.3.6: “Given the positioning of risankizumab **after** anti-TNF alpha drugs, all patients would either have been exposed to at least one biologic therapy or are not suitable for anti-TNF alpha drugs.”	Please amend as follows: Page 8 Section 2: “The company seek to position risankizumab as a treatment for patients with moderately to severely active UC, **in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough**.” Page 21 Section 4.4: “…the EAG believes that vedolizumab is also an important comparator with substantial market share in clinical use for **~~second line treatment after anti-TNF alpha drugs~~ patients in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough**” Page 26 Section 5.3.6.: “Given the positioning of risankizumab **for patients in whom TNF-α inhibitors are deemed unsuitable; or where prior**	Reference to the target patient population as ‘second line’ or ‘after TNF-α inhibitors’ is an oversimplification of the proposed positioning within the submission and should be updated to reflect the full positioning of risankizumab in this indication. This wording should be updated throughout the document, wherever the positioning is referred to as ‘second-line’ or ‘after TNF-α inhibitors’.	The EAG agrees with this and amended throughout.

	biological treatment is not tolerated or not working well enough, all patients would either have been exposed to at least one biologic therapy or are not suitable for anti-TNF alpha drugs."		
Page 10 Section 3.2: "…the **market share data illustrate** the position of vedolizumab as a potential additional comparator…" Page 21 Section 4.4: "…the EAG believes that vedolizumab is also an important comparator with **substantial market share** in clinical use for second line treatment after anti-TNF alpha drugs"	Vedolizumab having a substantial market share in the population should not be quoted as the sole justification for considering vedolizumab as a relevant comparator throughout.	As per the NICE user guide for the cost-comparison company evidence submission template, and as stated in the EAG report, the choice of comparator does not need to have the biggest market share.[1] Vedolizumab having a substantial market share should therefore not be quoted as a sole justification for considering vedolizumab as a comparator to risankizumab, which is the case for some instances in the report.	In the NICE Guidance for EAGs on cost comparison appraisals document, it states that having "a substantial market share" is a criterion for the choice of comparator. The EAG does not state that market share is the sole justification for including vedolizumab as a comparator, but one of the facts that supports advice from our clinical experts that vedolizumab is a relevant comparator and competitor. The EAG's position is clearly stated in page 9 section 3.2. "Based on its clinical advice and the 2019 market research data from Janssen (TA633),[7] the EAG notes that vedolizumab is the most frequently used biologic for treating UC" The EAG feels these statements are not factually inaccurate.
Page 8 Section 2:	Please amend as follows:	Feedback from UK clinical experts consulted as part	We have re-worded these sections to clarify that the different mechanism of action is not

"The EAG's clinical advisors **do not consider the mechanism of action** to be a key differentiator in clinical decision-making, and patients may try more than one treatment within a class if they had an initial response on a drug in that class." Page 9 Section 3.1: "Although the EAG accept that vedolizumab has a different mechanism of action, our clinical advisors suggest that **this is not a clinically important factor** in deciding treatment after anti-TNF alpha treatment failure or when deciding to move a patient from one treatment to another, and therefore it is a relevant comparator."	Page 8 Section 2: "The EAG's clinical advisors do not consider the mechanism of action to be a key differentiator in clinical decision-making, and patients may try more than one treatment within a class if they had an initial response on a drug in that class; **though clinical decisions are based on a number of other factors**." Page 9 Section 3.1: "Although the EAG accept that vedolizumab has a different mechanism of action, our clinical advisors suggest that this is not a clinically important factor in deciding treatment after anti-TNF alpha treatment failure or when deciding to move a patient from one treatment to another, and therefore it is a relevant comparator; **though clinical decisions are based on a number of other factors**." Page 9 Section 3.1: "…mechanism of action is not generally a highly influential factor in this decision, **though clinical**	of the Company Submission indicated that mechanism of action is an important consideration when determining treatment options for patients in whom TNF-α inhibitors are deemed unsuitable; or where prior biological treatment is not tolerated or not working well enough. The wording around mechanism of action not being a clinically important factor in deciding subsequent treatments should be updated to reflect that fact that clinical and patient choice of treatment is likely to depend on several factors including but not limited to: mechanism of action, failure to response or loss of response, contraindication or	a reason to exclude a treatment as a comparator. Page 8 Section 2: "The EAG's clinical advisors **state that clinical decision-making is multifactorial,** and patients may try more than one treatment within a class if they had an initial response on a drug in that class." Page 9 Section 3.1: "Although the EAG accepts that vedolizumab has a different mechanism of action, **this is not a reason to exclude it as a comparator. Clinical advisors to the EAG advised that clinical decision-making is multifactorial and that vedolizumab would be an option for patients they would treat with risankizumab or ustekinumab,** and therefore it is a relevant comparator." Page 9, section 3.1 "…mechanism of action is not **a reason to exclude a treatment as an option**."

Page 9 Section 3.1: "…mechanism of action is not generally a highly influential factor in this decision."	**decisions are based on a number of other factors**."	unsuitability and type of prior treatment received.	
Page 9 Section 3.1: "The company argues that vedolizumab has a different mechanism of action from risankizumab and **would not be considered an alternative treatment** in clinical practice."	Please amend as follows: "The company argues that vedolizumab has a different mechanism of action from risankizumab and **would not be displaced by risankizumab ~~would not be considered an alternative treatment~~** in clinical practice."	The Company Submission does not claim that vedolizumab is not an available treatment option within the target patient population in clinical practice (as evidenced by the market share data provided in their budget impact analysis). However, the Company instead notes that their view is that vedolizumab would be less likely *to be displaced* by risankizumab due to the differing mechanism of action.	The EAG agrees this was the company's position and made the change as requested.
Page 7 Section 1: "ustekinumab is a reasonable comparator for risankizumab based on current UK clinical	Please amend as follows: Page 7 Section 1: "ustekinumab is a reasonable comparator for risankizumab based	The Company Submission does not claim that ustekinumab has a substantial market share as a justification for relevance as a comparator; this	The EAG agrees that the company has not claimed market share and made the changes. The company also stated the additional sentence in their submission and the EAG is happy to reproduce it in Table 1.

practice **and market share**" Page 8 Section 2: "The company proposes that ustekinumab is a reasonable comparator for risankizumab based on similarity of mechanism of action, current UK clinical practice**, and market share**." Page 11 Section 3.2; Table 1: "The company claims that ustekinumab is the only relevant comparator to risankizumab for the following reasons: • Ustekinumab represents established UK clinical practice in the proposed target population **with substantial market share**.	on current UK clinical practice ~~**and market share**~~" Page 8 Section 2: "The company proposes that ustekinumab is a reasonable comparator for risankizumab based on similarity of mechanism of action, **and** current UK clinical practice.~~**, and market share**~~." Page 11 Section 3.2; Table 1: "The company claims that ustekinumab is the only relevant comparator to risankizumab for the following reasons: • Ustekinumab represents established UK clinical practice in the proposed target population ~~**with substantial market share**~~ • Both ustekinumab and risankizumab have a similar mechanism of action of targeting interleukin-23 inhibitors**. They also have a similar route of administration; IV in the**	wording should therefore be removed. The Company Submission reports the additional justification that ustekinumab and risankizumab have a similar route of administration, which was not included in the EAG report.	

• Both ustekinumab and risankizumab have a similar mechanism of action of targeting interleukin-23 inhibitors. • Evidence on a series of network meta-analyses submitted by the company claims comparable efficacy and safety (see section 3.9 in the company submission)"	**induction phase and SC in the maintenance phase** • Evidence on a series of network meta-analyses submitted by the company claims comparable efficacy and safety (see section 3.9 in the company submission)"		
Page 12 Section 3.2; Table 1: "The company claims all other comparators in the scope are not relevant for the following reasons:	Page 12 Section 3.2; Table 1: "The company claims all other comparators in the scope are not relevant for the following reasons: • Mirikizumab has a similar mechanism of action but not yet established UK clinical	The Company Submission made no claim that mirikizumab did not have a representative market share; this wording should therefore be removed.	The EAG agrees to make this change.

• Mirikizumab has a similar mechanism of action but not yet established UK clinical practice **and not representative market share.** • Etrasimod has not yet been appraised by NICE in this indication. • All other comparators have a different mechanism of action and therefore not comparable to risankizumab in this indication.”	practice ~~**and not representative market share.**~~ • Etrasimod has not yet been appraised by NICE in this indication • All other comparators have a different mechanism of action and therefore not comparable to risankizumab in this indication”		
Page 16 Section 4.1: “This included the **same** randomized comparison in the **same** population as sub-study 2.”	Please amend as follows: “This included **a similar** randomised comparison **between 1200 mg IV risankizumab and placebo** in **a similar** population as sub-study 2”	INSPIRE sub-study 1 was a dose-ranging study and therefore only a limited number of patients were recruited per arm. The sentence in the EAG report	The EAG agrees to amend the sentence to: “This included **a randomised comparison between 1200 mg IV risankizumab and placebo in a similar** population as sub-study 2.”

		implies that the 1200 mg IV risankizumab arm in INSPIRE sub-study 1 and sub-study 2 contained exactly the same population, however they are only similar.	We do not think the first use of “similar” is necessary when the nature of the randomised comparison is now included in the sentence.
Page 17 Section 4.3: “The company **do not report** results of the NMA for the ‘bio-unexposed’ population.”	This sentence should be removed.	This sentence is incorrect. NMA results for the bio-naïve (or bio-unexposed) population were presented in Appendix D.2.6 and as such this sentence should be removed, or an appropriate reference to the bio-naïve population results presented by the Company included.	The EAG agrees to remove this sentence.
Page 20 Section 4.3.1.1.2: “On the other hand, there is evidence **that more serious adverse events** are associated with risankizumab than with vedolizumab.”	Please amend as follows: “**There is also evidence that fewer serious adverse events are associated with risankizumab than with vedolizumab; this result is statistically significant.** On the other hand, there is evidence that more **serious infections** ~~**serious adverse events**~~ are associated with risankizumab than with	There are inaccuracies in the reporting of the safety NMA results versus vedolizumab that should be corrected.	The EAG agrees to make the proposed correction to the result about serious adverse events and apologises for the error. However, (i) we do not believe the notion of ‘statistical significance’ is useful (see https://www.bmj.com/content/322/7280/226.1 for the rationale) so do not include the statements about this; and (ii) we regard the evidence for serious infection as uncertain rather than evidence that more infections are associated with risankizumab.

	vedolizumab, **however this result is not statistically significant**."		We now write: "There is also evidence that fewer serious adverse events are associated with risankizumab than with vedolizumab. Results for serious infections are very uncertain."
Page 20 Section 4.3.1.1.2: "There is **reasonably strong** evidence, both for the overall population and the bio-exposed population, of greater efficacy of vedolizumab compared with risankizumab during the longer maintenance phase." Page 29 Section 6.3.5: "The NMA results (see Section 4.3.1.1.2) demonstrate that there **are meaningful** treatment effect differences between risankizumab and	Please amend as follows: Page 20 Section 4.3.1.1.2: "There is ~~**reasonably strong**~~ evidence, both for the overall population and the bio-exposed population, of greater efficacy of vedolizumab compared with risankizumab during the longer maintenance phase; **however, some of the credible intervals cross 1**." Page 29 Section 6.3.5: "The NMA results (see Section 4.3.1.1.2) demonstrate that there **may be ~~are meaningful~~** treatment effect differences between risankizumab and vedolizumab in terms of effectiveness and safety; **however, some of the credible intervals cross 1**."	As not all of the maintenance phase NMA results between risankizumab and vedolizumab are statistically significant, and therefore further context should be included in all instances for appropriate interpretation.	The EAG agrees to make the proposed edit (with slight rewording). In page 20 we now write: "There is evidence, both for the overall population and the bio-exposed population, of greater efficacy of vedolizumab compared with risankizumab during the longer maintenance phase, although some of the credible intervals include 1." The EAG agrees to change "are" to "may be" on page 29, although does not see the failure to replicate text already presented (as now the case) as a factual error. In page 33, the EAG does not agree that there is a factual inaccuracy in its assertion of a lack of evidence of equivalence of risankizumab and vedolizumab, given the results in our Tables 5, 6 and 7. However, we have modified the text to read "There is some evidence that vedolizumab is superior

vedolizumab in terms of effectiveness and safety” Page 33 Section 8: “There is some evidence that vedolizumab is superior to risankizumab for the maintenance phase at least, **so it cannot be argued that there is equivalence between these two drugs**.”	Page 33 Section 8: “There is some evidence that vedolizumab is superior to risankizumab for the maintenance phase at least, **~~so it cannot be argued that there is equivalence between these two drugs~~ however, some of the credible intervals cross 1**.”		to risankizumab for the maintenance phase at least, so the evidence does not demonstrate equivalence between these two drugs.”
Page 20 Section 4.3.1.1.2; Table 6 reports the odds ratio for serious adverse events as 0.84 (0.30, 2.37) for R 360 mg vs V 300 mg Q4W and 1.02 (0.32, 3.22) for R 360 mg vs V 300 mg Q8W.	Please amend to report 0.84 (0.30, 2.37) as the odds ratio for **R 360 mg vs V 300 mg Q8W** and 1.02 (0.32, 3.22) for **R 360 mg vs V 300 mg Q4W**.	These values are reported incorrectly and should be corrected.	The EAG agrees to make this change.
Page 22 Section 5.2.3: “Ustekinumab treatments delivered by subcutaneous (SC) injection were assumed to be delivered by patients and **incur no**	Please amend as follows: “**Risankizumab and** ustekinumab treatments delivered by subcutaneous (SC) injection were assumed to be delivered by patients and incur no additional administration costs.”	Both risankizumab and ustekinumab are both administered via subcutaneous injection and the sentence should reflect that.	The EAG agrees to make this change.

additional administration costs."			
Page 23 Section 5.2.3: "The company used appropriate NHS reference costs for a gastroenterology service to cost an IV administration **and applied administration costs for SC administrations of risankizumab**."	Please amend as follows: "The company used appropriate NHS reference costs for a gastroenterology service to cost an IV administration ~~**and applied administration costs for SC administrations of risankizumab**~~."	No administration costs for SC administrations were applied within the model and as such, this part of the sentence should be removed.	The EAG agrees to make this change. This was a typo on our end which meant to read "and applied **no** administration costs (...)" but agrees to remove altogether.
Page 23 Section 5.2.4: "The company's model assumes all treatment effects, **adverse events, and side effects**, are similar for risankizumab and ustekinumab throughout the period of analysis and **therefore excludes them** from the model."	Please amend as follows: "The company's model assumes all treatment effects **and** adverse events~~**, and side effects**~~ are similar for risankizumab and ustekinumab throughout the period of analysis and therefore excludes them from the model. **Following a request made at the clarification question stage, the company provided a scenario analysis including the costs of adverse events within the model.**"	Scenario analyses were presented as part of the clarification question responses (question B7) that included the cost of adverse events within the model. The sentence should be updated to provide that context. Additionally adverse events and side effects are synonymous and as such, the sentence should be simplified.	Adverse events and side effects are not synonymous, and therefore this is not a factual inaccuracy.[2] The EAG agrees that the company provided a scenario analysis including costs of some minor adverse events in the model. We have added the following text as requested to page 23 Section 5.2.4: **"Following a request made at the clarification question stage, the company provided a scenario analysis including the cost of treating serious adverse events (sepsis, pneumonia, urinary tract infection, respiratory infection, and bronchitis) within the model.**

Page 23 Section 5.2.4: "The clinical effectiveness of the two drugs appears broadly similar but the NMA results are **very** uncertain, so the results are also consistent with risankizumab being more or less effective and safe than ustekinumab…"	Please amend as follows: "The clinical effectiveness of the two drugs appears broadly similar but the NMA results are ~~**very**~~ uncertain, so the results are also consistent with risankizumab being more or less effective and safe than ustekinumab…"	It is not factually accurate to state that the NMA results are *very* uncertain without evidence that *all* confidence intervals are wide. In addition, please could the EAG re-word this sentence as it is unclear what the exact meaning is.	The EAG agrees with removing "very" in the sentence.
Page 24 Section 5.2.6: "The company have not provided analyses by any patient subgroups. Clinical advisors to the EAG suggest that treatment and adverse events may different between biologic naïve and treatment resistant sub-groups of this population."	Please amend as follows: "The company have not provided analyses by any patient subgroups, **as the model assumes equal efficacy between all treatments, based on the NMA results by subgroup that were provided within the submission.** Clinical advisors to the EAG suggest that treatment and adverse events may different between biologic naïve and treatment resistant sub-groups of this population, **however NMA results provided by the Company suggest comparable efficacy and safety in these subgroups**."	A series of NMAs were conducted by the Company in an overall population of patients with moderately to severely active UC regardless of prior biologic therapy exposure and in the subgroups of patients both with/without prior exposure to biologic therapies. Results from these NMAs showed comparable efficacy and safety in terms of clinical remission, clinical response, endoscopic improvement, serious	The EAG agrees that the company claims equivalence between the two groups. We have now clarified our point and amended to read: "The company have not provided analyses by any patient subgroups, **as the model assumes equal efficacy between all treatments. However, there may still be different discontinuation rates and dose-escalation rates in population subgroups which could influence the cost comparison results. Applying discontinuation rates, even if equally across the intervention and comparison groups affects the results** [redacted]."

		infections and serious AEs between risankizumab and ustekinumab in all populations. The EAG do not appear to refer to the NMA subgroup analyses presented in the Company Submission appendices.	
Page 24 Section 5.2.7: "After clarification questions from the EAG, the company provided an additional scenario comparing ustekinumab with vedolizumab."	Please amend as follows: "After clarification questions from the EAG, the company provided an additional scenario comparing ~~**ustekinumab**~~ **risankizumab** with vedolizumab **as well as scenarios including adverse events costs and phased dose escalation**."	The company provided an additional scenario comparing risankizumab with vedolizumab, as opposed to ustekinumab with vedolizumab. Further scenario analyses were provided at clarification question stage and should be noted within this sentence.	The EAG apologises for typographical error and for not referring to the additional scenarios received. Page 24 Section 5.2.7 is now amended to read: "After clarification questions from the EAG, the company provided an additional scenario comparing risankizumab with vedolizumab, a scenario including adverse event costs ([redacted] compared with company base case [redacted]) and a scenario including phased dose escalation ([redacted] compared with company base case [redacted])"
Page 26 Section 5.3.3: "Our clinical advisors have noted that it is possible that in clinical practice, patients may be treated more frequently,	Please remove all commentary and scenario analyses that include consideration of off-label risankizumab (e.g. use of Q6W risankizumab) from the report.	The use of Q6W risankizumab would be fully outside of the anticipated licence for risankizumab in this indication and scenario analyses considering off-	The EAG would argue that this is not a factual inaccuracy. Clinical advisors to the EAG suggest that the use of off-label drugs in UC is not uncommon, it can be very effective and well-tolerated. The EAG is clear

every 6 or 4 weeks for example, when dose effects wane quicker than 8-weekly." Page 29 Section 6.3.3: "After consultation with clinical advisors, the EAG assumes in sensitivity analyses that 10% and 20% of patients in risankizumab would require escalation to more frequent doses of **6-week intervals (Q6W)**" Page 31 Section 6.3.8; Table 12: • "10% of Risankizumab patients escalating **q6w** • 20% of Risankizumab patients escalating **q6w**" Page 32 Section 6.4:		label dosing for a new therapy should not be included for decision making.	that this is just a scenario, and not the base case. All scenario analyses are hypothetical. We now clarify this to read in page 31 section 6.3.8: "In these **hypothetical** sensitivity analyses, the EAG assumes: (...)"

"In sensitivity analysis, assuming 10% or 20% of patients would receive **risankizumab doses more frequently than SmPC**…" Page 33 Section 8: "…or the need of **more frequent dosing** schedules."			
Page 31 Section 6.3.8: The EAG include a hypothetical scenario where "only 30% ustekinumab patients were assumed to require escalation as per TA633".	Please amend as follows: "Risankizumab is [redacted] in the hypothetical scenario of only 30% ustekinumab patients were assumed to require escalation as per TA633; **however, this scenario analysis is not considered clinically plausible given the clinical advice received by the EAG that dose escalation for 92.5% ustekinumab patients is a reasonable estimate**."	Whilst the EAG refer to this scenario analysis as hypothetical, its inclusion within the report is contradictory to their previous agreement that dose escalation for 92.5% ustekinumab patients is a reasonable estimate. An appropriate caveat should be included with this contradiction.	The EAG would argue that this is not a factual inaccuracy. The EAG made clear that the scenario is hypothetical and not current practice. It is included as a scenario analysis and not the base case.
Page 32 Section 6.4: When describing the EAG base case, the EAG note that "had it been possible to incorporate adverse	Please amend as follows: "had it been possible to incorporate adverse events requiring re-initiation doses in the model, or different discontinuation rates between groups, the cost-	It is not accurate to state that [redacted] *in all* possible scenarios that incorporate	The EAG agrees that it may not be the case for all possible scenarios. It now reads: "had it been possible to incorporate adverse events requiring re-initiation doses in the model, or different discontinuation rates

events requiring re-initiation doses in the model, or different discontinuation rates between groups, the cost-differential **would again be** [redacted].	differential ~~**would again be**~~ [redacted] **could be different**; **however, the use of differing discontinuation rates would not be in line with a cost-comparison approach."**	different discontinuation rates (for example if the discontinuation rate for risankizumab was higher than that of ustekinumab) so this sentence should be adjusted. Nevertheless, the use of different discontinuation rates would also not be in line with a cost-comparison approach and this context is important to be included here.	between groups, **it is likely that the cost-differential would be different and could be** [redacted]."

Section 2: Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 8 Section 2: "This report provides a critique of the evidence submitted by the company (Abbie) in support of risankizumab for moderate to severely active ulcerative colitis (UC) for whom anti-TNF alpha drugs are	Please amend as follows: "This report provides a critique of the evidence submitted by the company (**AbbVie**) in support of risankizumab for moderate to severely active ulcerative colitis (UC) for whom anti-TNF alpha drugs are deemed unsuitable or where prior biological treatment is not tolerated or not working well enough"	Typographical error.	Thank you for raising this. It is now amended.

deemed unsuitable or where prior biological treatment is not tolerated or not working well enough."			
Page 11 Section 3.2; Table 1: • "• anti TNF-alpha drugs (such as infliximab, adalimumab or golimumab) • JAK inhibitors (such as tofacitinib, • filgotinib or upadacitinib) • ustekinumab • vedolizumab • ozanimod • etrasimod (subject to ongoing NICE evaluation) • • mirikizumab (subject to ongoing NICE evaluation)."	Please amend as follows: • "anti TNF-alpha drugs (such as infliximab, adalimumab or golimumab) • JAK inhibitors (such as tofacitinib**, filgotinib or upadacitinib)** • ustekinumab • vedolizumab • ozanimod • etrasimod (subject to ongoing NICE evaluation) mirikizumab (subject to ongoing NICE evaluation)"	Filgotinib and upadacitinib are both JAK inhibitors but were incorrectly reported separately to the JAK inhibitor group bullet point.	Thank you for raising this. It is now amended.
Page 16 Section 4.1: "We assessed the risk of bias to be low in INSPIRE and low for safety results from COMMAND but had	Please amend as follows: "We assessed the risk of bias to be low in INSPIRE and low for safety results from COMMAND but had some concerns about risk of bias in efficacy results **in**	Typographical error.	Thank you for raising this. It is now amended.

some concerns about risk of bias in efficacy results COMMAND due to imputation of missing data (see Appendix C)."	COMMAND due to imputation of missing data (see Appendix C)."		
Page 16 Section 4.1: "(including clinical remission, clinical response and endoscopic improvement: see Company Submission, Document B, Tables 23 **ad** 24)."	Please amend as follows: "(including clinical remission, clinical response and endoscopic improvement: see Company Submission, Document B, Tables 23 **and** 24)."	Typographical error.	Thank you for raising this. It is now amended.
Page 16 Section 4.2: "The systematic review sought trials treatments for moderately to severely active UC. In the first instance they used this to identify evidence directly comparing risankizumab and ustekinumab."	Please amend as follows: "The systematic review sought trials **of** treatments for moderately to severely active UC. In the first instance they used this to identify evidence directly comparing risankizumab and ustekinumab."	Typographical error.	Thank you for raising this. It is now amended.
Page 19 Section 4.3.1.1.2: "Using the company's NMA, we summarise the results of comparisons of risankizumab with vedolizumab in Table 5, Table **6and** Table 7."	Please amend as follows: "Using the company's NMA, we summarise the results of comparisons of risankizumab with vedolizumab in Table 5, Table **6 and** Table 7."	Typographical error (spacing between 'Table 6' and 'and'.	Thank you for raising this. It is now amended.

Page 23 Section 5.2.4: “Evidence submitted on similarity of treatment effects, adverse events, and side effects is immature. All evidence is short-term (52 weeks), and these relative **effectsmay** not persist over the 10-year period of the analysis.”	Please amend as follows: “Evidence submitted on similarity of treatment effects, adverse events, and side effects is immature. All evidence is short-term (52 weeks), and these relative **effects may** not persist over the 10-year period of the analysis.”	Typographical error	Thank you for raising this. It is now amended.
Page 23 Section 5.2.4: “Equivalency of treatment effects, adverse events, and side effects”	Please amend as follows: “Equivalency of treatment effects **and** adverse events , ~~**and side effects”**~~ This error is also repeated throughout the document and should be updated consistently.	Adverse events and side effects are synonymous and as such, the sentence should be simplified.	Not a typographical error nor factual inaccuracy. Adverse events and side effects are not synonymous.[2]
Page 24 Section 5.2.6: “Clinical advisors to the EAG suggest that treatment and adverse events **may different** between biologic naïve and treatment resistant sub-groups of this population.”	Please amend as follows: “Clinical advisors to the EAG suggest that treatment and adverse events **may differen~~t~~** between biologic naïve and treatment resistant sub-groups of this population.”	Typographical error	Thank you for raising this. It is now amended.
Page 28 Section 6.3: “The EAG base case attempts to address some of the key factors not included	Please amend as follows: “The EAG base case attempts to address some of the key factors not included in the	Typographical error.	Thank you for raising this. It is now amended.

in the company's model which would have an impact of the cost results."	company's model which would have an impact **on ~~of~~** the cost results."		
Page 29 Section 6.3.5: "There are a number possible vedolizumab dosing schedules"	Please amend as follows: "There are a number **of** possible vedolizumab dosing schedules"	Typographical error.	Thank you for raising this. It is now amended.
Page 30 Section 6.3.8: "…[redacted] than the EAG's base case if the annual discontinuation rate is 1,9%"	Please amend as follows: "…[redacted] than the EAG's base case if the annual discontinuation rate is **~~1,9%~~ 1.9%"**	Typographical error.	Thank you for raising this. It is now amended.

Section 3: Confidentiality highlighting amendments

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	
Page 22 Section 5.2.2	Although the "[redacted] part of the sentence is highlighted, it is not underlined. This should be updated to ensure that the document is correctly redacted.	"This is because risankizumab is [redacted] than ustekinumab in the induction phase, [redacted] in the maintenance phase; the longer the time horizon, the [redacted] risankizumab is compared with ustekinumab."	Thank you for raising this. It is now amended.

Page 22 Section 5.2.3	The current highlighting approach [redacted] and as such, should be updated. As it stands this sentence could be mis-read as [redacted].	"Risankizumab unit dose [redacted] ~~**includes a cPAS discount and it**~~ [redacted] ustekinumab unit dose (130mg or 90mg) at drug list prices."	Thank you for raising this. We agree with both points. It is now amended.
Page 27–28 Section 6; Table 9	The costs associated with ustekinumab do not need to be redacted here as they are based on BNF list prices.	All ustekinumab costs can be unredacted in Table 9.	Thank you for raising this. We agree this is an unnecessary redaction. It is now amended.

References

1. National Institute for Health and Care Excellence (NICE). User guide for company evidence submission template. Fast track cost-comparison case. Available at https://www.nice.org.uk/process/pmg32/resources/user-guide-for-the-cost-comparison-company-evidence-submission-template-pdf-72286772526277 [accessed 28 June 2023].
2. Peryer G, Golder S, Junqueira D, Vohra S, Loke YK. Chapter 19: Adverse effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook. [accessed 2 February 2024]