Single Technology Appraisal

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

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

Pre-technical engagement documents

1. **Company submission from Abbvie**

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions from:**
   - Crohns and Colitis UK

4. **External Assessment Report prepared by Peninsula Technology Assessment Group (PenTAG)**

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   - **a.** Dr Mark Samaan – clinical expert, nominated by AbbVie
   - **b.** Ms Kamila Kingstone – patient expert, nominated by Crohn's and Colitis UK

8. **External Assessment Group critique of company response to technical engagement prepared by Peninsula Technology Assessment Group (PenTAG)**

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

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

Document B

Company evidence submission

June 2022

File name	Version	Contains confidential information	Date
2c. ID3986_Risankizumab CD_NICE_DocB_Fv3_Fully redacted	V3	Yes [AiC/CiC]	19 Jan 2023

Contents

Tables and figures

Abbreviations

ADA	adalimumab
AE	adverse event
AESI	adverse events of special interest
AP	abdominal pain
APS	abdominal pain score
AZA	azathioprine
BF	biologic failure
BID	twice daily
Bio-IR	biologic inadequate response/intolerance
BSC	best supportive care
BSG	British Society of Gastroenterology
CCF	conventional care failure
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CEA	cost-effectiveness analysis
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CSR	clinical study report
Dbar	overall residual deviance
DIC	deviance information criteria
DSA	deterministic sensitivity analysis
EAMS	Early Access to Medicines Scheme
EIM	extraintestinal manifestation
EQ-5D	EuroQol-5 Dimensions health questionnaire
FACIT-F	The Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	full analysis set
FCP	fecal calprotectin
FE	fixed effects
GI	gastrointestinal
GLM	generalised linear model
HBI	Harvey Bradshaw Index
Hct	haematocrit
HCRU	healthcare resource use
HR	hazard ratio
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease
IBDQ	The Inflammatory Bowel Disease Questionnaire
ICER	incremental cost-effectiveness ratio
IFX	infliximab
IL	interleukin
IMM	immunomodulators
IR	inadequate response
ISPOR	The Professional Society for Health Economics and Outcomes Research
ITC	indirect treatment comparison
ITT	intention to treat
IV	intravenous
LS	least squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MoA	mechanism of action
MP	mercaptopurine
MTX	methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
OBD	on-body device

OL	open-label
OUS	outside-US
PAS	Patient Access Scheme
PBO	placebo
PIM	Promising Innovative Medicine
PRO2	patient-reported outcomes 2-item
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QxW	every x weeks
QALY	quality-adjusted life year
QD	once daily
QoL	quality of life
RD	risk difference
RE	random effects
RZB	risankizumab
SA	safety analysis
SAE	serious adverse event
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SMDM	The Society for Medical Decision Making
SmPC	Summary of Product Characteristics
STRIDE	The Selecting Therapeutic Targets in Inflammatory Bowel Disease
SS1	sub-study 1
SUCRA	Surface Under the Cumulative Ranking
TA	technology appraisal
TA MD	Therapeutic Area Medical Director
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
TSD	technical support document
UC	ulcerative colitis
UME	unrelated mean effects
UST	ustekinumab
VAS	visual analogue scale
VBA	Visual Basic for Applications
VDZ	vedolizumab

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

B.1.1 Decision problem

The full marketing authorisation for risankizumab is expected to be for the treatment of [redacted]. The submission covers the technology's expected full marketing authorisation for this indication.

The decision problem addressed is consistent with the National Institute for Health and Care Excellence (NICE) final scope for this appraisal, as outlined in Table 1.

The submission specifically addresses the clinical efficacy and safety, the comparative effectiveness and cost-effectiveness of the licensed doses (i.e., risankizumab 600 mg intravenous [IV] induction, followed by 360 mg subcutaneous [SC] maintenance every 8 weeks [Q8W]) for the treatment of moderately to severely active Crohn's disease (CD), in people aged 16 years and over.

Risankizumab currently holds marketing authorisation in the UK for treating moderate-to-severe plaque psoriasis as well as for the treatment of active psoriatic arthritis. Risankizumab received a recommendation from both NICE (NICE TA596) and the SMC (SMC2196) for treating moderate-to-severe plaque psoriasis. A recommendation from the SMC (SMC2459) and NICE (ID1399) has been received for risankizumab, alone or in combination with methotrexate (MTX), for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (1, 2).

Table 1: The decision problem

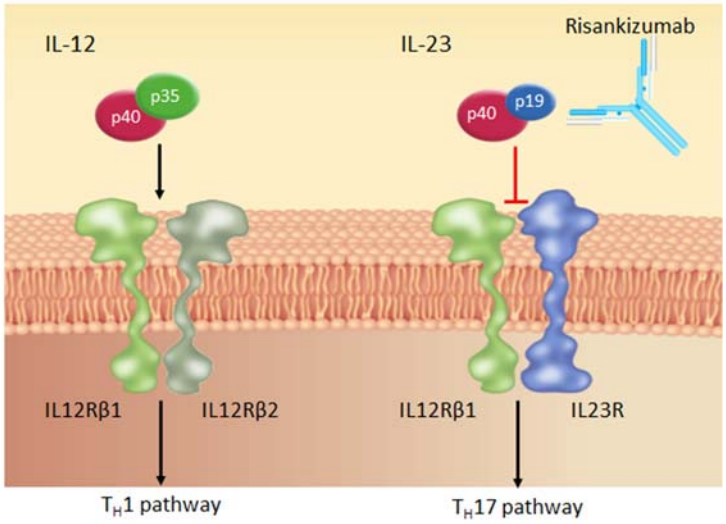
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated moderately to severely active CD	As per scope	NA
Intervention	RZB	As per scope	NA
Comparator(s)	• TNF-alpha inhibitors (IFX and ADA) • VDZ • UST For people for whom TNF-alpha inhibitors, VDZ and UST have been ineffective, are contraindicated or are not tolerated: • BSC	• TNF-alpha inhibitors (IFX and ADA) • UST • VDZ	The scope includes BSC as a comparator for those who have failed or are contraindicated to all currently available biologics (TNF-alpha inhibitors [ADA, IFX], UST and/or VDZ). BSC is not considered an appropriate comparator; in clinical practice, if a biologic therapy has failed or is contraindicated, the individual will be offered an alternative biologic therapy.
Outcomes	• Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Adverse effects of treatment • Health-related quality of life	• As per scope	NA
Subgroups to be considered	• If evidence allows; location of CD (Ileal, colonic and perianal)	• People who have had an inadequate response to conventional care (CCF) • People who have received ≥1 previous biologic and had an inadequate response (BF)	The trial design of RZB included the non-Bio-IR† and Bio-IR‡ populations, which were aligned in the model with CCF and BF populations. Separate analyses were conducted in these subpopulations as the comparators and clinical efficacy were different. Due to low subject numbers the analysis of outcomes by CD location was deemed untenable.
Special considerations including issues related to equity or equality	The availability and cost of biosimilars should be taken into consideration	• TNF-alpha inhibitors (ADA and IFX) are comparators which have biosimilars available	Cost of biosimilars have been taken into consideration where available i.e., for ADA and IFX.

Abbreviations: ADA, adalimumab; BF, biologic failure; BSC, best supportive care; Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CCF, conventional care failure; IFX, infliximab; NA, not applicable; RZB, risankizumab; TNF, tumour necrosis factor; UST, ustekinumab; VDZ, vedolizumab.; † Subjects who had an inadequate response or intolerance to conventional therapy (defined as one or more of the following: aminosalicylates, oral locally acting steroids [e.g., budesonide, beclomethasone], systemic corticosteroids [prednisone or equivalent], or immunomodulators). This population may include patients who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response (IR) or intolerance (e.g., change in reimbursement coverage, well-controlled disease); ‡ Subjects with documented intolerance or inadequate response (either failure to respond to induction treatment, or loss of response to maintenance therapy) to one or more biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab).

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission, including the mechanism of action, expected marketing authorisation, indications, method of administration, dosing and related costs, are provided in Table 2. The draft summary of product characteristics (SmPC) for risankizumab is provided in Appendix C (3, 4).

Table 2: Technology being appraised

UK approved name and brand name	Risankizumab (Skyrizi®)
Mechanism of action	Risankizumab is a humanised IgG1 monoclonal antibody that specifically binds with high affinity to the p19 subunit of human IL-23 cytokine blocking the binding of IL-23 to IL-23Rα without binding to IL-12 (5, 6). Increasing experimental and genetic evidence points to a fundamental role for IL-23 in driving inflammatory bowel disease, including CD (5). IL-23 is composed of two sub-units, p19 and p40 (see Figure below). The p40 subunit is also shared with another cytokine, IL-12 (see Figure below). IL-12 is important for the generation of T cells which are involved in protection against infection and cancer surveillance (5-8); however, evidence suggests that IL-12 has a limited role in driving inflammatory bowel disease (5). By targeting the p19 subunit of IL-23 with high specificity, risankizumab inhibits IL-23-dependent inflammation, whilst sparing IL-12 derived signals (9-12) and thus preserves TH1 pathway for the protection against infections and tumour immune surveillance (5-8). Risankizumab's IL-23-specific MoA via binding of IL-23 p19 is distinct from that of ustekinumab which inhibits both IL-23 (with 5-fold lower affinity than risankizumab) and IL-12 through the binding of IL-12 p40 (13). Risankizumab offers a novel treatment option for people with moderate-to-severe CD, and upon marketing authorisation would be the first and only IL-23 specific therapy for CD. **Figure 1: Inhibition of IL-23p19 by risankizumab**  Abbreviations: IL, interleukin; Th, T helper. Source: Singh et al. (2015) (12), Patel et al. (2012) (11), and Sofen et al. (2014) (10)

Marketing authorisation/ CE mark status	A marketing authorisation application was filed with the MHRA in [redacted] and EMA in [redacted]. Marketing authorisation is anticipated in Great Britain in [redacted] and in Northern Ireland in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Risankizumab is indicated for the treatment of [redacted]
Method of administration and dosage	The recommended induction dose is 600 mg administered IV at Week 0, Week 4 and Week 8, followed by a maintenance dose of 360 mg administered SC at Week 12 and Q8W thereafter. Risankizumab SC was delivered using SC injections in the risankizumab CD studies. In clinical practice, risankizumab SC will be delivered using an on-body device (OBD). See Appendix O for further information.
Additional tests or investigations	None
List price and average cost of a course of treatment	List price risankizumab 600mg: [redacted] List price risankizumab 360mg and OBD device [redacted] Average cost of course of treatment (year 1): [redacted]
Patient access scheme (if applicable)	The manufacturer has a simple PAS agreed with PASLU: PAS price risankizumab 600 mg vial: [redacted] PAS price risankizumab 360 mg vial (incl. OBD device): [redacted]

Abbreviations: EMA, European Medicines Agency; IgG1, immunoglobulin G1; IL, interleukin; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; MoA, mechanism of action; nM, nanomolar; OBD, on-body device; PAS, patient access scheme; PASLU, Patient Access Schemes Liaison Unit; Q8W, every 8 weeks; SC, subcutaneous; Th, T helper cell.

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

B.1.3.1 Disease overview

CD is a chronic relapsing systemic inflammatory bowel disease (IBD) that can cause inflammation and mucosal ulceration to the entire gastrointestinal tract (from the mouth to the anus), but most commonly affects the distal small intestine. Inflammation involves the whole thickness of the bowel wall (14, 15). The pathogenesis of CD involves the complex interaction of immunological, microbiological, environmental and genetic factors (14, 16, 17). Presenting symptoms can be heterogeneous and insidious. Symptoms commonly experienced by people with CD include abdominal pain, diarrhoea, fatigue, weight loss, and blood or mucus in stools (17, 18). Individuals typically suffer from recurrent relapses, with acute exacerbations interspersed with periods of remission (19-21). The symptoms of CD can significantly adversely affect individuals' lives, negatively impacting educational achievements, work productivity, mental health and quality of life (22-27). In addition, disease symptoms can also lead to extensive use of health services for disease management (24-26, 28). Timely intervention is required to promote mucosal healing and reduce long-term complications (29, 30). Inadequate treatment of mucosal inflammation leads to disease progression and increased likelihood of surgery (31).

Typically, CD severity is classified using clinical assessments which assess symptoms, including the Crohn's Disease Activity Index (CDAI), the patient reported outcomes 2-item (PRO2) and the Harvey Bradshaw Index (HBI) scores as well as endoscopic assessments (i.e., Simple Endoscopic Score for Crohn's Disease [SES-CD]) (32-36). An overview of the selected measures of disease severity frequently utilised in clinical trials and for the purposes of this submission are presented in Table 3 (for more details, see Appendix N).

Table 3: Overview of disease severity measures for CD

Measure	Definition of CD severity
CDAI	• The score ranges from 0–600, with index values of 150 and below associated with quiescent or non-active disease (i.e., clinical remission). • Values of 150 to 220 are indicative of mild-to-moderate disease, values of 220 to 450 are associated with moderate-to-severe disease, while values over 450 with severe-fulminant disease (37).
PRO2	• The score is generated using SF and AP to define the severity of disease activity in individuals with CD. • For the risankizumab CD studies, the PRO2 definition of moderate-to-severe CD was an average daily SF ≥4 and/or average daily AP score ≥2 at Baseline (38-40).
SES-CD	• Colonoscopies are scored based on a number of endoscopic categories (ulcer size, proportion of the surface covered by ulcers, proportion of the surface with any other lesions, and stenosis) in different locations (specifically the ileum, right colon, transverse colon, left colon, and rectum). • Each variable is scored from 0 to 3 in each segment and a total score is generated. • A higher score is indicative of more severe disease and a low score is indicative of mucosal healing. Values of 0–2, 3–6, 7–15 and ≥16 are indicative of inactive, mild, moderate, or severe disease, respectively (41, 42).

Abbreviations: AP, abdominal pain; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; PRO2, patient reported outcomes 2-item; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.

B.1.3.2 Disease burden

Epidemiology

Based on data from the Office of National Statistics, the total English population ≥16 years of age was estimated to be 46,911,788 in mid-2020 (43). The prevalence of CD in the UK in 2021 was 0.35 and 0.44 in males and females, respectively (44); given the latest population estimates (45), this leads to an estimated 185,668 people aged 16 and over in the England with CD. Approximately 40% of people with CD in the UK are estimated to have moderately to severely active disease at any time post diagnosis (46, 47). The estimated total prevalent number of people with moderate-to-severe CD in England based on this was approximately 74,267 in 2022.

In 2021, there were approximately 6,708 diagnosed incident cases of CD (a rate of 9 cases per 100,000) (48). Most individuals are diagnosed between 17 and 40 years of age, with incidence peaking at 14.9 per 100,000 person years in this age category in England (48). Although there has been a slight decrease in the incidence of CD in adults in the UK, the incidence is increasing in people aged <17 years of age (48).

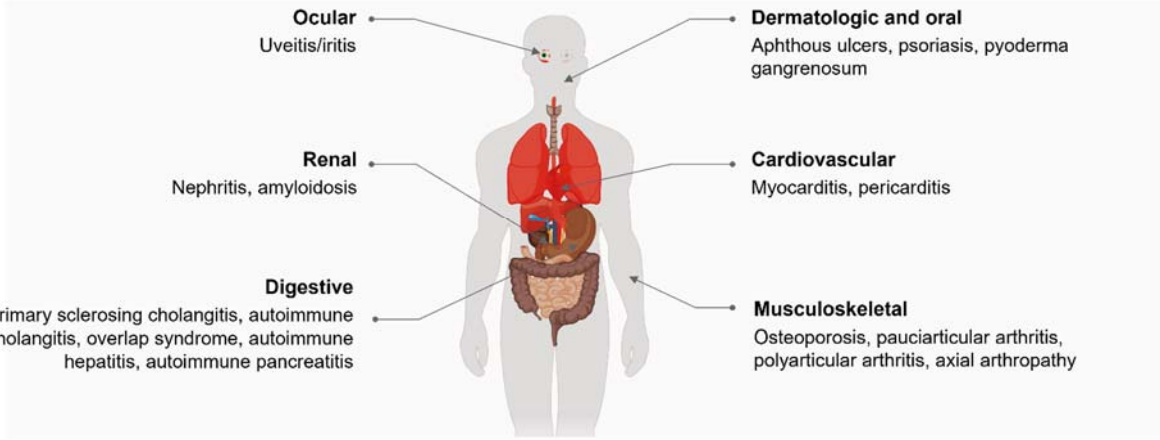
Symptoms of CD

The manifestations of CD vary from person to person, can change over time, and flare up during relapses (19-21, 49). The life expectancy of people with CD is slightly reduced when compared with the unaffected individuals (14, 44, 50, 51), with excess mortality mainly due to gastrointestinal causes linked to CD. Therefore, symptom management and minimisation of the impact of CD on quality of life are key considerations for disease management.

The symptoms of CD result from inflammation and commonly include the development of abdominal pain and distension, fever, weight loss, tiredness or fatigue, and clinical signs of bowel obstruction or diarrhoea with passage of blood or mucus, or both (14, 17, 18). Scar tissue can also develop, causing obstruction and the development of strictures, abscesses and/or fistulas (abnormal connections between the inflamed intestine and other areas). These complications are major causes of morbidity and can lead to surgery in up to 80% of people with CD (52, 53).

Due to the systemic nature of CD, individuals may also experience a broad range of extraintestinal manifestations (EIMs) as a result of abnormal immunological response (Figure 2) (14, 54). Up to 40% of people with CD develop dermatological, rheumatological, ocular and hepatic EIMs. In addition, CD is also commonly associated with cardiovascular disease, hepatic disorders, infections, gastrointestinal (GI) disorders and nutritional disorders (54-58). Psychological disorders are also more prevalent in people with CD compared with matched controls; 60% of people with CD have been reported to experience mental health problems, such as depression and anxiety, when symptoms are active (26, 27, 59). Issues with mental health are typically greater in individuals with more active or severe disease (27, 60), and may result in poor treatment compliance and risk of relapse (61).

Figure 2: Major extraintestinal manifestations for CD



Source: Image adapted from Baumgart et al. (2012) (14).

Health-related quality of life in individuals with CD

The symptoms of CD can have a substantial negative impact on individuals' functioning, daily activities, wellbeing, ability to work and health-related quality of life (HRQoL) (23-25). In one study of people with moderate-to-severe CD, 41% had problems with or were unable to perform usual activities, 7% had difficulties washing and dressing, and 14% reported problems with mobility (62). Fatigue has been reported in up to 43% of people with CD (63). The fatigue, pain, and anxiety and depression experienced by people with CD may all contribute to the impact of the disease on quality of life (QoL) and ability to perform daily activities (62, 64). Additionally, increased disease activity has been reported to negatively affect individuals' feelings about relationships, with individuals experiencing embarrassment and feeling socially restricted as a result of symptoms (60).

Loss of productivity

CD also negatively affects the educational achievements and work productivity of individuals (22). In a study of the long-term impact of CD and ulcerative colitis (UC) on the career aspirations, opportunities and choices of individuals aged 16–25 in the UK, 67% (n=91) reported that their IBD had delayed or was delaying their education and/or training, while 69% (n=91) felt IBD prevented them from reaching their full educational potential (22). Similarly, 40% (n=744) of individuals assessed stated that CD prevented them from pursuing their preferred job of choice, 57% (n=1,314) had to reduce working hours due to CD, and 54% (n=744) reported that CD had an impact on their career progression (22). The negative effect of CD on careers translates into

a perceived loss of earning for individuals (22). In a retrospective analysis of people with IBD (N=233), 50% of employed people with CD had some loss of employment days, with a median loss of earnings of £299[a] over a 6-month period (65). Similarly, significantly higher loss of productivity costs has been reported for the caregivers of people with CD aged ≤18 years compared with controls, highlighting that the indirect costs of CD can extend to caregivers (66).

Economic burden of CD

In 2006, IBD treatment cost the NHS in excess of £700 million per year (67). The medical requirements of people with CD place a significant burden on healthcare resources, with the average annual cost of care for treating CD in the UK estimated to be £6,156 per person[b] (68). CD is associated with higher rates of primary care visits and emergency attendances compared with matched controls (26). In 2019–2020, there were 139,303 finished consultant episodes and 128,692 hospital admissions related to CD in England (28). Additionally, many people with CD require surgery, which contributes to their healthcare resource use (HCRU); the risk of surgery five and 10 years after diagnosis of CD has been reported to be 33.3% and 46.6%, respectively (18, 52, 69). Higher costs for treatment, adverse events and complications are associated with individuals in relapse or experiencing flare-up compared with those in remission (total cost: £10,513 versus £1,800 for relapse versus remission) (68), while worsening disease severity is associated with increasing healthcare costs (65).

B.1.3.3 Treatment aims and clinical guidelines

Aim of treatment

CD is not medically or surgically curable. Treatment choices rely on clinical judgement and individual preference (35). The aim of medical treatment in CD has been focused on maintaining a symptom-free remission state whilst controlling inflammation, reducing risk of complications, and minimising surgery to preserve the patient's nutritional independence by maintaining sufficient intestinal luminal length. Whilst surgical rates have decreased over time in the era of biologic therapies, surgery is still required in significant proportion of individuals with CD, with up to 8 in 10 people with

CD requiring surgery at some point in their lives (69-71). In addition, approximately 25% of people with CD who undergo surgery will require additional surgery within 5 years of the first surgery (72). From an individual perspective, people with CD considered abdominal pain and bowel movement urgency the most important symptoms when prioritising disease control (73).

The use of both clinical and endoscopic treatment targets can facilitate effective disease control on a long-term basis (35). Endoscopic outcomes, such as mucosal healing, are now recognised as an important treatment target (35, 74, 75). The evolution of treatment goals from a focus on symptom control to also include endoscopic improvements is based on available evidence that mucosal healing is associated with better long-term outcomes, such as reduced risk of relapse, decreased hospitalisation rates, steroid-free remission in follow-up examination, resection free intervals and improved HRQoL (76, 77). There is increasing evidence of the benefits of mucosal healing in reducing future relapse rate (78). Additionally, people with CD with mucosal healing have a decreased risk of penetrating complications (i.e., development of fistulae) and probability of surgery as compared with those with severe ulcerations (77).

Recently updated guidance by the British Society of Gastroenterology (BSG) recognises the importance of mucosal healing, as measured by endoscopy, as a target for individuals and clinicians (35). Furthermore, evidence- and consensus-based recommendations from The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) (74) and STRIDE-II (75) programs recommended treatment targets for the management of IBD. In addition to short-term treatment targets of symptomatic response and remission, endoscopic response, normalised QoL and absence of disability were recognised as long-term treatment targets.

Disease management guidance

The treatment guidelines that are considered relevant for moderately to severely active CD in UK clinical practice are listed below:

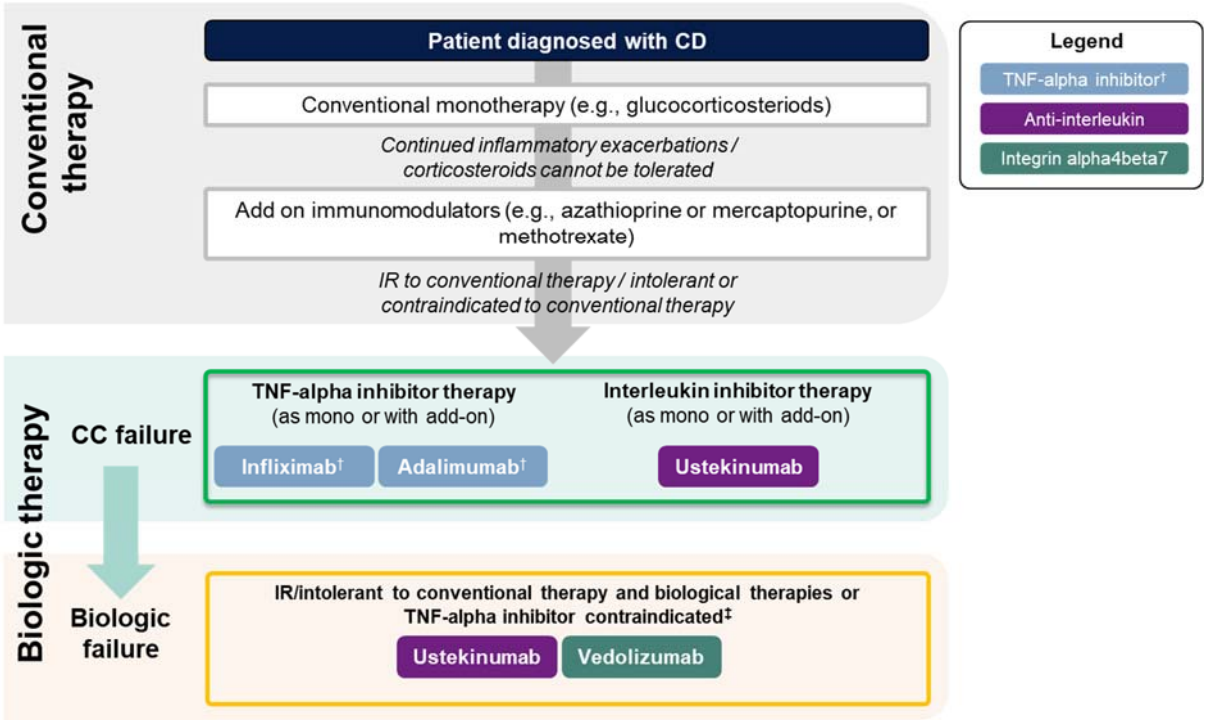
- Crohn’s disease: management (NICE guidance, NG129) (53)
- BSG consensus guidelines on the management of IBD in adults (35)

- European Crohn's and Colitis Organisation Guidelines on Therapeutics in Crohn's Disease: Medical Treatment (79)

In England, current NICE guidance (NG129) for adults recommends initial pharmacotherapy with conventional care to induce remission (initial presentation or during a flare-up), which typically includes corticosteroids (e.g., prednisolone) or aminosalicylates, typically followed by immunomodulators (IMM), such as azathioprine, to induce remission. IMM can also be given in addition to corticosteroids in the presence of continued inflammatory exacerbations (Figure 3) (53). Of note, aminosalicylates are rarely used in UK clinical practice (80) and other treatment guidelines do not recommend their use for CD (35, 79).

The treatment pathway based on NICE management guidance (53), including the typical biologic therapy sequence observed in UK clinical practice, is presented in Figure 3.

Figure 3: Treatment pathway based on CD management guidance by NICE



Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor. Figure adapted from NICE guidance. Source: Crohn's disease: management (NG129). 2019. NHS England, Clinical Commissioning Policy. 2020 (53). † Biosimilars are also available; The only approved biologic therapy for use in children and adolescents (>6–17 years old) with moderate-to-severe CD (53). ‡ TNF-alpha contraindicated people with CD are considered as part of the biologic failure population, in line with CEM and BIM. The majority (69%) of the TNF-alpha contraindicated population were expected to have failed a prior biologic (81) and analyses presented are split between the CC failure and biologic failure populations. Note: For paediatric patients, enteral nutrition or steroids are generally used for mild disease. For severe disease,

For adults, biologic medicines are introduced if there is a poor response to initial therapy with conventional care, if the therapy is not tolerated, or is contraindicated. For individuals with moderate-to-severe CD who have an inadequate response, are intolerant or are contraindicated to conventional care, TNF-alpha inhibitors (adalimumab, infliximab [both have biosimilars available]) and an interleukin 12/23 inhibitor (ustekinumab) are available as biologic treatment options.

For individuals who have biologic failure (those treated with a biologic therapy and subsequently have a loss of response, an inadequate response or are intolerant) ustekinumab or vedolizumab (an integrin α4β7 inhibitor) are the therapy options. Ustekinumab and vedolizumab are also the therapy options when TNF-alpha inhibitors are contraindicated (Figure 3) (53).

NICE recommend starting biologic treatment with the least expensive option, and that clinicians, after 12 months of treatment with a biologic therapy, assess individuals to determine if they are responding and should continue on the same therapy (53). The use of biologic therapies is beneficial but may be associated with loss of response in almost half of individuals within the first year (83), requiring dose escalation or therapy change, subsequently limiting the treatment options for clinicians and people with CD. The BSG guidance recommends that the choice between TNF-alpha inhibitor treatment, ustekinumab and vedolizumab should be made on an individual basis, considering individual preference, cost, likely adherence, safety data and speed of response to the drug (35).

For children and adolescents with CD, the treatment aim is to manage symptoms and ensure normal growth velocity in children. Enteral nutrition or steroids are generally induction treatments for all disease severity, with subsequent use of stronger immunosuppressive medications, such as azathioprine and methotrexate, to maintain remission (82). TNF-alpha inhibitors (infliximab, adalimumab) are the only biologic therapies licensed for those aged 6-17 years (53). For children and adolescents who have failed all these treatments, there is no alternative licensed therapy.

Ultimately, clinical management depends on disease activity, site, behaviour of disease (inflammatory, fistulising or stricturing), response to previous treatments, side-effect profiles of treatments and extra-intestinal manifestations, such as uveitis and arthritis, and patient preference (35, 53, 84).

Surgery is another treatment option for people with CD (53); the most common reasons for surgery include poor response to drug or nutritional treatment, strictures, fistulas and delayed growth in children as result of adequate control of inflammation. The benefits of surgery can include relief from pain, reduction of symptoms (e.g., diarrhoea, vomiting and fatigue), and reduction or cessation of treatments which may cause side effects (71). However, surgery is not curative, and use of biologic therapies may still be required (85).

In general, guidance from the BSG aligns with the NICE guidance presented before, with people with CD starting treatment on conventional care and progressing to biologic therapies if the disease is not adequately controlled with conventional care (35). The BSG guidance also recommends early use of biologic therapies in individuals with adverse prognostic factors.

Dosing of biologic therapies

Dosing of currently available biologic treatments requires induction therapy, where the drug is administered at a higher dose initially to reduce inflammation and improve CD symptoms (i.e., achieve remission). Following induction, a standard dose is administered at regular intervals to maintain control of the disease. People with moderately to severely active CD who experience loss of response to a particular TNF-alpha inhibitor are advised to reduce the interval between maintenance doses or escalate the dose before switching to another TNF-alpha inhibitor (86-88). Similarly, there is clinical flexibility for dose escalation for other classes of biologics (i.e., IL-12/23 [ustekinumab] and integrin α4β7 [vedolizumab] inhibitors) as per their respective SmPCs (89, 90). Specifically, ustekinumab may be initiated at a standard dose (Q12W) or a higher dose (Q8W), and both ustekinumab and vedolizumab may be escalated from the standard dose (Q12W and Q8W, respectively) to a higher dose during treatment (Q8W and Q4W, respectively) (89, 90). Feedback from clinical

experts indicates that dose escalation may be necessary in 30% and 92.5% of individuals receiving vedolizumab or ustekinumab, respectively (80).

B.1.3.4 Unmet need

As CD is a chronic condition which needs to be managed throughout the individual's lifetime, there is a significant unmet need for treatments in CD. Priorities include improved and sustained efficacy, including improved sustained corticosteroid-free remission.

CD is not always adequately controlled by currently available conventional and biologic therapies; it is estimated that there are approximately 4,000 people in the UK that have had an inadequate response to all currently available conventional and biologic therapies[c] (46). Approximately 50% of people with moderately to severely active CD do not respond to or cannot tolerate conventional treatment (46). Although advanced biologic therapies offer additional treatment options, individuals may still experience disease flares resulting in the appearance or worsening of disease symptoms such as abdominal pain and fatigue, which may require a dose escalation, therapy change or treatment with additional therapies, such as corticosteroids (83, 91-94). Furthermore, response to biologic therapy is often not sustained over time. Based on an international online survey (Canada, France, Germany, Italy, Spain, UK and USA) of individuals with CD, the response to biologic therapy is often not sustained over time, with loss of response to prior treatment reported in 69% of individuals (81).

TNF-alpha inhibitor treatments for CD (i.e., infliximab, adalimumab [including their biosimilars]) are commonly associated with therapy failure. Up to 30% of individuals do not respond to TNF-alpha inhibitor therapy (primary non-responders) and almost half of individuals who experience a benefit with these drugs will lose clinical benefits within the first year, requiring dose escalation or therapy change (secondary loss of response) (83). Moreover, people with CD who lose response to a specific TNF-alpha inhibitor have a lower chance of responding to a second TNF-alpha inhibitor (95). Primary loss of treatment response is also an issue with other classes of biologic therapies. A loss of response rate of approximately 30% at 52 weeks has been

[c] Figure estimated before the introduction of ustekinumab.

reported for vedolizumab (integrin α4β7 inhibitor) and ustekinumab (IL-12/23 inhibitor) (92, 94).

In addition to loss of response, another key limitation of existing treatments is their association with adverse side effects leading to potential increased HCRU and costs. For example:

- Long-term exposure to corticosteroids (often used alongside biologic therapies) results in an increased risk of numerous adverse events, including infection, psychological disturbances, diabetes, hypertension and osteoporosis (96); current BSG guidance does not recommend their long-term use (35).
- TNF-alpha inhibitors are associated with an increased risk of malignancy, demyelination and infection, including tuberculous infection (83, 89, 92).
- The development of anti-drug antibodies are associated with a loss of response (89, 97). The rates of anti-drug antibody development with TNF-alpha inhibitors are high and, consequently, are often given in combination with IMMs (e.g., azathioprine, mercaptopurine, methotrexate) to prevent anti-drug antibody formation (98). TNF-alpha inhibitor anti-drug antibody rates of 28.5% and 62.8% have been reported for adalimumab and infliximab, respectively (98). Additionally, the use of thiopurines (e.g., azathioprine) is associated with a risk for the development of lymphoma, non-melanoma skin cancer, liver inflammation bone marrow suppression and severe infections (99-102).

B.1.3.5 Risankizumab for the treatment of CD

Risankizumab is a humanised antibody which inhibits binding of the IL-23 proinflammatory cytokine to the IL-23 receptor complex. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines (10-12, 92). Increasing experimental and genetic evidence points to a fundamental role for IL-23 in driving inflammatory bowel disease, including CD (5).

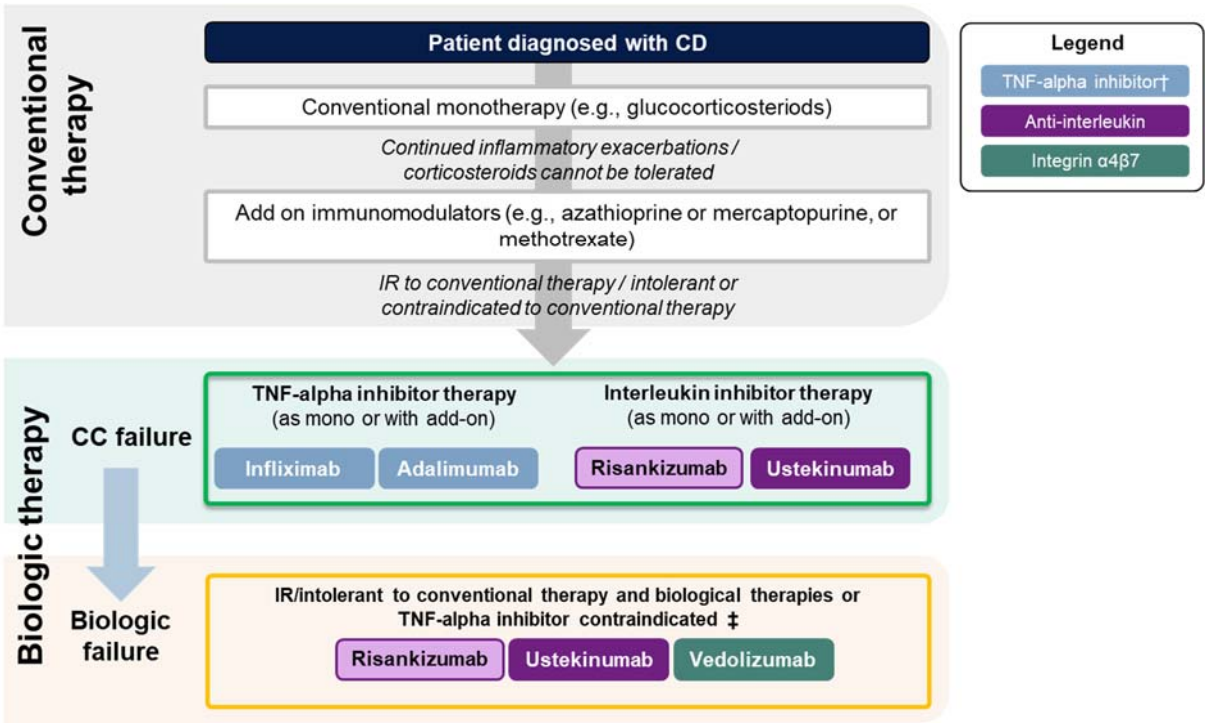
In line with the NICE recommendations for the clinical pathway in moderate-to-severe CD as detailed in Section B.1.3.3, the proposed UK treatment pathway including

risankizumab for CD is depicted Figure 4, the proposed positioning for risankizumab is equivalent to that of ustekinumab.

The positioning of risankizumab is in line with the expected marketing authorisation for CD, which is expected to be for the treatment of [redacted]. Therefore, risankizumab is expected to provide an additional treatment option in UK clinical practice for people with moderate-to-severe CD who are suitable for biologic therapy (Figure 4, green outline box). Risankizumab will also provide an additional treatment option for individuals with incomplete response to other biologic therapies (Figure 4, yellow outline box).

Risankizumab is a new class of biologic with a novel mode of action that selectively targets IL-23. Given that up to 50% of people with moderate-to-severe CD do not respond to, or cannot tolerate conventional treatment (46) and approximately 30% of individuals will lose response to biologic therapy within the first year of treatment (83, 92, 94) (previously discussed in Section B.1.3.4), risankizumab fulfils and important unmet need by providing an additional biologic therapy option for the management of individuals with CD.

Figure 4: Proposed treatment pathway including risankizumab for CD in the UK



Abbreviations: CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor. Figure adapted from NICE guidance. Source: NICE. Crohn's disease: management (NG129). 2019. NHS England, Clinical Commissioning Policy. 2020. (53). † Biosimilars are also available; The only approved biologic therapy for use in children and adolescents (>6–17 years old) with moderate-to-severe CD (53). ‡ TNF-alpha contraindicated people with CD are considered as part of the biologic failure population, in line with CEM and BIM. The majority (69%) of the TNF-alpha contraindicated population were expected to have failed a prior biologic (81) and analyses presented are split between the CC failure and biologic failure populations. Note: For paediatric patients, enteral nutrition or steroids are generally used for mild disease. For severe disease, stronger immunosuppressive add-on therapies, such as azathioprine, are used (82).

B.1.4 Equality considerations

No equality issues associated with the use of risankizumab in this indication have been identified or are foreseen.

B.2 Clinical effectiveness

Evidence for risankizumab in moderately-to-severely active CD

The Phase 3 pivotal induction studies (ADVANCE, MOTIVATE) and maintenance study (FORTIFY) provide the evidence for risankizumab for the treatment of moderately to severely active CD.

- ADVANCE and MOTIVATE were Phase 3, multicentre, randomised, double-blind, 12-week induction studies which evaluated the efficacy and safety of risankizumab (600 mg or 1,200 mg IV at weeks 0, 4 and 8) versus placebo in subjects aged ≥16 years with moderately-to-severely active CD.
- ADVANCE enrolled subjects with either inadequate response/intolerance to prior biologic therapy (Bio-IR) or with inadequate response/intolerance to conventional therapy (non-Bio-IR) for CD, whereas MOTIVATE enrolled subjects with only a documented inadequate response or intolerance to ≥1 biologic therapy/therapies for CD (Bio-IR).
  - Subjects in the risankizumab treatment arms who did not achieve PRO2 (SF/APS) clinical response† at Week 12 were re-randomised 1:1:1 to receive risankizumab 1,200 mg IV, risankizumab 360 mg SC or risankizumab 180 mg SC. Subjects in the placebo arm who did not achieve PRO2 (SF/APS) clinical response† at Week 12 of Induction Period 1 received risankizumab 1,200 mg IV during the 12-week Induction Period 2
- FORTIFY is a Phase 3, multicentre, partially randomised, double-blind, placebo-controlled, 52-week maintenance study with an ongoing open-label (OL) extension which evaluated the efficacy and safety of risankizumab in subjects with moderately-to-severely active CD. The study enrolled subjects who achieved SF/APS clinical response† at the last visit of induction (Induction Period [Week 12] or Induction Period 2 [Week 24]) for ADVANCE or MOTIVATE.
  - Subjects who achieved SF/APS clinical response† to 12 weeks of IV risankizumab induction (either at Week 12 or 24) from ADVANCE and MOTIVATE and a Baseline induction eligibility SES-CD of ≥6 (≥ 4 for isolated ileal disease) were re-randomised in a 1:1:1 ratio to receive risankizumab at either 180 mg SC Q8W or 360 mg SC Q8W, or to receive placebo SC Q8W (referred to as placebo SC [withdrawal]‡).

Definition of subpopulations of interest

The naming conventions used to describe the populations of interest in the pivotal risankizumab clinical trials in CD (Bio-IR and non-Bio-IR) are different from naming conventions used in previous TAs for this indication (conventional care failure [CCF] and biologic failure [BF]). Definitions of the specific populations are as follows:

- **Non-Bio-IR:** Subjects who had an inadequate response or intolerance to conventional therapy.§ This population may also include subjects who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response (IR) or intolerance (e.g., change in reimbursement coverage, well-controlled disease); however, the majority of subjects (>[redacted]%) had not received a prior biologic therapy (103). This population is analogous to the CCF population which has been described in previous submissions.¶

- **Bio-IR:** Subjects with documented intolerance or IR (either failure to respond to induction treatment, or loss of response to maintenance therapy) to one or more biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab). This population is analogous to the BF population which has been described in previous submissions.¶

Consequently, the Bio-IR and non-Bio-IR naming conventions are used in the context of the risankizumab clinical trials only, whilst through the remainder of the submission (i.e., the NMA and cost-effectiveness model), CCF and BF are used for consistency with previous appraisals.

Efficacy

- Treatment with risankizumab in the induction (risankizumab 600 mg IV) and maintenance (risankizumab 360 mg SC) studies were superior to placebo for the co-primary endpoints of clinical remission (CDAI or PRO2 [SF/APS]††) and endoscopic response.‡‡
- In the induction studies, symptomatic improvements were seen as early as Week 4 and mucosal improvement (measured by SES-CD) observed at Week 12 after treatment with risankizumab 600 mg IV.
- For risankizumab maintenance, symptomatic and mucosal improvements were also observed after 52 weeks of treatment. Outcomes indicative of mucosal healing, specifically ulcer-free endoscopy§§ and the composite endpoint of deep remission¶¶ were achieved by approximately 30% of subjects receiving risankizumab 360 mg SC.
- Subjects treated with risankizumab 600 mg IV in ADVANCE and MOTIVATE had significantly improved HRQoL (EQ-5D-5L) as early as 4 weeks and at Week 12 when compared with placebo.

Safety

- Across the risankizumab induction (ADVANCE and MOTIVATE) and maintenance (FORTIFY) studies, no new safety risks were identified, and the overall safety profile was consistent with the known safety profile of risankizumab in the management of psoriasis.

Indirect treatment comparisons

- In the absence of head-to-head clinical trial evidence for risankizumab versus other biologic therapies, an indirect treatment comparison was performed. Overall, the indirect treatment comparison (ITC) results indicate that that risankizumab has similar efficacy compared with other biologics across most clinically relevant outcomes, in both CCF and BF populations.

Conclusion

- Risankizumab is an innovative therapy that is associated with significant symptomatic, clinical and mucosal improvements from as early as Week 4 versus placebo, with similar improvements observed over the 52-week SC maintenance phase. Risankizumab is also well tolerated. In an ITC, risankizumab has similar efficacy compared with other biologics across the majority of clinically relevant outcomes, in both CCF and BF populations.

† For this submission, only CDAI outcomes are presented as the cost-effectiveness model utilises CDAI outcomes to define CD health states (i.e. PRO2 [SF/APS] outcomes are not used in the model) and CDAI outcomes facilitate

indirect treatment comparisons with previous trials of treatments for CD (104, 105). Overall, the results for PRO2 [SF/APS] and CDAI outcomes were similar for risankizumab in CD. Consequently, all PRO2 (SF/APS) outcomes, including the co-primary endpoint of PRO2 [SF/APS] clinical remission and endoscopic response, are presented in Appendix M; ‡ Subjects re-randomised to receive placebo are referred to as the placebo SC (withdrawal) group as these subjects previously received risankizumab in the induction studies and have subsequently had it withdrawn for the maintenance study (i.e., re-randomised to placebo); § Defined as one or more of the following: aminosalicylates, oral locally acting steroids [e.g., budesonide, beclomethasone], systemic corticosteroids [prednisone or equivalent], or immunomodulators; ¶ Clinicians at an expert advisory board (80) have also concluded that the non-Bio-IR and Bio-IR populations in the risankizumab clinical trials are analogous to the CCF and BF populations, respectively; †† Ulcer-free endoscopy defined as SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥1 at baseline of the induction study, as scored by a central reviewer; CDAI clinical remission defined as CDAI <150; ‡‡ Endoscopic remission is defined as SES-CD ≤4 and at least a 2 point reduction versus baseline of the induction study and no subscore greater than 1 in any individual variable, as scored by a central reviewer.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of risankizumab and relevant comparators for the treatment of people aged ≥16 years with moderate-to-severe CD. An overview of the methodology, including search strategy, PRISMA flow diagram, list of included studies and list of excluded studies at full paper review is provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence for risankizumab is provided in Table 4, Table 5 and Table 6.

The primary data for risankizumab CD in this submission is taken from clinical study reports (CSRs) and published manuscripts. At the time of submission, only data from the CSRs were deemed commercial in confidence.

Table 4: Clinical effectiveness evidence – ADVANCE (pivotal induction study)

Study	ADVANCE (Study M16-006) Data sources: CSR (38), trial publication (106)				
Study design	A Phase 3, international, multicentre, randomised, double-blind, placebo-controlled induction study				
Population	Subjects aged ≥16 years with moderately-to-severely active CD with inadequate response or intolerance to prior biologic therapy (Bio-IR), or with inadequate response or intolerance to conventional therapy (non-Bio-IR)				
Intervention(s)	Risankizumab 600 mg IV at Week 0, 4 and 8 Risankizumab 1,200 mg IV at Week 0, 4 and 8				
Comparator(s)	Placebo IV at Week 0, 4 and 8				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Reported outcomes specified in the decision problem	Disease activity (remission, response, relapse) Mucosal healing Surgery Adverse effects of treatment Health-related quality of life				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CSR, clinical study report; IV, intravenous; non-Bio-IR, conventional therapy inadequate response/intolerance.

Table 5: Clinical effectiveness evidence – MOTIVATE (pivotal induction study)

Study	MOTIVATE (Study M15-991) Data sources: CSR (39), trial publication (106)				
Study design	A Phase 3, international, multicentre, randomised, double-blind, placebo-controlled induction study				
Population	Subjects aged ≥16 years with moderately-to-severely active CD with inadequate response or intolerance to one or more biologic therapies (Bio-IR)				
Intervention(s)	Risankizumab 600 mg IV at Week 0, 4 and 8 Risankizumab 1,200 mg IV at Week 0, 4 and 8				
Comparator(s)	Placebo IV at Week 0, 4 and 8				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Reported outcomes specified in the decision problem	Disease activity (remission, response, relapse) Mucosal healing Surgery Adverse effects of treatment Health-related quality of life				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CSR, clinical study report; IV, intravenous.

Table 6: Clinical effectiveness evidence – FORTIFY (pivotal maintenance study)

Study	FORTIFY (Study M16-000) Data sources: CSR (40), trial publication (107)				
Study design	A Phase 3, international, multicentre, partially randomised, double-blind, placebo-controlled maintenance study with an ongoing open-label extension phase				
Population	Subjects aged ≥16 years with moderately-to-severely active CD who achieved clinical response† at the last visit of the induction studies (ADVANCE or MOTIVATE)				
Intervention(s)	Risankizumab 360 mg SC Q8W Risankizumab 180 mg SC Q8W				
Comparator(s)	Placebo SC Q8W				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Reported outcomes specified in the decision problem	Disease activity (remission, response, relapse) Mucosal healing Surgery Adverse effects of treatment Health-related quality of life				

Abbreviations: CD, Crohn's disease; CSR, clinical study report; Q8W, every 8 weeks; SC, subcutaneous.
† SF/APS clinical response defined as ≥ 30% decrease in average daily stool frequency (SF) and/or ≥ 30% decrease in average daily abdominal pain score (APS) and both not worse than Baseline of the induction study.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Comparative summary of trial methodology

The Phase 3 pivotal induction studies (ADVANCE, MOTIVATE) and maintenance study (FORTIFY) provide the evidence for risankizumab for the treatment of moderately-to-severely active CD in people aged 16 years and older.

B.2.3.1.1 Induction studies (ADVANCE and MOTIVATE)

ADVANCE and MOTIVATE were Phase 3, multicentre, randomised, double-blind induction studies which evaluated the efficacy and safety of risankizumab (600 mg or 1,200 mg IV Q4W) versus placebo in subjects with moderately-to-severely active CD aged 16 years and older. ADVANCE enrolled subjects with inadequate response or intolerance to prior biologic therapy (Bio-IR), or with inadequate response or intolerance to conventional therapy (non-Bio-IR). MOTIVATE enrolled subjects with a documented inadequate response or intolerance to ≥1 biologic therapy/therapies for CD (Bio-IR). These populations were defined as following:

- ***Bio-IR population:*** Included subjects with documented inadequate response or intolerance to one or more biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab) (refer to Appendix M for full definition).
- ***Non-Bio-IR population:*** included subjects who had an inadequate response or intolerance to conventional therapy (defined as one or more of the following: aminosalicylates, oral locally acting steroids [e.g., budesonide, beclomethasone], systemic corticosteroids [prednisone or equivalent], or immunomodulators). This population included subjects who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease), however, the majority of subjects had not received a prior biologic therapy (refer to Appendix M for full definition).

The percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab was to be no more than 20% in the ADVANCE and MOTIVATE.

In ADVANCE and MOTIVATE, subjects received placebo IV or risankizumab IV (600 mg or 1,200 mg) at weeks 0, 4, and 8. The final study visit was at Week 12 (Induction Period 1). Subjects who did not achieve a clinical response during Induction Period 1 were re-randomised to receive a further 12 weeks of induction treatment (Induction Period 2) (Figure 5).

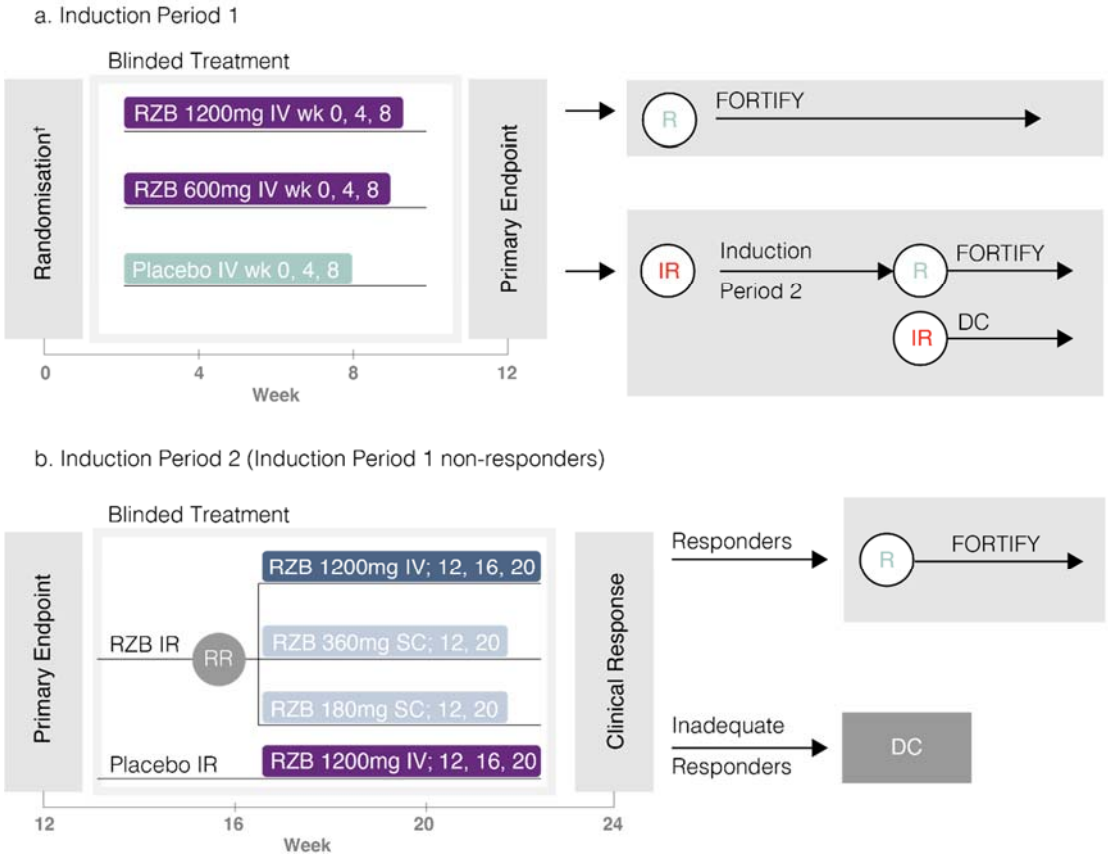
An overview of the analysis sets and contributing subject populations is presented in Table 7, with the two induction periods detailed as follows:

- ***Induction Period 1:*** After a screening period of up to 35 days, subjects were randomised in a 2:2:1 (ADVANCE; Figure 5) or 1:1:1 ratio (MOTIVATE; Figure 5) into risankizumab 1,200 mg IV, risankizumab 600 mg IV or placebo IV arms for the 12-week Induction Period 1, with subjects in all arms receiving treatment at Week 0, 4 and 8. Visits for clinical evaluation occurred at Baseline, and Weeks 4, 8, and 12, or premature discontinuation.
- ***Induction Period 2:*** Subjects in risankizumab treatment arms who did not achieve PRO2 (SF/APS) clinical response (see Table 11 for definition) at Week 12 were re-randomised 1:1:1 to receive risankizumab 1,200 mg IV, risankizumab 360

mg SC or risankizumab 180 mg SC (see Figure 5 for more details). Subjects in the placebo arm who did not achieve PRO2 (SF/APS) clinical response at Week 12 of Induction Period 1 received risankizumab 1,200 mg IV during the 12-week Induction Period 2 (Figure 5).

Study duration for ADVANCE and MOTIVATE was up to 49 weeks (comprised of 5 weeks screening, up to 24 weeks' treatment and a 20-week follow up for subjects who discontinued and did not go on to enter FORTIFY. Subjects who achieved PRO2 (SF/APS) clinical response at the last visit of Induction Period 1 (Week 12) or Induction Period 2 (Week 24) in ADVANCE or MOTIVATE were enrolled in the FORTIFY maintenance study (see B.2.3.1.2).

Figure 5: Trial design for ADVANCE and MOTIVATE



Abbreviations: DC, discontinuation; IR, inadequate response/intolerance; IV, intravenous; R, randomisation / response; RZB, risankizumab; RR, re-randomisation; SC, subcutaneous. † Subjects were randomised 2:2:1 (ADVANCE) or 1:1:1 (MOTIVATE). Colours refer to trial population flow in FORTIFY (see Figure 6)

Table 7: Definitions of analysis sets – ADVANCE and MOTIVATE

Analysis sets	Definition
ITT1	• ITT population for Induction Period 1 which included randomised subjects who received ≥1 dose of study drug during this period
ITT1A	• Primary population for the efficacy analysis • Subjects who were randomised and received ≥1 dose of RZB during Induction Period 1 • Included subjects who had a baseline eligible SES-CD of ≥6 (≥4 for isolated ileal disease)
ITT2	• ITT population for Induction Period 2 included subjects who were randomised and received ≥1 dose of RZB during Induction Period 2, and subjects who received PBO induction treatment during Induction Period 1 and entered Induction Period 2 (denoted as PBO/RZB)
ITT2A	• Subjects who were randomised and received ≥1 dose of RZB during Induction Period 2, and subjects who received PBO induction treatment during Induction Period 1 and entered Induction Period 2 (denoted as PBO/RZB) • Included subjects who had a baseline eligible SES-CD of ≥6 (≥4 for isolated ileal disease)
SA1	• Primary population for the safety analysis • Consisted of all subjects who received ≥1 dose of RZB during Induction Period 1

Abbreviations: ITT, intention to treat; PBO, placebo; RZB, risankizumab; SA, safety analysis; SES-CD, Simple Endoscopic Score for Crohn's Disease.

B.2.3.1.2 Maintenance study (FORTIFY)

FORTIFY is a Phase 3, multicentre, partially randomised, double-blind, placebo-controlled, 52-week maintenance study with an ongoing OL extension which evaluated the efficacy and safety of risankizumab in subjects with moderately-to-severely active CD aged 16 years and older. The study enrolled subjects who achieved PRO2 (SF/APS) clinical response (defined as 30% decrease in average daily SF and/or ≥30% decrease in average daily AP score and both not worse than Baseline of induction study) at the last visit of induction (Induction Period [Week 12] or Induction Period 2 [Week 24]) for ADVANCE or MOTIVATE.

FORTIFY consists of 3 sub-studies. This submission presents the results from FORTIFY Sub-study 1 (SS1)[d], which was a 52-week randomised, double-blind, placebo-controlled maintenance study. FORTIFY SS1 had a randomised portion and non-randomised portion. An overview of the analysis sets and contributing subject populations is presented in Table 8 and the trial design is presented in Figure 6.

- ***FORTIFY SS1 randomised responders:*** Included all subjects from ADVANCE and MOTIVATE who had a clinical response to induction treatment with IV risankizumab (either during Induction Period 1 or Induction Period 2) and a

[d] Sub-Study 2 was a 52-week randomised, exploratory maintenance study of 2 different dosing regimens (TDM vs clinical assessment for dose escalation) and is not presented in this submission. Sub-Study 3 is an OL long-term extension for which data collection is still ongoing.

Baseline induction eligibility SES-CD of ≥6 (≥ 4 for isolated ileal disease) – denoted as the purple and dark blue populations in Figure 6).

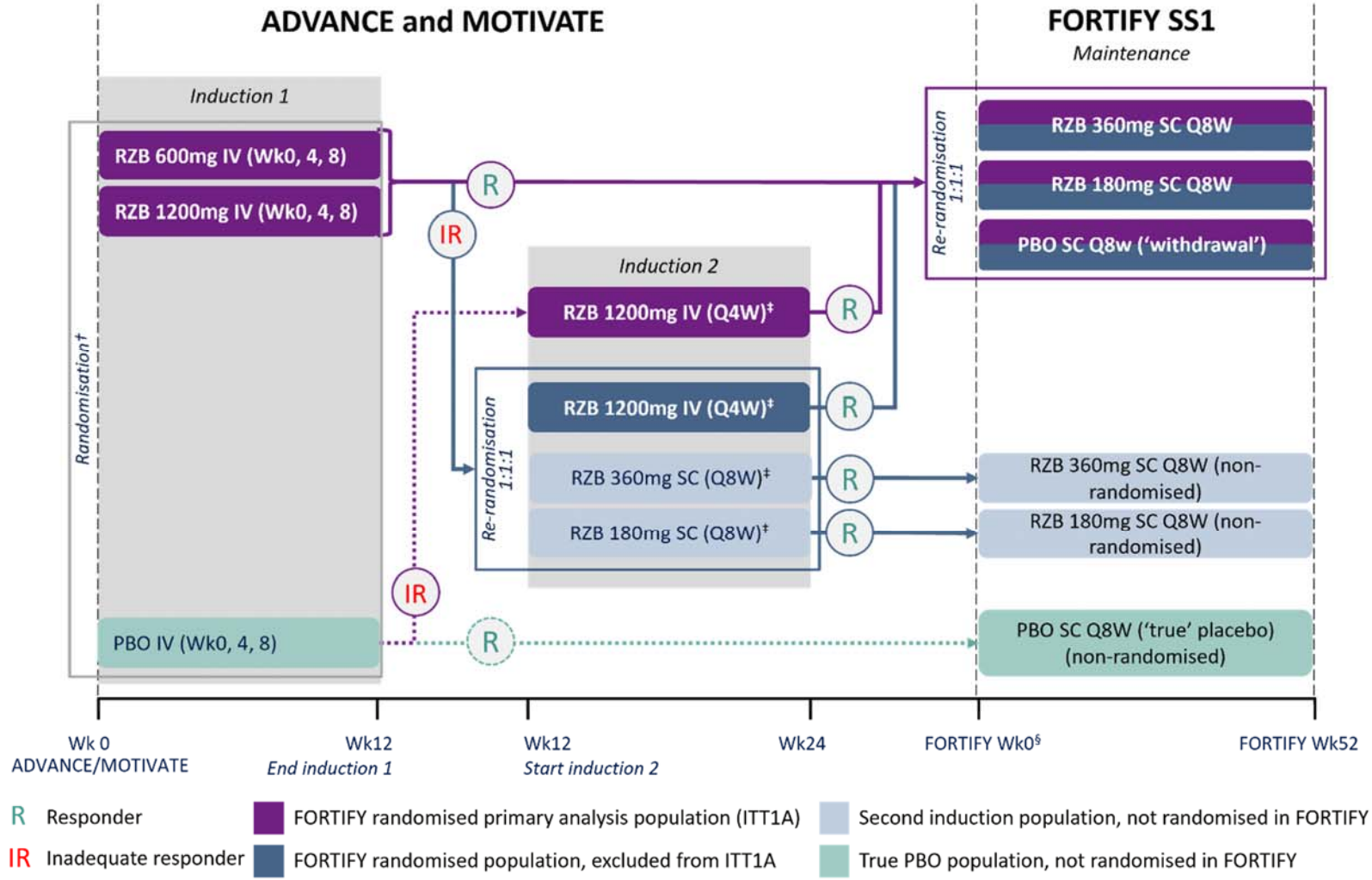
- Subjects were re-randomised in a 1:1:1 ratio to receive either risankizumab 180 mg SC Q8W, risankizumab 360 mg SC Q8W or placebo SC Q8W. The placebo will henceforth referred to as placebo SC (withdrawal). This reflects the placebo 'withdrawal' arm as all subjects in this arm received and clinically responded to risankizumab IV during induction in ADVANCE and MOTIVATE.
  - The primary efficacy analysis included subjects with PRO2 (SF/APS) clinical response to IV risankizumab induction at Week 12 (Induction Period 1) or subjects who had an IR to placebo at Week 12 (Induction Period 1) and a subsequent response to IV risankizumab at Week 24 (Induction Period 2) (purple population in Figure 6).
  - Subjects who had an IR to IV risankizumab at Week 12 (Induction Period 1), and a subsequent response to IV risankizumab at Week 24 (Induction Period 2) were re-randomised but were not included in the primary efficacy analysis (dark blue population in Figure 6).
  - The main safety population (SA1) consisted of all randomised subjects who received at least 1 dose of study risankizumab.
- ***FORTIFY SS1 non-randomised responders:*** Included subjects with either PRO2 (SF/APS) clinical response to IV placebo at the end of Induction Period 1 or risankizumab 360mg/180mg SC induction treatment at the end of Induction Period 2 in ADVANCE or MOTIVATE.
  - Subjects who achieved a clinical response to IV placebo at the end of Induction Period 1 were assigned to continue receiving placebo SC in FORTIFY (referred to as 'true' placebo, as these subjects did not receive any risankizumab treatment in the induction or maintenance trials; turquoise population in Figure 6).
  - Subjects who achieved a clinical response to risankizumab 360mg/180mg SC induction treatment at the end of Induction Period 2 were assigned to continue to receive the same blinded study drug in FORTIFY (light blue populations in Figure 6).

Table 8: Definitions of analysis sets – FORTIFY SS1

Analysis sets	Definition
ITT1	• ITT population included subjects (randomised and non-randomised) who received ≥1 dose of study drug from SS1 (purple and dark blue populations)
ITT1A	• Primary population for efficacy analysis in SS1 • Included randomised subjects in the ITT1 set who had eligibility SES-CD of ≥6 (≥4 for isolated ileal disease) at Baseline of the induction study (ADVANCE or MOTIVATE) and received IV RZB for only 1 period of 12 weeks in the induction study (ADVANCE or MOTIVATE). This population includes subjects who had PRO2 (SF/APS) clinical response to IV RZB at Week 12 and subjects with placebo IR at Week 12, proceeded to receive IV RZB in Induction Period 2, and had PRO2 (SF/APS) clinical response at Week 24 (purple population)
ITT1C	• Includes the non-randomised subjects in the ITT1 set. This population includes subjects with PRO2 (SF/APS) clinical response at the last visit of the induction studies (ADVANCE or MOTIVATE) to IV placebo (Week 12) (turquoise population) and SC RZB (Week 24) (light blue populations) and was used for exploratory efficacy analyses
SA1	• The main safety population, as it contains the primary treatment population (subjects who achieved PRO2 [SF/APS] clinical response to IV RZB) • Consists of all randomised subjects who received ≥1 dose of study RZB in SS1

Abbreviations: APS, abdominal pain score; ITT, intention to treat; IV, intravenous; PROS, patient reported outcomes 2-item; RZB, risankizumab; SA, safety analysis; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; SS, sub study.

Figure 6: Trial design for FORTIFY (Sub Study 1)



Abbreviations: IR, inadequate response/intolerance; IV, intravenous; PBO, placebo; Q8W, every 8 weeks; R, response RZB, risankizumab; SC, subcutaneous; SSI, Sub Study 1. † Randomisation ratio for ADVANCE (2:2:1) and MOTIVATE (1:1:1); ‡ Any IR subjects at Wk24 did not enter FORTIFY; § FORTIFY Wk0 is the last dose of the induction period (i.e., either Wk12 or Wk24 of treatment).

Subjects who demonstrated IR during FORTIFY SS1 received OL risankizumab rescue therapy starting at the Week 16 visit (up to 2 rescue therapy visits) based upon increased symptom activity and confirmation with objective markers of inflammation. Rescue therapy consisted of OL risankizumab at 1,200 mg IV as a single dose, followed by OL risankizumab 360 mg SC dosing Q8W. Please note, these subjects are not considered further in this submission as this population is not in line with the licensed indication.

Subjects who were taking corticosteroid therapy at the Week 0 visit of FORTIFY had their corticosteroid therapy tapered. If an Investigator believed that the steroid taper was not advisable for a particular subject, the sponsor Therapeutic Area Medical Director (TA MD) was consulted for evaluation and approval. The corticosteroid tapering schedule is available in Appendix M.3

For subjects who enrolled in FORTIFY SS1, Baseline was defined as the Baseline visit of the induction studies ADVANCE or MOTIVATE for efficacy analyses. For safety analyses, Baseline was defined as the last measurement prior to the first dose of study drug in ADVANCE or MOTIVATE.

Week 0 was defined as the first study visit in FORTIFY SS1. The final visit of ADVANCE or MOTIVATE (Week 12 or Week 24) was considered as the Week 0 visit of SS1.

Visits during FORTIFY SS1 occurred at Weeks 0, 8, 16, 24, 32, 40, 48 and 52/premature discontinuation. Subjects who discontinued from the study early or completed FORTIFY SS1 and did not continue into Sub-Study 3 had an additional 140 days of safety follow-up from the last dose administration of study drug.

The methodologies of ADVANCE, MOTIVATE and FORTIFY are summarised in Table 9.

Table 9: Comparative summary of trial methodology

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
Study objective	To evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in a Bio-IR and non-Bio-IR population aged ≥16 years with moderately to severely active CD	To evaluate the efficacy and safety of risankizumab versus placebo during induction therapy in a Bio-IR population aged ≥16 years with moderately-to-severely active CD	To evaluate the efficacy and safety of continuing risankizumab treatment as maintenance therapy versus placebo (withdrawal of risankizumab treatment) in a mixed Bio-IR and Non-Bio-IR population aged ≥16 years with moderately-to-severely active CD
Trial design	Phase 3, international, multicentre, randomised, double-blind, placebo-controlled induction study		Phase 3, international, multicentre, partially randomised, double-blind, placebo-controlled maintenance study with an ongoing open-label extension phase
Method of randomisation	All subjects were assigned a unique identification number by the IRT at the Screening visit that was used throughout the study. Subjects were randomised in a 2:2:1 (ADVANCE) or 1:1:1 ratio (MOTIVATE) • Randomisation stratified by: number of prior biologics failed (0, 1, > 1 [ADVANCE] or 1, >1 [MOTIVATE]), steroid use at Baseline (yes, no), and Baseline SES-CD (original, alternative), where the stratum of 'original' includes the patients with baseline SES-CD of ≥6 (or ≥4 for subjects with isolated ileal disease)[†]		All subjects maintained the unique identification number that was assigned at the Screening visit of ADVANCE or MOTIVATE • Randomisation stratified by endoscopic response (per local read) and clinical remission status from the last visit of ADVANCE or MOTIVATE as well as by risankizumab induction dose
Method of blinding (care provider, patient and outcome assessor)	All personnel with direct oversight of the conduct and management of the study (with the exception of the Drug Supply Management Team and unblinded CRA/monitor [as applicable]) as well as the Investigator, the blinded study site personnel and the subject remained blinded to each subject's treatment throughout the study. The IRT provided access to blinded subject treatment information in the case of medical emergency To maintain the blinding, certain site staff remained unblinded (unblinded licensed pharmacist or qualified designee) to prepare the IV solutions and blind the doses. Study personnel who administered the infusions remained blinded		All personnel with direct oversight of the conduct and management of the study (with the exception of the Drug Supply Management Team and unblinded CRA/monitor [as applicable]) as well as the Investigator, the blinded study site personnel and the subject remained blinded to each subject's treatment throughout the study. The IRT provided access to blinded subject treatment information in the case of medical emergency To maintain the blind, the risankizumab and placebo kits provided for the blinded period of the study were identical in appearance

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
Eligibility criteria for participants	***Inclusion criteria (full list in Appendix M.1, Table 83):*** • Males or females aged ≥18 to ≤80 years at Baseline • Where locally permissible, subjects aged 16 to <18 years who meet the definition of Tanner stage 5 for development • Confirmed diagnosis of CD for at least 3 months prior to Baseline • Moderately-to-severely active CD, defined as: – CDAI score 220 – 450 at Baseline – Endoscopic evidence of mucosal inflammation: SES-CD of ≥6 for ileocolonic or colonic disease or SES-CD of ≥4 for isolated ileal disease – Average daily SF ≥4 and/or average daily AP score ≥2 at Baseline		***Inclusion criteria (full list in Appendix M.1, Table 83):*** • Entry and completion of ADVANCE, MOTIVATE • Achieved clinical response, defined as ≥30% decrease in average daily SF and/or ≥ 30% decrease in average daily AP score, and both not worse than Baseline of the induction study, at the last visit of ADVANCE or MOTIVATE
	Demonstrated intolerance (requires no minimum dose or duration of use)‡ or IR (see Appendix M.1, Table 83 for definitions) to ≥1 of the following: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunomodulators, and/or biologic therapies	Demonstrated intolerance (requires no minimum dose or duration of use) or IR (see Appendix M.1, Table 83 for definitions) to ≥1 of the following biologic therapies: IFX, ADA, certolizumab pegol, natalizumab, VDZ and/or UST	
	Exclusion criteria (full list in Appendix M.1, Table 83): • Subject taking oral corticosteroids (budesonide >9 mg/day, beclomethasone >5 mg/day, prednisone or equivalent >20 mg/day, or has not been on the current course for ≥14 days prior to Baseline and on a stable dose for ≥7 days prior to Baseline • Subject on immunomodulators (AZA, MP, MTX) who had not been on the current course for ≥42 days prior to Baseline and had not been on a stable dose for ≥35 days prior to Baseline • Subject who received any approved biologic agent (infliximab, adalimumab, certolizumab, vedolizumab, natalizumab) ≤8 weeks prior to baseline or ustekinumab ≤12 weeks prior to Baseline, or any investigational biologic or other agent or procedure within 35 days or 5 half-lives prior to Baseline, whichever is longer		***Exclusion criteria (full list in Appendix M.1, Table 83):*** • High grade colonic dysplasia or colon cancer identified during ADVANCE, MOTIVATE or another AbbVie RZB CD study if the final endoscopy was performed prior to entering FORTIFY or subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study. • Subject not in compliance with prior and concomitant medication requirements through ADVANCE, MOTIVATE or other AbbVie RZB CD study

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
	• Subject with known CD complications, such as abscess (abdominal or perianal), symptomatic bowel strictures, >2 missing segments (of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum), fulminant colitis, toxic megacolon, any other manifestation that might require surgery during study enrolment		
Settings and locations where the data were collected	297 study sites across Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czech Republic, Estonia, Germany, Greece, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Ukraine, UK, and USA	214 study sites across Argentina, Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czechia, Denmark, Egypt, Estonia, France, Germany, Greece, Ireland, Israel, Italy, Latvia, Lithuania, Netherlands, New Zealand, Poland, Portugal, Romania, Russian Federation, Serbia, Singapore, Slovakia, South Africa, South Korea, Spain, Switzerland, Taiwan, UK, and USA	273 sites across Argentina, Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Canada, Chile, China, Columbia, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Greece, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Ukraine, UK, and USA
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	***Intervention (Induction Period 1):*** • RZB 600 mg IV Q4W (n=342) ***Comparators:*** • RZB 1,200 mg IV Q4W (n=342) • Placebo IV Q4W (n=171) Subjects in the risankizumab treatment arms who did not achieve PRO2 (SF/APS) clinical response (see Table 11 for definition) at Week 12 were then re-randomised 1:1:1 to receive risankizumab 1,200 mg IV, risankizumab 360 mg SC or risankizumab 180 mg SC. Subjects in the placebo arm who did not achieve PRO2 (SF/APS) clinical response at Week 12 of Induction Period 1	***Intervention (Induction Period 1):*** • RZB 600 mg IV Q4W (n=193) ***Comparators:*** • RZB 1,200 mg IV Q4W (n=193) • Placebo IV Q4W (n=193) Subjects in the risankizumab treatment arms who did not achieve PRO2 (SF/APS) clinical response (see Table 11 for definition) at Week 12 were then re-randomised 1:1:1 to receive risankizumab 1,200 mg IV, risankizumab 360 mg SC or risankizumab 180 mg SC. Subjects in the placebo arm who did not achieve PRO2 (SF/APS) clinical response at Week 12 of Induction	***Intervention:*** • RZB 180 mg SC Q8W (n=179) ***Comparators:*** • RZB 360 mg SC Q8W (n=179) • Placebo SC Q8W (n=184) Each dose of blinded study drug was administered using a pre-filled syringe. Subjects were not to be routinely pre-medicated prior to infusion of study drug[§]

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
	received risankizumab 1,200 mg IV during the 12-week Induction Period 2 Each dose of blinded study drug was administered intravenously. Subjects were not to be routinely pre-medicated prior to infusion of study drug[§]	Period 1 received risankizumab 1,200 mg IV during the 12-week Induction Period 2 Each dose of blinded study drug was administered intravenously. Subjects were not to be routinely pre-medicated prior to infusion of study drug[§]	
Permitted and disallowed concomitant medications	***Permitted concomitant therapy*** Aminosalicylates, immunomodulators, and/or CD-related antibiotics • Subjects taking these therapies continued their concomitant treatment for the duration of the study • Initiating and/or increasing doses of these therapies during the study was prohibited • Decreasing doses of these therapies was prohibited except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD • Discontinuation of CD-related antibiotics in the blinded Induction Period 2 was at the discretion of the Investigator Steroids • Subjects taking corticosteroids at Baseline continued their concomitant treatment at the Baseline dose for the duration of the 12-week induction period • Initiation and/or increasing doses of systemic and/or CD related corticosteroids during the entire study was prohibited • Decreasing doses of corticosteroids was prohibited during the 12-week induction period, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD • Subjects who receive blinded therapy in Induction Period 2 during Weeks 12 to 24 will be allowed to taper their corticosteroids at the discretion of the Investigator. While stopping the taper is permitted, increasing doses above the Baseline dose was prohibited		***Permitted concomitant therapy*** Aminosalicylates, immunomodulators, and/or CD-related antibiotics • All subjects receiving stable doses of aminosalicylates or immunomodulators (AZA, MP, or MTX) at Week 0 maintained their concomitant treatments through the end of the study • Subjects receiving stable doses of CD-related antibiotics were permitted to discontinue treatment starting at Week 0 of FORTIFY at the discretion of the Investigator • Decrease in the doses of aminosalicylates or immunomodulators was permitted in the event of moderate-to-severe treatment related toxicities or after discussion with the AbbVie TA MD • Increasing doses of or starting CD related antibiotics, aminosalicylates, systemic and/or CD-related corticosteroids, or immunomodulators was prohibited Steroids • Subjects were only allowed to change the dosage of systemic corticosteroids as specified:

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
	• Subjects may not be on both budesonide and prednisone (or equivalent) simultaneously, with exception of inhalers within 14 days prior to Screening		– At the Week 0 visit of FORTIFY, subjects who were taking corticosteroid therapy had their corticosteroid therapy tapered according to a tapering schedule – Subjects taking corticosteroids at Week 0 who had a loss of satisfactory clinical response per the Investigator's judgment after the steroid taper had been initiated could have had their corticosteroid dose increased up to the dose used at Baseline of ADVANCE or MOTIVATE per the Investigator's discretion during the study • Subjects were not permitted to be on both budesonide and prednisone (or equivalent) simultaneously
	Disallowed concomitant therapy • All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following: – Etanercept (Enbrel®); Abatacept (Orencia®); Anakinra (Kineret®); Rituximab (Rituxan®); Natalizumab (Tysabri®); Tocilizumab (Actemra®); Ustekinumab (Stelara®); Belimumab (Benlysta®); Infliximab (Remicade®); Certolizumab pegol (Cimzia®); Golimumab (Simponi®); Adalimumab (Humira®) Vedolizumab (Entyvio®); • Investigational agents (e.g., tofacitinib, baracitinib, filgotinib) • Live or attenuated vaccines were not allowed during the study and for 140 days after the last dose of study drug¶ • Ciclosporin, tacrolimus, or mycophenolate mofetil • Concomitant cannabis use either recreational or for medical reasons • Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy • Apheresis • Exclusive enteral nutrition or any parenteral nutrition		
Primary outcomes (including scoring methods and timings of assessments)	**Definitions of co-primary endpoints (for interpretation, see Section B.2.3.2)** • ***CDAI clinical remission at Week 12:*** CDAI <150		**Definitions of co-primary endpoints** • ***CDAI clinical remission at Week 52:*** CDAI <150 • ***PRO2 (SF/APS) clinical remission at Week 52:*** average daily SF ≤2.8 and not worse than

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
	• ***PRO2 (SF/APS) clinical remission at Week 12:*** average daily SF ≤2.8 and not worse than Baseline, and average daily AP score ≤1 and not worse than Baseline • ***Endoscopic response at Week 12:*** decrease in SES-CD >50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline), as scored by central reviewer **Assessments** • ***CDAI clinical remission:*** CDAI scores were calculated using a central laboratory Hct value from the same visit for all visits (Week 4, 8, 12/premature discontinuation, 16, 20, 24 or any unscheduled visit) except Baseline, where the most recent Screening Hct value was used‡‡ • ***PRO2 (SF/APS):*** Average daily SF, average daily AP score, and well-being were calculated from the subject diary at all visits (Baseline, Week 4, 8, 12/premature discontinuation, 16, 20, 24 or any unscheduled visit). The Screening period was a minimum of 7 days to calculate the Baseline scores. • ***Endoscopic response***: an endoscopy was performed during screening,†† Week 12/premature discontinuation, Week 24 – The same endoscopist, where possible, performed all endoscopies – Where possible, the Investigator or sub-Investigator was an endoscopist. All endoscopies were reviewed by a blinded central reviewer		Baseline of the induction study, and average daily AP score ≤1 and not worse than Baseline of the induction study • ***Endoscopic response at Week 52:*** decrease in SES-CD >50% from Baseline of the induction study (or for subjects with isolated ileal disease and a SES-CD of 4 at Baseline of the induction study, at least a 2-point reduction from Baseline of the induction study), as scored by central reviewer **Assessments** • The CDAI was calculated at each visit (Week 24, 52/premature discontinuation, any unscheduled visit, or rescue therapy visit). The scores calculated at the final visit in ADVANCE or MOTIVATE served as the Week 0 scores‡‡ • PRO2 (SF/APS): Average daily SF, average daily AP score, and well-being were calculated from the subject diary at each visit (Week 8, 16, 24, 32, 40, 48, 52/premature discontinuation, any unscheduled visit or rescue therapy visit). The scores calculated at the final visit in ADVANCE or MOTIVATE served as the Week 0 scores • Endoscopic response: An endoscopy was performed at Week 52/premature discontinuation – An endoscopy may have been performed at unscheduled visits to confirm inadequate response if hs-CRP and FCP are not elevated – The same endoscopist, where possible, performed all endoscopies – Where possible, the Investigator or sub-Investigator was an endoscopist. All

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
			endoscopies were reviewed by a blinded central reviewer
Other outcomes used in the economic model/specified in the scope	• Endoscopic remission at Week 12 • CDAI clinical response at Week 4 or Week 12 • EQ-5D-5L at Week 4 or Week 12		• Endoscopic remission at Week 52
Pre-planned subgroups	• Bio-IR and non-Bio-IR • 16–18-year-old population • Prior TNF-alpha failure	• 16–18-year-old population • Prior TNF-alpha failure	• Bio-IR and non-Bio-IR • 16–18-year-old population • Prior TNF-alpha failure

Abbreviations: MP, mercaptopurine; ADA, adalimumab; AP, abdominal pain; APS, abdominal pain score; AZA, azathioprine; Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRA, clinical research associate; EQ-5D-5L, EuroQoL five dimensions five levels; FCP, faecal calprotectin; Hct, haematocrit; hs-CRP, high-sensitivity C-reactive protein; IFX, infliximab; IR, inadequate response; IRT, Interactive Response Technology; MTX, methotrexate; non-Bio-IR, conventional therapy inadequate response/intolerance; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TA MD, Therapeutic Area Medical Director; TNF, tumour necrosis factor; TPMT, thiopurine methyltransferase; UST, ustekinumab; VDZ, vedolizumab.
† All eligible scores excluded the presence of narrowing component and were confirmed by a central reader (once cap of subjects was reached (no more than 85 in ADVANCE and no more than 58 in MOTIVATE); subjects with a SES-CD of <3 were enrolled as an experimental subset (results from this population are excluded from this submission); ‡ intolerance included patients with a known TPMT genetic mutation or low activity; § Permitted pre-medication included with diphenhydramine hydrochloride and acetaminophen (or equivalents); ¶ Examples of such vaccines included but were not limited to the following: live attenuated influenza, herpes zoster (e.g., Zostavax®), rotavirus, varicella (chicken pox), smallpox, yellow fever. †† An endoscopy performed before the Screening visit, independently of the study, may have been used as the Screening endoscopy, with the approval of the AbbVie TA MD, if the following conditions were met: 1. Biopsy confirmation of the diagnosis was available according to section "Biopsy During Endoscopy" below, as applicable, 2. The endoscopy took place within 45 days prior to Baseline visit, 3. The endoscopy was recorded in a video format as the endoscopic eligibility will be determined by the central reviewers; ‡‡ The final CDAI for all other visits was calculated once the Hct value was received from the central lab. If the Hct was missing due to technical issues, the Hct value from the preceding visit may have been used.

B.2.3.2 Trial endpoints

The co-primary and secondary endpoints for the ADVANCE, MOTIVATE and FORTIFY studies are presented in Table 10. Definition and interpretation of these endpoints are defined in Table 11.

Two protocols were used in the studies, a US protocol and an OUS protocol due to regional differences in regulatory requirements, which resulted in two co-primary endpoints which differ based on the clinical measures described in Table 10.

The main body of this submission only presents results for CDAI outcomes, given that CD clinical trials have historically used this measure, and this is consistent with the outcomes reported in both the ustekinumab and vedolizumab clinical trials for CD (35, 104, 105). CDAI outcomes are also used to define health states in the cost-effectiveness model (the model does not utilise the PRO2 [SF/APS] outcomes), also aligning with previous CD NICE submissions (46, 47).

Although CDAI is not commonly used as a measure to assess disease severity in UK clinical practice, it is the most frequently utilised measure used in clinical trials for this indication (35, 104, 105). However, CDAI has some relevance to the HBI, a commonly used measure of disease severity in the UK, given that both disease severity measures share several common items for disease measurement (32). For completeness the PRO2 (SF/APS) outcomes are included in Appendix M (M.2 for ADVANCE and MOTIVATE and M.4 for FORTIFY).

From hereon, endpoints are defined as per Table 11 unless stated otherwise.

Table 10: Primary and secondary efficacy endpoints in ADVANCE, MOTIVATE and FORTIFY trials

	ADVANCE	MOTIVATE	FORTIFY
Co-primary efficacy endpoint	• Proportion of subjects with CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12 (US protocol) • Proportion of subjects with PRO2 (SF/APS) clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12 (OUS protocol)		• Proportion of subjects with CDAI clinical remission at Week 52 and proportion of subjects with endoscopic response at Week 52 (US protocol) • Proportion of subjects with PRO2 (SF/APS) clinical remission at Week 52 and proportion of subjects with endoscopic response at Week 52 (OUS protocol)

	ADVANCE	MOTIVATE	FORTIFY
Key secondary	• Endoscopic remission at Week 12 • CDAI clinical response at Weeks 4 and 12 • PRO2 (SF/APS) clinical response at Weeks 4 and 12 • EQ-5D-5L at Weeks 4 and 12		• Endoscopic remission at Week 52 • CDAI clinical response at Week 52 • PRO2 (SF/APS) clinical response at Week 52 • EQ-5D-5L at Week 52
Other efficacy endpoints	N/A		• CDAI clinical remission at Week 52 among subjects with CDAI clinical remission at Week 0 • Ulcer-free endoscopy at Week 52 • FACIT-fatigue change from baseline at Week 52 • SF remission at Week 52 • AP remission at Week 52 • CDAI clinical remission and endoscopic response at Week 52 • Deep remission at Week 52 • Exposure adjusted of CD-related hospitalisations from Week 0 to Week 52 • Change from Baseline of the Induction Study in IBDQ Total Score at Week 52 • Change from Baseline of the Induction Study in SF-36 Physical Component Summary Score at Week 52

Abbreviations: APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; EQ-5D-5L, EuroQoL five dimensions five levels; IBDQ, Inflammatory Bowel Disease Questionnaire; OUS, outside of the United States; PRO2, patient reported outcomes 2-item; SF, stool frequency; SF-36, short form 36-item.

Table 11: Definition of disease-specific endpoints used in ADVANCE, MOTIVATE and FORTIFY

Endpoint	Definition and interpretation
CDAI clinical remission[†]	• CDAI clinical remission defined as CDAI <150 • Overview of CDAI score and disease severity: – Values of 150 to 220 are indicative of mild-to-moderate disease 150–200 – Values of 220 to 450 are associated with moderate-to-severe disease – Values over 450 with severe-fulminant disease (37)
PRO2 (SF/APS) clinical remission	Defined as SF ≤2.8 and not worse than Baseline,[‡] APS ≤1 and not worse than Baseline[†]
Endoscopic response	Defined as a decrease in SES-CD >50% from baseline[‡] (or for subjects with isolated ileal disease and a baseline[‡] SES-CD of 4, ≥2-point reduction from baseline[†]) • Scores are marked based on a number of endoscopic categories (ulcers, proportion of the surface covered by ulcers, proportion of the surface with

Endpoint	Definition and interpretation
	any other lesions, and stenosis) in different locations (especially the ileum, right colon, transverse colon, left colon, and rectum) • Each variable is scored from 0 to 3 in each segment and a total score is generated • A higher score is indicative of more severe disease and a low score is indicative of mucosal healing. Values of 0–2, 3–6, 7–15 and ≥16 are indicative of inactive, mild, moderate, or severe disease, respectively (23, 24)
Endoscopic remission	Defined as SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer
Ulcer-free endoscopy	Defined as SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline, as scored by a central reviewer
CDAI clinical response†	Defined as reduction of CDAI ≥100 points from Baseline‡
PRO2 (SF/APS) clinical response	Defined as ≥30% decrease in average daily SF and/or ≥30% decrease in average daily AP score and both not worse than Baseline‡
SF remission	Defined as average daily SF ≤2.8 and not worse than Baseline‡
AP remission	Defined as average daily AP score ≤1 and not worse than Baseline‡
CDAI clinical remission and endoscopic response§	Defined as CDAI <150 and decreasing in SES-CD > 50% from Baseline‡ (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from Baseline‡), as scored by central reviewer
Deep remission	Deep remission is defined as CDAI clinical remission and endoscopic remission
Exposure adjusted CD-related hospitalisations from Week 0 to 52§	Incidence rates for hospitalisation, calculated as the number of subjects with the respective event divided by the time at risk
EQ-5D-5L (index value and VAS) (108)	EQ-5D-5L index value: EQ-5D-5L health states (defined on the EQ-5D-5L descriptive system, which comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) converted into a single index value to facilitate the calculation of quality-adjusted life years EQ-5D-5L VAS: records the respondent's self-rated health on a 20 cm vertical, VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'
Change in IBDQ Total Score§	Defined as change from Baseline‡ in IBDQ Total Score

Abbreviations: AP, abdominal pain; APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; PRO2, patient reported outcomes 2-item; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; VAS, visual analogue scale.
† CDAI clinical remission is an outcome used in the NMA base case analyses and the trial definition aligns with the NMA definition. CDAI clinical response is also assessed in the NMA, but the outcome is named 'CDAI-100 response' in the NMA analyses; both CDAI clinical response and CDAI-100 response have the same definitions. See Section B.2.9.1.4 for the definition of outcomes used in the NMA; ‡ FORTIFY used induction study Baseline values as Baseline; § Endpoints only applicable to FORTIFY.

B.2.3.3 Baseline characteristics and demographics

The baseline characteristics from the induction (ADVANCE, MOTIVATE) and maintenance (FORTIFY) trials are summarised in Table 12. The baseline demographics and clinical characteristics of subjects were well balanced between the treatment groups in each trial and were generally similar across studies.

For the induction studies (ADVANCE, MOTIVATE), the mean age of subjects across the study arms ranged from 38.3 to 40.2 years in the risankizumab 600 mg IV arm and 37.1 to 39.3 years in the placebo IV arm. Across the induction studies, mean disease duration ranged from 9.0 to 10.9 years in the risankizumab 600 mg IV arm and 8.2 to 12.5 years in the placebo IV arm. Similar baseline characteristics were observed for the maintenance study (FORTIFY); the mean age of subjects was 37.0 in the risankizumab 360 mg SC arm and 38.0 years in the placebo SC (withdrawal) arm, while mean disease duration was 9.3 years in the risankizumab 360 mg SC arm and 9.6 years in the placebo SC arm. Of note, the risankizumab CD studies enrolled subjects aged 16 to 80 years, with those aged <18 years representing approximately 1% of subjects in each study.

Across the trial arms of the induction studies (ADVANCE, MOTIVATE), disease severity baseline characteristics were reflective of moderately-to-severely active CD (mean CDAI scores of 310.7 to 319.6, mean SES-CD scores of 13.8 to 15.0, mean SF scores of 5.8 to 6.4, and mean AP scores of 1.8 to 1.9 [see Appendix N.1 for interpretation of disease severity scores]). Disease severity baseline characteristics were broadly similar for the maintenance study (FORTIFY [mean CDAI scores of 307.4 to 308.9, mean SES-CD scores of 14.0 to 14.3, mean SF scores of 5.8 to 5.9, and mean AP scores of 1.8 to 1.9]).

With regard to treatment history, the proportion of subjects with corticosteroid and immunomodulator use at baseline across the induction studies (ADVANCE, MOTIVATE) ranged from 28.6% to 36.4% and 18.8% to 26.2%, respectively. For the maintenance study (FORTIFY), similar results were observed for corticosteroid (29.8–31.1%) and immunomodulator (24.4–28.4%) use. A substantial proportion of the subjects enrolled in the risankizumab studies were treatment refractory, having failed more than one previous biologic therapy (ADVANCE, [30%], MOTIVATE [52%] and

FORTIFY [36%]). Across the studies, the majority of subjects with previous biologic therapy failure had failed TNF-alpha inhibitor therapy (ADVANCE, [94–100%], MOTIVATE [93–97%] and FORTIFY [89–97%]).

B.2.3.4 Expert elicitation/opinion

UK clinical and health economic expert opinion was sought to support the submission for risankizumab in people with moderate-to-severe CD, with expert opinion collected at a virtual advisory board meeting, via virtual 'round table' discussions, [redacted]. AbbVie approached eight experts (six clinicians and two health economic experts), who all participated. The criteria for selecting suitable experts were expertise and experience of treating CD in the UK (clinician) and specialised technical expertise in economic evaluation and health technology assessment (health economic expert).

Experts were provided with pre-read material prior to the advisory board which contained a CD disease overview, UK epidemiological data, methods for assessing disease severity and activity, current UK treatment landscape, risankizumab product information and clinical trial data, and risankizumab health economic model information. All information provided to the experts was consistent with the evidence provided in this submission. UK clinical and health economic expert opinion was also sought during development of this submission. Expert opinion was gathered through review of the submission document by four clinical and one health economic expert. The criteria for selecting suitable experts were the same as previously described.

Table 12: Characteristics of participants in the studies across treatment groups (ITT1A population)

	ADVANCE		MOTIVATE		FORTIFY[¥]	
Characteristic	**RZB 600 mg IV N=336**	**PBO IV N=175**	**RZB 600 mg IV N=191**	**PBO IV N=187**	**RZB 360 mg SC N=141**	**PBO SC[††] N=164**
Age, mean years (SD)	38.3 (13.3)	37.1 (13.4)	40.2 (13.6)	39.3 (13.5)	37.0 (12.8)	38.0 (13.0)
Age category, n (%)						
16 to <18 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18–40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40–65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	189 (56.3)	88 (50.3)	92 (48.2)	99 (52.9)	81 (57.4)	89 (54.3)
Female	147 (43.8)	87 (49.7)	99 (51.8)	88 (47.1)	60 (42.6)	75 (45.7)
Race						
White	258 (76.8)	134 (76.6)	176 (92.1)	162 (86.6)	111 (78.7)	126 (76.8)
Black or African American	9 (2.7)	9 (5.1)	7 (3.7)	7 (3.7)	8 (5.7)	10 (6.1)
Asian	65 (19.3)	31 (17.7)	8 (4.2)	15 (8.0)	20 (14.2)	28 (17.1)
American Indian/Alaska Native	0	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (0.6)	0	2 (1.1)	0	0
Multiple	4 (1.2)	0	0	1 (0.5)	2 (1.4)	0
Ethnicity						
Non-Hispanic/Latino	325 (96.7)	165 (94.3)	175 (91.6)	168 (89.8)	134 (95.0)	157 (95.7)
Hispanic/Latino	11 (3.3)	10 (5.7)	16 (8.4)	19 (10.2)	7 (5.0)	7 (4.3)
BMI (kg/m^2), mean (SD)	24.1 (5.6)	24.3 (5.8)	25.3 (6.4)	25.1 (5.8)	23.9 (5.4)	24.8 (6.3)
CD duration (years), mean (SD)	9.0 (8.8)	8.2 (7.1)	10.9 (7.7)	12.5 (9.7)	9.3 (8.1)	9.6 (8.8)

	ADVANCE		MOTIVATE		FORTIFY[¥]	
Characteristic	**RZB 600 mg IV N=336**	**PBO IV N=175**	**RZB 600 mg IV N=191**	**PBO IV N=187**	**RZB 360 mg SC N=141**	**PBO SC[††] N=164**
Disease location						
Ileocolic	180 (53.6)	90 (51.4)	96 (50.3)	98 (52.4)	72 (51.1)	83 (50.6)
Colonic disease	76 (22.6)	39 (22.3)	38 (19.9)	45 (24.1)	32 (22.7)	44 (26.8)
Ileal	62 (18.5)	37 (21.1)	49 (25.7)	33 (17.6)	25 (17.7)	30 (18.3)
Ileal - involving upper GI tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colonic disease - involving upper GI tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ileocolic - involving upper GI tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Faecal calprotectin (mg/kg), median (mean [SD])	n=141 960 (1767.3 [2272.7])	n=284 1200 (2499.3 [4308.8])	n=150 1367 (2379.2 [3879.6])	n=146 987.5 (2648.9 [4831.2])	n=114 1543 (2182.5 [2471.7])	n=140 794.5 (1640.7 [2055.7])
Average daily SF, mean (SD)	5.8 (2.7)	6.1 (2.8)	6.2 (3.1)	6.4 (2.9) (n=186)	5.9 (2.6)	5.8 (2.7)
Average daily AP, mean (SD)	1.9 (0.6)	1.9 (0.6)	1.8 (0.5)	1.9 (0.5) (n=186)	1.8 (0.5)	1.9 (0.5)
CDAI, mean (SD)	311.2 (62.4)	319.2 (59.4)	310.7 (63.6)	319.6 (69.8) (n=186)	308.9 (61.1)	307.4 (64.9)
SES-CD, mean (SD)	14.7 (7.7)	13.8 (6.8)	14.4 (7.6)	15.0 (8.1)	14.3 (7.4)	14.0 (7.1)
Immunomodulator use, n (%)	88 (26.2)	42 (24.0)	36 (18.8)	40 (21.4)	40 (28.4)	40 (24.4)
Biologic failure, n (%)						
0	141 (42.0)	78 (44.6)	0	0	39 (27.7)	41 (25.0)
1	100 (29.8)	41 (23.4)	92 (48.2)	88 (47.1)	51 (36.2)	60 (36.6)
2	40 (11.9)	30 (17.1)	54 (28.3)	45 (24.1)	27 (19.1)	36 (22.0)
3	35 (10.4)	20 (11.4)	22 (11.5)	29 (15.5)	17 (12.1)	22 (13.4)
>1 (2-7)	95 (28.3)	56 (32.0)	99 (51.8)	99 (52.9)	51 (36.2)	63 (38.4)

	ADVANCE		MOTIVATE		FORTIFY[¥]	
Characteristic	**RZB 600 mg IV N=336**	**PBO IV N=175**	**RZB 600 mg IV N=191**	**PBO IV N=187**	**RZB 360 mg SC N=141**	**PBO SC[††] N=164**
TNF-alpha failure, n (%)	n=195[†]	n=97[†]			n=102[†]	n=123[†]
0	12 (6.2)	0	14 (7.3)	6 (3.2)	11 (10.8)	4 (3.3)
1	110 (56.4)	57 (58.8)	101 (52.9)	103 (55.1)	49 (48.0)	71 (57.7)
>1	73 (37.4)	40 (41.2)	76 (39.8)	78 (41.7)	42 (41.2)	48 (39.0)
Vedolizumab failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab failure, n (%)	n=195[†]	n=97[†]			n=102[†]	n=123[†]
	43 (22.1)	19 (19.6)	36 (18.8)	40 (21.4)	17 (16.7)	15 (12.2)
CD medication[‡] at baseline[§], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aminosalicylates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressants/immunomodulators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diarrhoeal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AP, abdominal pain; Bio-IR, biologic inadequate response/intolerance; BMI, body mass index; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IV, intravenous; PBO, placebo; RZB, risankizumab; SC, subcutaneous; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF, tumour necrosis factor; WHO, World Health Organization.
[†]Bio-IR population; [‡]generic name (WHO 2018Q1); [§]for FORTIFY, baseline refers to baseline of the induction study; [¥]Data reported for randomised subjects only from FORTIFY SS1; [††] The placebo SC (withdrawal) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy in ADVANCE or MOTIVATE and were randomised to receive placebo in FORTIFY.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Definitions of subject population analysis sets

Definitions of the subject population analysis sets of the induction (ADVANCE, MOTIVATE) and maintenance (FORTIFY) studies are provided in Section B.2.3.1 Table 7 and Table 8, respectively. All analyses of co-primary endpoints were performed using the ITT1A analysis set, while all analyses of secondary endpoints were performed using the ITT analysis set. The subject numbers comprising each data set are presented in Appendix D.2.

B.2.4.2 Statistical analysis

A summary of the statistical analysis plan for each of the ADVANCE, MOTIVATE and FORTIFY trials is provided in Table 13. For all studies, a multiple testing procedure was used to provide strong control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses comparing each risankizumab dose level to placebo with respect to the co-primary endpoints and ranked secondary endpoints.

For ADVANCE and MOTIVATE, a sequence of hypothesis testing for the co-primary endpoints was utilised, followed by the ranked secondary endpoints and started with each of the co-primary endpoints using alpha of 0.025 (2-sided) for each dose compared with placebo. If both co-primary endpoints achieved statistical significance within a dose level, continued testing followed a pre-specified weight of alpha allocation between the single hypothesis within the family as well as between the families of hypotheses across the doses. Additionally, for ADVANCE, the analysis of co-primary efficacy endpoints was performed in the bio-IR and non-bio-IR populations.

For FORTIFY, a sequence of hypothesis testing for the co-primary endpoints of risankizumab 360 mg SC dose versus placebo using alpha of 0.05 (2-sided) was utilised, followed by testing the co-primary endpoints of risankizumab 180 mg SC dose versus placebo using alpha of 0.05 (2-sided). If both co-primary endpoints achieved statistical significance for both dose levels, continued testing of the ranked secondary endpoints for 360 mg and 180 mg followed a pre-specified weight of alpha allocation

between the single hypothesis within the family as well as between the families of hypotheses across the doses.

For ADVANCE, MOTIVATE and FORTIFY, secondary efficacy endpoints were divided into two groups. The first group included ranked secondary endpoints, which were ranked by clinical importance. Statistical significance was assessed at the pre-specified alpha level (two-sided) in ranked endpoint order until the significant level exceeded the pre-specified alpha level. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint failed to achieve the pre-specified alpha level. The second group includes all other additional secondary variables.

B.2.4.3 Participant flow in the relevant randomised controlled trials

See Appendix D for details of participant flow.

Table 13: Summary of statistical analysis approach in ADVANCE, MOTIVATE and FORTIFY

	ADVANCE	MOTIVATE	FORTIFY
Statistical analysis	CMH test adjusted for co-primary endpoints by number of prior biologics failed (0, 1, >1) and steroid use at Baseline (yes, no).	CMH test adjusted for co-primary endpoints by number of prior biologics failed (1, >1) and steroid use at Baseline (yes, no).	CMH test adjusted for co-primary endpoints by FORTIFY Week 0 clinical remission status (yes, no), FORTIFY Week 0 endoscopic response status (yes, no), and RZB induction dose (600 mg IV, 1,200 mg IV).
	A CMH based two-sided 95% confidence interval for the difference between treatment groups was calculated.		
Sample size, power calculation	For the OUS protocol, assuming the PRO2 (SF/APS) clinical remission rate at Week 12 would be 27.8% for one of the RZB treatment arms and 12% for the placebo arm, a sample size of 342 subjects for each of the RZB arms and 171 for the placebo arm would have 97% power to detect the treatment difference between RZB and placebo using a Fisher's exact test at alpha of 0.025 (two-sided). For the US protocol, assuming the CDAI clinical remission rate at Week 12 would be 37% for one of the RZB treatment arms and 17% for the placebo arm, this sample size would have 99% power to detect the treatment difference between RZB and placebo using a Fisher's exact test at a 0.025 significant level (two-sided). Assuming the endoscopic response rate at Week 12 (co-primary endpoint for both protocols) would be 25.5% for one of the RZB treatment arms and 8% for the placebo arm, this sample size would have 99% power to detect a treatment difference between RZB and placebo using a Fisher's exact test at a 0.025 significant level (two-sided). In addition, with a sample size of approximately 540 bio-IR subjects, this study had approximately 80% power for the bio-IR population to detect a treatment difference between one of the RZB dose groups and placebo in clinical remission rates at Week 12 using	For the OUS protocol, assuming the clinical remission (SF/APS) rate at Week 12 would be 23.5% for one of the RZB treatment arms and 10% for the placebo arm, a sample size of 193 subjects for each RZB arm and 193 for the placebo arm had approximately 89% power to detect the treatment difference between RZB and placebo using a Fisher's exact test at alpha level of 0.025 (two-sided). For the US protocol, assuming the CDAI clinical remission rate at Week 12 would be 34% for one of the RZB treatment arms and 15% for the placebo arm, this sample size had 97% power to detect a treatment difference between RZB and placebo using a Fisher's exact test at a 0.025 significant level (two-sided).	For the OUS protocol, assuming the PRO2 (SF/APS) clinical remission rate at Week 52 was 38.7% for one of the RZB dose arms and 20% for the placebo arm, a sample size of 150 subjects for each of the RZB dose arms and 150 for the placebo arm had 93% power to detect a treatment difference between one of the RZB dose arms and placebo using Fisher's exact test at alpha of 0.05 (two-sided). For the US protocol, assuming the CDAI clinical remission rate at Week 52 would be 46% for one of the RZB dose arms and 28% for the placebo arm, a sample size of 150 subjects for each of the RZB dose arms and 150 for the placebo arm had 87% power to detect the treatment difference between one of the RZB dose arms and placebo in CDAI clinical remission rates at Week 52 using Fisher's exact test at alpha of 0.05 (two-sided). Assuming the endoscopic response rate at Week 52 (co-primary endpoint for both protocols) was 32.6% for one of the RZB dose arms and 10% for the

	ADVANCE	MOTIVATE	FORTIFY
	Fisher's exact test at alpha of 0.025 (two-sided) for the bio-IR population, assuming the Week 12 clinical remission rate was 24.2% for the RZB dose groups and 10% for the placebo group. Similarly, with sample size of approximately 315 non-bio-IR subjects, this study had 72% power to detect a treatment difference between one of the RZB dose groups and placebo in clinical remission rates at Week 12 using Fisher's exact test at alpha of 0.025 (two-sided) for the non-bio-IR population, assuming the Week 12 clinical remission rate was 35% for the RZB dose groups and 15% for the placebo group for non-bio-IR subjects.	Assuming the endoscopic response rate at Week 12 (co-primary endpoint for both protocols) was 17% for one of the RZB treatment arms and 5% for the placebo arm, this sample size had 93% power to detect treatment difference between RZB and placebo using a Fisher's exact test at a 0.025 significant level (two-sided).	placebo arm, this sample size had >95% power to detect a treatment difference between the RZB dose arms and placebo in endoscopic response rates at Week 52 using a Fisher's exact test at alpha of 0.05 (two-sided).
Data management, subject withdrawals	**NRI-C:** The Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) categorised any subject 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 or COVID-19 logistical restriction were handled by multiple imputation. At each visit, subjects were characterised as responders or non-responders based on multiple imputation imputed values if missing due to COVID-19, otherwise subjects were considered as non-responder for missing due to other reasons in the NRI-C approach. Of note, subjects were counted as non-responders thereafter and were not imputed by multiple imputation after the CD-related corticosteroids censoring time point.		
	NRI-NC: Subjects who prematurely discontinue the study prior to efficacy assessment at Week 12 were considered non-responders with respect to the efficacy endpoint. Missing subjects due to COVID-19 or COVID-19 logistical restriction were also counted as non-responders.		**NRI-NC**: NRI-NC was performed in the same way as NRI-C without the exception of missing due to COVID-19. Missing subjects due to COVID-19 or COVID-19 logistical restriction were counted as non-responders.

Abbreviations: APS, abdominal pain score; Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CMH, Cochran–Mantel–Haenszel; non-Bio IR, conventional therapy inadequate response/intolerance; NRI, non-responder imputation; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; NRI-NC, NRI with no special data handling for missing due to COVID-19; OUS, outside of the United States; PRO2, patient reported outcomes 2-item; RZB, risankizumab; SF, stool frequency.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of quality assessment results for the risankizumab trials is provided in Table 14. A complete quality assessment for each trial is provided in Appendix D.

Table 14: Quality assessment results for parallel group RCTs

	ADVANCE (NCT03105128)	MOTIVATE (NCT03104413)	FORTIFY (NCT03105102)
Randomisation			
Was randomisation carried out appropriately?	YES	YES	YES
Baseline comparability			
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	YES	YES	YES
Blinding			
Was the concealment of treatment allocation adequate?	YES	YES	YES
Were the care providers, participants and outcome assessors blind to treatment allocation?	YES	YES	YES
Follow-up			
Were there any unexpected imbalances in dropouts between groups?	NO	NO	NO
Selective Reporting			
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO	NO	NO
Analysis			
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	YES

B.2.6 Clinical effectiveness results of the relevant studies

The clinical benefits of risankizumab versus placebo have been demonstrated in two pivotal induction studies (ADVANCE, MOTIVATE) and one pivotal maintenance study (FORTIFY). The results from the maintenance study (FORTIFY) support continued maintenance treatment with risankizumab 360 mg SC in subjects with clinical response to risankizumab IV induction treatment (106, 107).

Key results for risankizumab induction studies (ADVANCE and MOTIVATE)

- In both ADVANCE and MOTIVATE, symptomatic improvements were seen as early as Week 4 and mucosal improvement measured by SES-CD observed at Week 12 after treatment with risankizumab 600 mg IV. Risankizumab 600 mg IV was superior to placebo for the co-primary endpoints of clinical remission (CDAI or PRO2 [SF/APS]†) and endoscopic response (106).
- In ADVANCE, when compared with placebo, risankizumab 600 mg IV also demonstrated beneficial treatment effects for subjects in the subgroups of biologic inadequate response/intolerance (Bio-IR) or inadequate response/intolerance to conventional therapy (non-Bio-IR) for CDAI clinical remission and endoscopic response (38, 39, 106).
- Subjects treated with risankizumab 600 mg IV in ADVANCE and MOTIVATE had significantly improved HRQoL as early as 4 weeks and at Week 12 when compared with placebo (38, 39).

Key results for risankizumab maintenance study (FORTIFY)

- In the overall study population for FORTIFY, risankizumab 360 mg SC was superior to placebo SC (withdrawal) for the co-primary endpoints of clinical remission (CDAI) or (PRO2 [SF/APS]†) and endoscopic response (107).
- When compared with placebo SC (withdrawal), risankizumab 360 mg SC also demonstrated beneficial treatment effects for subjects with biologic inadequate response/intolerance (Bio-IR) or inadequate response/intolerance to conventional therapy (non-Bio-IR) for CDAI clinical remission and endoscopic response (107).
- More than one third of subjects (39%) treated with risankizumab 360 mg SC achieved endoscopic remission at Week 52 when compared with those who received placebo SC (withdrawal) (107)

† For this submission, only CDAI outcomes are presented as the cost-effectiveness model utilises CDAI outcomes to define CD health states (i.e. PRO2 [SF/APS] outcomes are not used in the model) and CDAI outcomes facilitate indirect treatment comparisons with previous trials of treatments for CD (104, 105). Overall, the results for PRO2 [SF/APS] and CDAI outcomes were similar. The co-primary endpoint of PRO2 [SF/APS] clinical remission and endoscopic response is presented in Appendix M.

This section presents the results from the risankizumab induction and maintenance studies. As previously discussed in Section B.2.3.2, for this submission, CDAI outcomes are presented across the three pivotal trials (ADVANCE, MOTIVATE, FORTIFY) as this endpoint facilitates indirect treatment comparisons with previous trials of treatments for CD (104, 105) and the cost-effectiveness model utilises CDAI outcomes to define CD health states (i.e., PRO2 [SF/APS] outcomes are not used in the model) in alignment with previous CD NICE submissions (46, 47).

For completeness, the co-primary endpoint of PRO2 [SF/APS] clinical remission is presented in Appendix M (Section M.2 for ADVANCE and MOTIVATE and Section M.4 for FORTIFY). Co-primary endpoints which included CDAI clinical remission or PRO2 (SF/APS) clinical remission, in addition to endoscopic response, were both superior to placebo in the induction and maintenance studies.

A key point to highlight regarding the outcomes from the risankizumab induction and maintenance studies is that they are based on data obtained from subjects aged 16 to <18 years old and adult subjects. This approach was deemed appropriate given the low overall proportion of subjects aged 16–17 years in the risankizumab studies (approximately 1% across the studies) and expert clinical opinion. Based on expert clinical opinion of the populations enrolled in the risankizumab studies, treatment response to risankizumab was expected to be similar between the 16–18-year-old and adult populations if treatment history was comparable between the groups (i.e., bio-naïve or treatment refractory) (80). The 16–17-year-old and adult populations in the risankizumab studies show a similar pattern of treatment response, albeit this comparison is based on treatment response observed in a low number of subjects aged 16–17 years (see Appendix E). In addition, evidence highlighting the efficacy of TNF-alpha inhibitors in paediatric subjects is available in several trials, and results are generally consistent with observations from previous trials of adults with moderate-to-severe CD (109-112)[e].

Note that risankizumab data are presented for the anticipated licensed doses only (600 mg IV induction dose from ADVANCE and MOTIVATE, and 360 mg SC maintenance

[e] TNF-alpha inhibitors are the only biologic therapies approved for use in individuals aged <18 years (53, 113, 114).

dose from FORTIFY). All study outcome definitions have been previously described in Section B.2.3.2. Study outcomes are also defined in the footnotes of the results tables in the following sections.

The primary data for risankizumab CD in this submission is taken from clinical study reports (CSRs) and published manuscripts. At the time of submission, only data from the CSRs were deemed commercial in confidence.

B.2.6.1 ADVANCE

B.2.6.1.1 Co-primary efficacy outcome: Proportion of subjects with CDAI clinical remission and/or endoscopic response at Week 12

In ADVANCE, the co-primary endpoints of clinical remission (CDAI and PRO2 [SF/APS]) and endoscopic response were met for the risankizumab 600 mg IV arm when compared with the placebo IV arm (38, 106). At Week 12, a significantly greater proportion of subjects in the risankizumab 600 mg IV arm achieved the co-primary endpoint of CDAI clinical remission versus the placebo IV arm (45.2% vs 24.6%, respectively; $p<0.001$) (Table 15). Additionally, a clear treatment effect was demonstrated in non-Bio-IR and Bio-IR populations, with a greater proportion of subjects achieving CDAI clinical remission and a larger effect size noted in the non-Bio-IR population compared with the Bio-IR population (Table 15). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 15).

Table 15: CDAI clinical remission at Week 12 (NRI-C) – total and by prior biologic failure status (ADVANCE ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adj. Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	336	152 (45.2)	[39.9, 50.5]	[redacted]	20.6	20.7	[12.4, 29.0]	<0.001¶
Placebo IV	175	43 (24.6)	[18.2, 31.0]	[redacted]	-	-	-	-
Prior biologic failure status								
Bio-IR								
RZB 600 mg IV	195	83 (42.5)	[35.5, 49.4]	[redacted]	16.7	-	[5.5, 27.8]	-
Placebo IV	97	25 (25.8)	[17.1, 34.5]	[redacted]	-	-	-	-
Non-Bio-IR								
RZB 600 mg IV	141	69 (48.9)	[40.7, 57.2]	[redacted]	25.8	-	[13.3, 38.3]	-
Placebo IV	78	18 (23.1)	[13.8, 32.5]	[redacted]	-	-	-	-

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; non-Bio-IR, conventional therapy inadequate response/intolerance; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab.
Source: ADVANCE CSR (38), D'Haens et al (2022) (106). Notes: CDAI clinical remission defined as CDAI <150
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US protocol.

At Week 12, a statistically significantly greater proportion of subjects in the risankizumab 600 mg IV arm achieved endoscopic response compared with the placebo IV arm (40.3% vs 12.0%, respectively; p<0.001) (Table 16). Additionally, a clear treatment effect was demonstrated in the non-Bio-IR and Bio-IR populations, with a greater proportion of subjects achieving endoscopic response and a larger effect size noted in the non-Bio-IR population compared with the Bio-IR population (Table 16). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 16).

Table 16: Endoscopic response at Week 12 (NRI-C) - total and by prior biologic failure status (ADVANCE ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	336	135 (40.3)	[35.0, 45.6]	[redacted]	28.2	28.3	[21.2, 35.4]	<0.001¶
Placebo IV	175	21 (12.0)	[7.2, 16.8]	[redacted]	-	-	-	-
Prior biologic failure status								
Bio-IR								
RZB 600 mg IV	195	64 (32.9)	[26.2, 39.5]	[redacted]	21.5	-	[12.3, 30.7]	-
Placebo IV	97	11 (11.4)	[5.0, 17.7]	[redacted]	-	-	-	-
Non-Bio-IR								
RZB 600 mg IV	141	71 (50.5)	[42.2, 58.8]	[redacted]	37.7	-	[26.5, 48.8]	-
Placebo IV	78	10 (12.8)	[5.4, 20.2]	[redacted]	-	-	-	-

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; non-Bio IR, conventional therapy inadequate response/intolerance; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Source: ADVANCE CSR (38), D'Haens et al (2022) (106). Notes: endoscopic response defined as decrease in SES-CD >50% from baseline (or for subjects with isolated ileal disease and a baseline SES-CD of 4, ≥2-point reduction from baseline).
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-1; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for both the US-specific and OUS protocols.

B.2.6.1.2 Secondary efficacy outcomes - ADVANCE

B.2.6.1.2.1 CDAI clinical response at Week 4 and Week 12

Significant improvements in CDAI clinical response were observed as early as Week 4, with 40.8% of subjects in the risankizumab 600 IV mg arm versus 25.2% of subjects in the placebo IV arm achieving CDAI clinical response (p<0.001) (38, 106) (Table 17).

Table 17: Achievement of CDAI clinical response at Week 4 (NRI-C) (ADVANCE ITT1A population)

Subgroup Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	336	137 (40.8)	[35.5, 46.0]	[redacted]	15.6	15.4	[7.2, 23.7]	<0.001¶
Placebo IV	175	44 (25.2)	[18.7, 31.6]	[redacted]	-	-	-	-

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab
Source: ADVANCE CSR (38), D'Haens et al (2022) (106). Notes: CDAI clinical response defined as reduction of CDAI ≥100 points from baseline.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Endpoint achieved statistical significance based on the pre-specified graphical testing procedure for both the US-specific and OUS protocols.

At Week 12, a statistically greater proportion of subjects in the risankizumab 600 mg IV arm achieved CDAI clinical response compared with placebo (59.7% vs 36.7%, respectively; p<0.001) (38, 106) (Table 18). A clear treatment effect was demonstrated in both the non-Bio-IR and Bio-IR populations, with a greater proportion of subjects achieving CDAI clinical response and effect size observed in the non-Bio-IR population (Table 18). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 18).

Table 18: Summary of achievement of CDAI clinical response at Week 12 (NRI-C) (ADVANCE ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]	P-value
All subjects§								
RZB 600 mg IV	336	201 (59.7)	[54.5, 65.0]	[redacted]	23.0	23.1	[14.2, 31.9]	<0.001¶
Placebo IV	175	64 (36.7)	[29.6, 43.9]	[redacted]	-	-	-	-
Prior biologic failure status								
Bio-IR††								
RZB 600 mg IV	195	114 (58.3)	[51.3, 65.2]	[redacted]	24.2	-	[12.4, 35.9]	-
Placebo IV	97	33 (34.1)	[24.6, 43.5]	[redacted]	-	-	-	-
Non-Bio-IR††								
RZB 600 mg IV	141	87 (61.8)	[53.7, 69.8]	[redacted]	21.7	-	[8.2, 35.3]	-
Placebo IV	78	31 (40.0)	[29.1, 51.0]	[redacted]	-	-	-	-

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; non-Bio IR, conventional therapy inadequate response/intolerance; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab.
Notes: CDAI clinical response defined as reduction of CDAI ≥100 points from baseline.
Source: ADVANCE CSR (38), D'Haens et al (2022) (106). † 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Endpoint achieved statistical significance based on the pre-specified graphical testing procedure for both the US-specific and OUS protocols; †† 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.2.6.1.2.2 Endoscopic remission at Week 12

A significantly greater proportion of subjects in the risankizumab 600 mg IV arm achieved endoscopic remission at Week 12 versus the placebo IV arm (24.2% vs 9.1%, respectively; p<0.001) (38, 106) (Table 19). A clear treatment effect was demonstrated in the non-Bio-IR and Bio-IR populations, with a greater proportion of subjects achieving endoscopic remission and larger effect size noted in the non-Bio-

IR population (Table 19). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 19).

Table 19: Achievement of endoscopic remission at Week 12 (NRI-C) (ADVANCE ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]	P-value
All subjects§								
RZB 600 mg IV	336	81 (24.2)	[19.6, 28.7]	[redacted]	15.0	15.1	[9.0, 21.2]	<0.001 ¶
Placebo IV	175	16 (9.1)	[4.9, 13.4]	[redacted]	-	-	-	-
Prior biologic failure status								
Bio-IR††								
RZB 600 mg IV	195	36 (18.5)	[13.0, 23.9]	[redacted]	13.3	-	[6.3, 20.3]	-
Placebo IV	97	5 (5.2)	[0.8, 9.6]	[redacted]	-	-	-	-
Non-Bio-IR††								
RZB 600 mg IV	141	45 (32.0)	[24.3, 39.7]	[redacted]	17.9	-	[7.0, 28.8]	-
Placebo IV	78	11 (14.1)	[6.4, 21.8]	[redacted]	-	-	-	-

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; non-Bio IR, conventional therapy inadequate response/intolerance; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Source: ADVANCE CSR (38), D'Haens et al (2022) (106). Notes: Endoscopic remission defined as SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [0, 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each stratum, 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Endpoint achieved statistical significance based on the pre-specified graphical testing procedure for both the US-specific and OUS protocols; †† 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.2.6.1.2.3 EQ-5D-5L at Week 4 and Week 12

The risankizumab 600 mg IV arm was associated with statistically significant improvements in EQ-5D-5L at Week 4 and Week 12 compared with the placebo IV arm (38). For EQ-5D-5L Index Value scores, subjects in the risankizumab 600 mg IV

arm had a greater improvement from baseline (least squares [LS] mean) when compared with the placebo IV arm at Week 4 ([redacted]) and Week 12 ([redacted]) (Table 20). Similar results were observed for EQ-5D visual analogue scale (VAS) scores; subjects in the risankizumab 600 mg IV arm had a greater improvement from baseline (LS mean) when compared with the placebo IV arm at Week 4 ([redacted]) and Week 12 ([redacted]) (Table 20).

Table 20: Change from baseline in EQ-5D-5L at Weeks 4 and 12 (MMRM) (ADVANCE ITT1A population)

Parameter / Timepoint / Treatment	Within Group Change from Baseline					Between Group Difference vs Placebo			
	N	Missing due to COVID-19	Baseline Mean	Visit Mean	LS Mean	LS Mean	[95% CI]	SE	P-value
EQ-5D-5L Index Value									
Week 4									
RZB 600 mg IV	[redacted]								
Placebo IV	[redacted]					-	-	-	-
Week 12									
RZB 600 mg IV	[redacted]								
Placebo IV	[redacted]					-	-	-	-
EQ-5D VAS									
Week 4									
RZB 600 mg IV	[redacted]								
Placebo IV	[redacted]					-	-	-	-
Week 12									
RZB 600 mg IV	[redacted]								
Placebo IV	[redacted]					-	-	-	-

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5 dimensions 5 levels; ITT, intention to treat; IV, intravenous; LS, least squares; MMRM, Mixed-Effect Model Repeat Measurement; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab; SE, standard error; VAS, visual analogue scale.
Source: ADVANCE CSR (38). Notes: MMRM is the Mixed-Effect Model Repeat Measurement with the categorical fixed effects of treatment, visit and treatment-by-visit interaction, stratification factors (Number of prior biologics failed [0, 1, >1] and baseline steroid use [Yes, No]), and the continuous fixed covariates of baseline measurements included in the model. An unstructured covariance matrix is used.

B.2.6.1.3 Other outcomes

Outcomes for change from Baseline in IBDQ Total Score at Week 12 in the ITT1A population are presented in Appendix M.

B.2.6.1.4 Conclusion – ADVANCE

ADVANCE demonstrated significant clinical benefits associated with risankizumab 600 mg IV compared with placebo IV in a population of Bio-IR and non-Bio-IR subjects with moderately to severely active CD. Risankizumab 600 mg IV was superior to placebo IV for the co-primary endpoints of clinical remission (CDAI) and endoscopic response (38, 106). Furthermore, significant improvements in CDAI clinical response were seen as early as Week 4 for risankizumab 600 mg IV compared with placebo IV and was maintained over 12 weeks. Significant improvements in HRQoL were also seen with risankizumab 600 mg IV compared with placebo IV from as early as Week 4.

B.2.6.2 MOTIVATE

B.2.6.2.1 Co-primary efficacy outcome: Proportion of subjects with CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12

In MOTIVATE, the co-primary endpoints of clinical remission (CDAI) and endoscopic response were met for the risankizumab 600 mg IV arm when compared with the placebo IV arm (39, 106). At Week 12, a significantly greater proportion of subjects in the risankizumab 600 mg IV arm achieved the co-primary endpoint of CDAI clinical remission versus the placebo IV arm (42.0% vs 19.8%, respectively; $p<0.001$) (Table 21). Additionally, a clear treatment effect was demonstrated in both the ≤1 prior biologics failed and >1 prior biologics failed populations, with a greater proportion of subjects achieving CDAI clinical remission and a larger effect size noted in the ≤1 prior biologics failed population (Table 21). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 21).

Table 21: CDAI clinical remission at Week 12 (NRI-C) – total and by prior biologic failure status (MOTIVATE ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	191	80 (42.0)	[34.9, 49.0]	[redacted]	22.2	22.1	[13.1, 31.0]	<0.001 ¶
Placebo IV	187	37 (19.8)	[14.1, 25.5]	[redacted]	-	-	-	-
Prior biologic failure status								
≤1								
RZB 600 mg IV	92	42 (45.7)	[35.5, 55.8]	[redacted]	25.2	-	[12.0, 38.4]	-
Placebo IV	88	18 (20.5)	[12.0, 28.9]	[redacted]	-	-	-	-
>1								
RZB 600 mg IV	99	38 (38.5)	[28.9, 48.1]	[redacted]	19.3	-	[7.0, 31.7]	-
Placebo IV	99	19 (19.2)	[11.4, 26.9]	[redacted]	-	-	-	-

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab.
Source: MOTIVATE CSR (39), D'Haens et al (2022) (106). Notes: CDAI clinical remission defined as CDAI <150. † 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each subgroup, 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US protocol.

At Week 12, a statistically significantly greater proportion of subjects in the risankizumab 600 mg IV arm achieved endoscopic response compared with the placebo IV arm (28.8% vs 11.2%, respectively; p<0.001) (Table 22). Additionally, a clear treatment effect was demonstrated in the ≤1 prior biologics failed and >1 prior biologics failed populations, with a greater proportion of subjects achieving endoscopic response and a larger effect size noted in the ≤1 prior biologics failed population (Table 22). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 22).

Table 22: Endoscopic response at Week 12 (NRI-C) – total and by prior biologic failure status (MOTIVATE ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	191	55 (28.8)	[22.4, 35.3]	▌	17.6	17.6	[9.9, 25.4]	<0.001¶
Placebo IV	187	21 (11.2)	[6.7,15.8]	▌	-	-	-	-
Prior biologic failure status								
≤1								
RZB 600 mg IV	92	33 (36.0)	[26.1, 45.8]	▌	20.1	-	[7.6, 32.5]	-
Placebo IV	88	14 (15.9)	[8.3, 23.6]	▌	-	-	-	-
>1								
RZB 600 mg IV	99	22 (22.2)	[14.0, 30.4]	▌	15.2	-	[5.5, 24.8]	-
Placebo IV	99	7 (7.1)	[2.0, 12.1]	▌	-	-	-	-

Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Source: MOTIVATE CSR (39), D'Haens et al (2022) (106). Notes: Endoscopic response defined as decrease in SES-CD >50% from baseline (or for subjects with isolated ileal disease and a baseline SES-CD of 4, ≥2-point reduction from baseline).
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each subgroup, 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US protocol.

B.2.6.2.2 Secondary efficacy outcomes - MOTIVATE

B.2.6.2.2.1 CDAI clinical response at Week 4 and Week 12

Significant improvements in CDAI clinical response were observed as early as Week 4, with 36.6% of subjects in the risankizumab 600 IV mg arm versus 20.9% of subjects in the placebo IV arm achieving CDAI clinical response (p=0.001) (39, 106) (Table 23).

Table 23: Achievement of CDAI clinical response at Week 4 (NRI-C) (MOTIVATE ITT1A population)

Subgroup Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adj. Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	191	70 (36.6)	[29.8, 43.5]	▌	15.8	15.7	[6.8, 24.6]	0.001¶
Placebo IV	187	39 (20.9)	[15.0, 26.7]	▌	-	-	-	--

Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab. Source: MOTIVATE CSR (39), D'Haens et al (2022) (106). Notes: CDAI clinical response defined as reduction of CDAI ≥100 points from baseline. † 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each subgroup, 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US protocol.

At Week 12, approximately 60% of subjects in the risankizumab 600 mg IV arm achieved CDAI clinical response (39, 106). A significantly greater proportion of subjects in the risankizumab 600 mg arm achieved CDAI clinical response at Week 12 versus the placebo IV arm (59.5% vs 30.0%, respectively; p<0.001) (Table 24).

Table 24: Achievement of CDAI clinical response at Week 12 (NRI-C) (MOTIVATE ITT1A population)

Subgroup Treatment	Responder (NRI-C)				Response Rate Diff vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19	Diff (%)‡	Adj. Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	191	114 (59.5)	[52.5, 66.5]	▌	29.5	29.4	[19.9, 39.0]	<0.001¶
Placebo IV	187	56 (30.0)	[23.4, 36.6]	▌	-	-	-	--

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab. Source: MOTIVATE CSR (39), D'Haens et al (2022) (106). Notes: CDAI clinical response defined as reduction of CDAI ≥100 points from baseline. † 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each subgroup, 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US protocol.

B.2.6.2.2.2 Endoscopic remission at Week 12

A significantly greater proportion of subjects in the risankizumab 600 mg IV arm achieved endoscopic remission at Week 12 versus the placebo IV arm (19.4% vs 4.3%, respectively; p<0.001) (39, 106) (Table 25).

Table 25: Achievement of endoscopic remission at Week 12 (NRI-C) (MOTIVATE ITT1A population)

Subgroup Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 600 mg IV	191	37 (19.4)	[13.8, 25.1]	[redacted]	15.1	15.0	[8.9, 21.2]	<0.001¶
Placebo IV	187	8 (4.3)	[1.4, 7.2]	[redacted]	-	-	-	-

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Source: MOTIVATE CSR (39), D'Haens et al (2022) (106). Notes: Endoscopic remission defined as SES-CD ≤4 and at least a 2-point reduction versus baseline and no sub-score greater than 1 in any individual variable, as scored by a central reviewer.

† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (Number of prior biologics failed [≤ 1, > 1] and baseline steroid use [Yes, No]) for the comparison of two treatment groups. Within each subgroup, 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US protocol.

B.2.6.2.2.3 EQ-5D-5L at Week 4 and Week 12

The risankizumab 600 mg IV arm was associated with statistically significant improvements in EQ-5D-5L from as early as Week 4 and also at Week 12 compared with the placebo IV arm (39). For the EQ-5D Index Value scores, subjects in the risankizumab 600 mg IV arm had a greater improvement from baseline (LS mean) when compared with the placebo IV arm at Week 4 ([redacted]) and Week 12 ([redacted]) (Table 26). Similar results were observed for EQ-5D VAS scores; subjects in the risankizumab 600 mg arm had a greater improvement from baseline (LS mean) when compared with the placebo IV arm at Week 4 ([redacted]) and Week 12 ([redacted]) (Table 26).

Table 26: Change from Baseline in EQ-5D-5L at Week 4, Week 12 (MMRM) (MOTIVATE ITT1A population)

Parameter / Timepoint / Treatment	Within Group Change from Baseline					Between Group Difference vs Placebo			
	N	Missing due to COVID-19	Baseline Mean	Visit Mean	LS Mean	LS Mean	[95% CI]	SE	P-value
EQ-5D-5L Index Value									
Week 4									
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	--
Week 12									
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
EQ-5D VAS									
Week 4									
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Week 12									
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5 dimensions 5 levels; ITT, intention to treat; IV, intravenous; LS, least squares; MMRM, Mixed-Effect Model Repeat Measurement; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab; SE, standard error; VAS, visual analogues scale.
Source: MOTIVATE CSR (39). Notes: MMRM is the Mixed-Effect Model Repeat Measurement with the categorical fixed effects of treatment, visit and treatment-by-visit interaction, stratification factors (Number of Prior Biologics Failed (<= 1, > 1) and Baseline Steroid Use (Yes, No), and the continuous fixed covariates of baseline measurements included in the model.

B.2.6.2.3 Other outcomes

Outcomes for change from Baseline in IBDQ Total Score at Week 12 in the ITT1A population are presented in Appendix M.

B.2.6.2.4 Conclusion – MOTIVATE

MOTIVATE demonstrated significant clinical benefits associated with risankizumab 600 mg IV compared with placebo IV in a population of Bio-IR subjects with moderately to severely active CD (39, 106). In line with the results of ADVANCE, risankizumab 600 mg IV was superior to placebo IV for the co-primary endpoints of CDAI clinical

remission and endoscopic response. Furthermore, significant improvements in CDAI clinical response were seen as early as Week 4 for risankizumab 600 mg IV compared with placebo IV and maintained over 12 weeks. Significant improvements in HRQoL were also seen with risankizumab 600 mg IV compared with placebo IV from as early as Week 4.

B.2.6.3 FORTIFY

B.2.6.3.1 Primary efficacy outcome: Proportion of subjects with CDAI clinical remission and/or endoscopic response at Week 52

In FORTIFY, the co-primary endpoint of CDAI clinical remission and endoscopic response for the risankizumab 360 mg SC arms compared with the placebo SC (withdrawal) arm were met (40, 107). At Week 52, a significantly greater proportion of subjects in the risankizumab 360 mg SC arm achieved the co-primary endpoint of CDAI clinical remission (CDAI <150) versus the placebo SC (withdrawal) (52.2% vs 40.9%, respectively; p=0.005) (Table 27). Additionally, a greater proportion of subjects achieved CDAI clinical remission in the non-Bio-IR population compared with the Bio-IR population (Table 27). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 27).

Table 27: CDAI clinical remission at Week 52 (NRI-C) – total, by prior biologic failure status and last risankizumab induction dose (FORTIFY ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 360 mg SC	141	74 (52.2)	[43.9, 60.5]	[redacted]	11.3	14.6	[4.3, 25.0]	0.005¶
Placebo SC (withdrawal)††	164	67 (40.9)	[33.3, 48.4]	[redacted]	-	-	-	--
Prior biologic failure status								
Bio-IR								
RZB 360 mg SC	102	49 (47.6)	[37.8, 57.4]	[redacted]	12.7	-	[–0.2, 25.6]	-
Placebo SC (withdrawal)††	123	43 (35.0)	[26.5, 43.4]	[redacted]	-	-	-	-
Non-Bio-IR								
RZB 360 mg SC	39	25 (64.1)	[49.0, 79.2]	[redacted]	5.6	-	[–15.7, 26.9]	-
Placebo SC (withdrawal)††	41	24 (58.5)	[43.5, 73.6]	[redacted]	-	-	-	-

Abbreviations: APS, abdominal pain score; Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; non-Bio IR, conventional therapy inadequate response/intolerance; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; RZB, risankizumab; SC, subcutaneous; SF, stool frequency.
Source: FORTIFY CSR (40), Ferrante et al (2022) (107). Notes: CDAI clinical remission defined as CDAI <150.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § For overall population, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (endoscopic response at Week 0 [yes or no], SF/APS clinical remission status at Week 0 [yes or no] and last IV dose during risankizumab induction periods [1200 mg or 600 mg]) for the comparison of 2 treatment groups. Within each subgroup (i.e. prior biologic failure status and last risankizumab induction dose), 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US protocol; †† The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy and were randomised to receive placebo in the maintenance study.

At Week 52, a significantly greater proportion of subjects in the risankizumab 360 mg SC arm achieved the co-primary endpoint of endoscopic response versus the placebo SC (withdrawal) arm (46.5% vs 22.0%, respectively; p<0.001) (Table 28). Additionally, a clear treatment effect was demonstrated in both the non-Bio-IR and Bio-IR populations, with a greater proportion of subjects achieving endoscopic response and

a larger effect size noted in the non-Bio-IR population compared with the Bio-IR population (Table 28). Overall, a consistent treatment effect was observed in the overall and prior biologic failure populations (Table 28).

Table 28: Endoscopic response at Week 52 (NRI-C) – total, by prior biologic failure status and last risankizumab induction dose (FORTIFY ITT1A population)

Subgroup Category Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 360 mg SC	141	66 (46.5)	[38.3, 54.8]	[redacted]	24.6	27.8	[18.7, 37.0]	<0.001¶
Placebo SC (withdrawal)††	164	36 (22.0)	[15.6, 28.3]	[redacted]	-	-	-	--
Prior biologic failure status								
Bio-IR								
RZB 360 mg SC	102	45 (43.7)	[34.1, 53.4]	[redacted]	23.4		[11.4, 35.4]	-
Placebo SC (withdrawal)††	123	25 (20.3)	[13.2, 27.4]	[redacted]	-	-	-	-
Non-Bio-IR								
RZB 360 mg SC	39	21 (53.8)	[38.2, 69.5]	[redacted]	27.0		[6.3, 47.7]	-
Placebo SC (withdrawal)††	41	11 (26.8)	[13.3, 40.4]	[redacted]	-	-	-	-

Abbreviations: APS, abdominal pain score; Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; IV, intravenous; non-Bio IR, conventional therapy inadequate response/intolerance; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; NS, not significant; RZB, risankizumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.
Source: FORTIFY CSR (40), Ferrante et al (2022) (107). Notes: Endoscopic response defined as decrease in SES-CD >50% from induction study baseline (or for subjects with isolated ileal disease and an induction study baseline SES-CD of 4, ≥2-point reduction from induction study baseline).
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § For overall population, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (endoscopic response at Week 0 [yes or no], SF/APS clinical remission status at Week 0 [yes or no] and last IV dose during risankizumab induction periods [1200 mg or 600 mg]) for the comparison of 2 treatment groups. Within each subgroup (i.e. prior biologic failure status and last risankizumab induction dose), 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Co-primary endpoint achieved statistical significance based on the pre-specified graphical testing procedure for the US and OUS protocol; †† The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy and were randomised to receive placebo in the maintenance study.

B.2.6.3.2 Secondary efficacy outcomes

B.2.6.3.2.1 Endoscopic remission at Week 52

More than one third of subjects (39%) treated with risankizumab 360 mg SC achieved endoscopic remission at Week 52 when compared with those who received placebo SC (withdrawal) (12.8%; nominal p-value <0.001) (40, 107) (Table 29).

Table 29: Achievement of endoscopic remission at Week 52 (NRI-C) (FORTIFY ITT1A population)

Subgroup Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	Adjusted Diff (%)‡	[95% CI]§	P-value§
All subjects								
RZB 360 mg SC	141	55 (39.1)	[31.0, 47.1]	▌	26.3	28.5	[19.9, 37.0]	<0.001NS¶
Placebo SC (withdrawal)††	164	21 (12.8)	[7.7, 17.9]	▌	-	-	-	-

Abbreviations: APS, abdominal pain score; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; NS, not significant; RZB, risankizumab; SC, subcutaneous; SF, stool frequency.
Source: FORTIFY CSR (40), Ferrante et al (2022) (107). Notes: Endoscopic remission defined as SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § For overall population, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (endoscopic response at Week 0 [yes or no], SF/APS clinical remission status at Week 0 [yes or no] and last IV dose during risankizumab induction periods [1200 mg or 600 mg]) for the comparison of 2 treatment groups. Within each subgroup (i.e. prior biologic failure status and last risankizumab induction dose), 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Did not achieve statistical significance (NS) based on the pre-specified graphical testing procedure for the US-specific protocol; †† The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy and were randomised to receive placebo in the maintenance study.

B.2.6.3.2.2 CDAI clinical response at Week 52

A greater proportion of subjects in the risankizumab 360 mg SC arm achieved CDAI clinical response (reduction of CDAI ≥100 points from baseline of the induction study) at Week 52 versus the placebo SC (withdrawal) arm (61.6% vs 48.2%, respectively; nominal p-value=0.002) (40, 107) (Table 30).

Table 30: Achievement of CDAI clinical response at Week 52 (NRI-C) (FORTIFY ITT1A population)

Subgroup Treatment	Responder (NRI-C)				Response Rate Difference vs Placebo			
	N	n (%)	[95% CI][†]	Missing due to COVID-19, n	Diff (%)[‡]	Adjusted Diff (%)[‡]	[95% CI][§]	P-value[§]
All subjects								
RZB 360 mg SC	141	87 (61.6)	[53.5, 69.6]	[redacted]	13.4	16.2	[5.7, 26.6]	0.002[NS¶]
Placebo SC (withdrawal)[††]	164	79 (48.2)	[40.5, 55.8]	[redacted]	-	-	-	-

Abbreviations: APS, abdominal pain score; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intention to treat; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; NS, not significant; RZB, risankizumab; SC, subcutaneous; SF, stool frequency.
Source: FORTIFY CSR (40), Ferrante et al (2022) (107). Notes: CDAI clinical response defined as reduction of CDAI ≥100 points from baseline of the induction study. † 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo). Adjusted difference is calculated based on the CMH test; § For overall population, 95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for strata (endoscopic response at Week 0 [yes or no], SF/APS clinical remission status at Week 0 [yes or no] and last IV dose during risankizumab induction periods [1200 mg or 600 mg]) for the comparison of 2 treatment groups. Within each subgroup (i.e. prior biologic failure status and last risankizumab induction dose), 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ Did not achieve statistical significance (NS) based on the pre-specified graphical testing procedure for the US-specific protocol; †† The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy and were randomised to receive placebo in the maintenance study.

B.2.6.3.2.3 EQ-5D-5L at Week 52

For the EQ-5D-5L Index Value scores, subjects in the risankizumab 360 mg SC arm had a similar improvement from baseline of the induction study (LS mean) at Week 52 when compared with the placebo SC (withdrawal) arm (40) (Table 31). Comparing the change from baseline scores between treatment arms, there was no significant difference in EQ-5D-5L Index Value scores between the risankizumab 360 mg SC arm and placebo SC (withdrawal) arm at Week 52 ([redacted]) (Table 31).

For the EQ-5D VAS scores, subjects in the risankizumab 360 mg SC arm had a numerically greater, non-significant improvement from baseline (LS mean) at Week 52 when compared with the placebo SC (withdrawal) arm (Table 31). Comparing the change from baseline scores between treatment arms, there was no significant

difference in EQ-5D VAS scores between the risankizumab 360 mg SC arm and placebo SC (withdrawal) arm at Week 52 ([redacted]) (Table 31).

Table 31: Change from Baseline in EQ-5D-5L at Week 52 (MMRM) (FORTIFY ITT1A population)

Parameter Timepoint Treatment	Within Group Change from Baseline					Between Group Difference vs Placebo		
	N	Baseline Mean	Visit Mean	LS Mean	LS Mean	[95% CI]	SE	P-value†
EQ-5D-5L Index Value								
Week 52								
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo SC (withdrawal)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
EQ-5D VAS								
Week 52								
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo SC (withdrawal)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5 dimensions 5 levels; ITT, intention to treat; LS, least squares; MMRM, Mixed-Effect Model Repeat Measurement; RZB, risankizumab; SC, subcutaneous; SE, standard error; VAS, visual analogue scale.
Source: FORTIFY CSR (40).
† 95% CI for within group LS Mean and 95% CI for LS Mean in treatment difference and p-value are calculated according to the ANCOVA with strata (endoscopic response at Week 0 [yes or no], clinical remission status at Week 0 [yes or no] and last IV dose during risankizumab induction periods [1200 mg or 600 mg]) and induction baseline EQ-5D-5L and Week 0 EQ-5D-5L as covariates for the comparison of two treatment groups.

B.2.6.3.3 Other outcomes

Additional outcomes for the ITT1A population are listed below and are presented in Appendix M.

- CDAI clinical remission at Week 52 among subjects with CDAI clinical remission at Week 0
- Ulcer-free endoscopy at Week 52
- Deep remission
- Change from Baseline of the Induction Study in IBDQ Total Score at Week 52
- The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) change from baseline at Week 52
- SF remission Week 52

- AP remission Week 52
- CDAI clinical remission and endoscopic response Week 52
- Change from Baseline of the Induction Study in SF-36 Physical Component Summary Score at Week 52
- Exposure-adjusted occurrence of CD-related hospitalisations from Week 0 to 52
- Achievement of steroid-free remission, endoscopic remission and response

B.2.6.3.4 Conclusion - FORTIFY

The results of FORTIFY SS1 demonstrate that subjects with a clinical response to 12 weeks of induction risankizumab continue to benefit from treatment with risankizumab 360 mg SC in a maintenance phase (40, 107). The re-randomised responder with withdrawal placebo design for FORTIFY permitted subjects with previous risankizumab exposure from the induction studies to be randomised to the maintenance placebo SC (withdrawal) arm. Consequently, there was prolonged efficacy observed in the placebo SC (withdrawal) arm for symptomatic endpoints in the maintenance study (further discussed in Section B.2.12.2.1). Despite this, the co-primary endpoints of CDAI clinical remission and endoscopic response both met statistical significance for the risankizumab 360 mg SC arm compared with the placebo SC (withdrawal) arm. In addition, these results were achieved in a notably treatment refractory population, with approximately 36% of subjects in both treatment arms having failed more than one previous biologic therapy. When compared with placebo SC withdrawal, risankizumab 360 mg SC also demonstrated beneficial treatment effects for CDAI clinical remission and endoscopic response in subjects who were Bio-IR or non-Bio-IR. In addition, subjects who received risankizumab 360 mg SC achieved greater responses for objective outcomes (nominal p-values only), including endoscopic remission and ulcer-free endoscopy when compared with placebo SC (withdrawal).

B.2.7 Subgroup analysis

Across the risankizumab CD studies (ADVANCE, MOTIVATE, FORTIFY), pre-planned and post-hoc subgroup analyses were conducted. Those relevant to the submission are outlined in Table 32; results are presented in Appendix E.

Table 32: Pre-planned and post-hoc subgroup analyses

	ADVANCE	MOTIVATE	FORTIFY
Pre-planned subgroups	• 16–18-year-olds • Prior TNF-alpha inhibitor failure		
Post-hoc analyses	• Responders and non-responders in the mild or moderate-to-severe CD health states after induction with risankizumab IV or placebo IV		NA

Abbreviations: NA, not applicable; TNF, tumour necrosis factor; UST, ustekinumab.

In addition to the subgroups outlined in Table 32, a post-hoc analysis of outcomes by CD location was conducted. In the analysis, treatment with induction or maintenance risankizumab was shown to be effective versus placebo in all CD locations except where CD was limited to the ileum. However, the subgroup with ileal CD represents a small proportion of the total trial study population such that no meaningful conclusions can be drawn from this analysis.

B.2.8 Meta-analysis

A comprehensive network meta-analysis (NMA) was conducted instead of a meta-analysis of RCTs as the absence of head-to-head data prevented a standard meta-analysis from being performed. This enabled comparisons with other biologic therapies included in the NICE scope and allowed for more precise estimates of treatment effects to be calculated when compared with a naive comparison of trials (see Section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Methodology

Full details of the methodology for the indirect/mixed treatment comparison are provided in Appendix D. A brief overview of the methodology is presented in Section B.2.9.1.3.

B.2.9.1.1 Analysis scope

As discussed in Section B.2.1, an SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of risankizumab and potential comparators for the treatment of people with moderate-to-severe active CD. In the absence of head-to-head RCTs between all comparators specified in the NICE scope, an NMA was

performed to assess the relative efficacy of risankizumab compared with relevant comparators (adalimumab, infliximab, ustekinumab, vedolizumab) in adults with moderate-to-severe CD who experienced CCF or BF. The non-Bio-IR and Bio-IR populations in the risankizumab clinical trials are considered analogous to the CCF and BF populations, respectively (see Section B.2 summary for more details). The methodology of the SLR that identified studies used in the NMAs is described in Appendix D.

B.2.9.1.2 Study selection for the NMA

As described in Appendix D, a total of 281 records met the inclusion criteria of the clinical SLR, reporting on 69 original studies. After applying the inclusion/exclusion criteria, 16 unique trials reported by 30 records were included for analysis in the NMA. A list of all studies excluded from the NMA (including reason for exclusion) is available in Appendix D.1.2.2.

The interventions and doses of interest included in the NMAs for the induction and maintenance phases are presented in Appendix D. For each of the interventions, only licensed UK doses were included in the analysis. A summary of the trials used to conduct the NMA is presented in Table 33.

Table 33: Summary of trials used in the NMA

Trial reference	RZB	IFX	ADA	UST	VDZ
ACCENT 1 (109)		✓			
ADVANCE† (38)	✓				
CHARM (111)			✓		
CLASSIC 1 (115)			✓		
FORTIFY† (40)	✓				
GAIN (110)			✓		
GEMINI 2 (105)					✓
GEMINI 3 (116)					✓
IM-UNITI (104)				✓	
MOTIVATE† (39)	✓				
Targan et al. (1997) (117)		✓			
UNITI 1 (118)				✓	

Trial reference	RZB	IFX	ADA	UST	VDZ
UNITI 2 (118)				✓	
VISIBLE 2 (119)					✓
Watanabe et al. (2012) (120)			✓		
Watanabe et al. (2020) (121)					✓

Abbreviations: ADA, adalimumab; CSR, clinical study report; IFX, infliximab; NMA, network meta-analysis; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.
† CSR data used in NMA.

CDAI outcomes were the outcomes of interest for the NMA as they facilitate comparison with comparator therapies and are used in the cost-effectiveness model (see Section B.2.3.2 for further details). In general, outcomes were assessed after an induction phase of 4 to 12 weeks and a maintenance phase of 44 to 60 weeks (see Appendix D for more details).

For CDAI outcomes, CDAI clinical remission and CDAI clinical response (CDAI-100) were assessed for induction trials, while CDAI clinical remission was assessed for the maintenance trials (Table 34).

Table 34: Trials reporting CDAI outcomes used in the NMA

Treatment population	CCF		BF	
Treatment phase	**Induction**	**Maintenance**	**Induction**	**Maintenance**
Studies reporting CDAI outcomes	• ADVANCE • CLASSIC I • GEMINI 2 • GEMINI 3 • Targan et al. (1997) • UNITI-2 • Watanabe et al. (2020) • Watanabe et al. (2012)	• ACCENT 1 • CHARM • FORTIFY • GEMINI 2 • IM-UNITI • VISIBLE 2 • Watanabe et al. (2020)	• ADVANCE • GAIN • GEMINI 2 • GEMINI 3 • MOTIVATE • UNITI-1 • Watanabe et al. (2020) • Watanabe et al. (2012)	• CHARM • FORTIFY • GEMINI 2 • IM-UNITI • VISIBLE 2 • Watanabe et al. (2020)

Abbreviations: BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; NMA, network meta-analysis.

B.2.9.1.3 Summary of trials included in the NMA

A summary of the trials included in the base case and sensitivity analysis NMAs as well as the reporting of outcomes from each study considered for inclusion is detailed in Appendix D.

B.2.9.1.4 Overview of NMA methodology

A Bayesian NMA approach was selected to accomplish the study objective using an evidence base of published RCTs. Binary outcomes were modelled with a binomial likelihood and either a logit or risk difference (RD) link (as recommended by NICE decision support unit [DSU] technical support document [TSD] 2 (122, 123)). The feasibility of the NMAs based on the included RCTs was assessed (for full details on methodology and feasibility assessment, see Appendix D). In addition, an RD NMA methodology was used in the base case analysis (for more detail, refer to Section B.2.9.3 and Appendix D).

The maintenance network was separated into two networks based on biologic half-life, induction duration, and study heterogeneity, grouping risankizumab and ustekinumab together, and analysing other therapies (adalimumab, infliximab and vedolizumab) in a separate network (for further details, see Section B.2.9.3.2). Given the general data sparsity, a fixed effects (FE) framework was used in the base case analysis to avoid producing credible intervals that did not pass validity. In addition, given the similar deviance information criteria (DIC) values between the FE and random effect (RE) models, the FE model was preferred since it is easier to interpret (as recommended by NICE DSU TSD 2 (122)). The rationale for selecting this approach is further described in Appendix D. The impacts of the RE models on the cost-effectiveness results were investigated in a scenario analysis (see Section B.3.11.3).

For each combination of outcome and NMA, league tables of the relative effect estimate for all possible pair-wise comparisons are presented.

Additional results for base case analysis are presented in Appendix P:

- Relative effect estimates for each relevant comparator versus placebo on the RD scale

- Predicted absolute outcomes for each treatment
- Surface Under the Cumulative RAnking (SUCRA) values for each treatment[f]

Outcomes assessed include CDAI clinical remission and CDAI-100 response (see Table 35 for definitions). The definitions used in the NMA for CDAI clinical remission and CDAI-100 response align with those used in the risankizumab CD studies (see Section B.2.3.2). The NMA presents results for CDAI outcomes as CD clinical trials have historically used this measure, and this is consistent with the trial outcomes reported for both ustekinumab and vedolizumab, the most recently approved biologic therapies for CD (35, 104, 105).

Table 35: Outcomes assessed in the NMA

Outcome	Definition
CDAI remission	Clinical remission was defined as CDAI score <150 points at endpoint measurement
CDAI-100 response	Clinical response (≥100 CDAI response) was defined as a ≥100-point decrease from baseline in CDAI score (or score <150) at endpoint measurement timepoints

Abbreviations: CDAI, Crohn's disease activity index; NMA, network meta-analysis.

B.2.9.1.4.1 Sensitivity analysis methodology

In the RE sensitivity analysis, the methodology remains the same as that described for the base case analysis (see Section B.2.9.1.4) except that an RE model was used instead of an FE model.

B.2.9.1.5 NMA networks

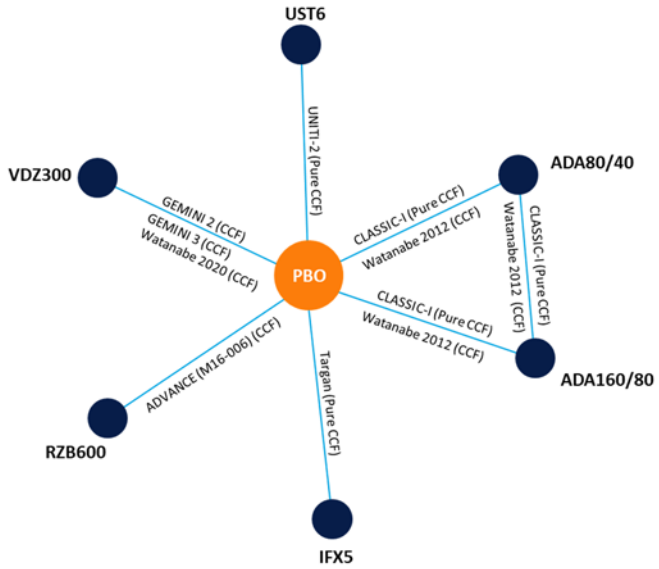
The treatment networks for the studies included in the base case analyses for the CCF and BF populations are presented in the following sections. In all networks, placebo was included as the common comparator.

B.2.9.1.5.1 CCF population

The CCF population network diagrams created in the induction and maintenance phases are presented in Figure 7 and Figure 8, respectively.

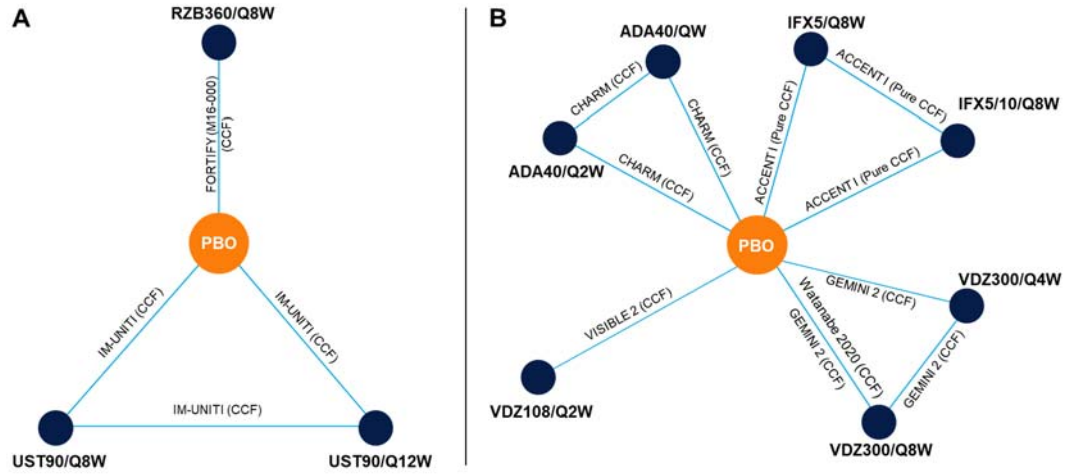
[f] SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst (124)

Figure 7: Network diagram of included induction studies in a CCF population



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

Figure 8: Network diagrams of included maintenance studies in a CCF population: (A) risankizumab and ustekinumab; (B) adalimumab, infliximab and vedolizumab

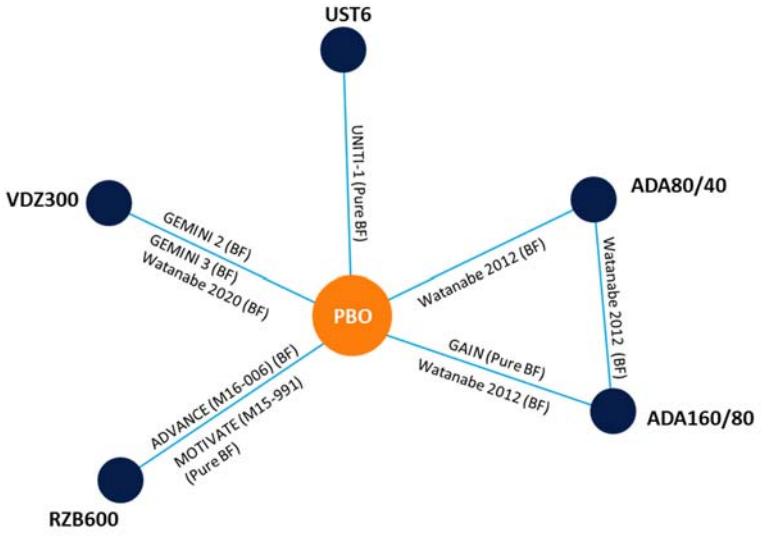


Abbreviations: ADA, adalimumab; CCF, conventional care failure; IFX, infliximab; PBO, placebo; QxW, every x weeks; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

B.2.9.1.5.2 BF population

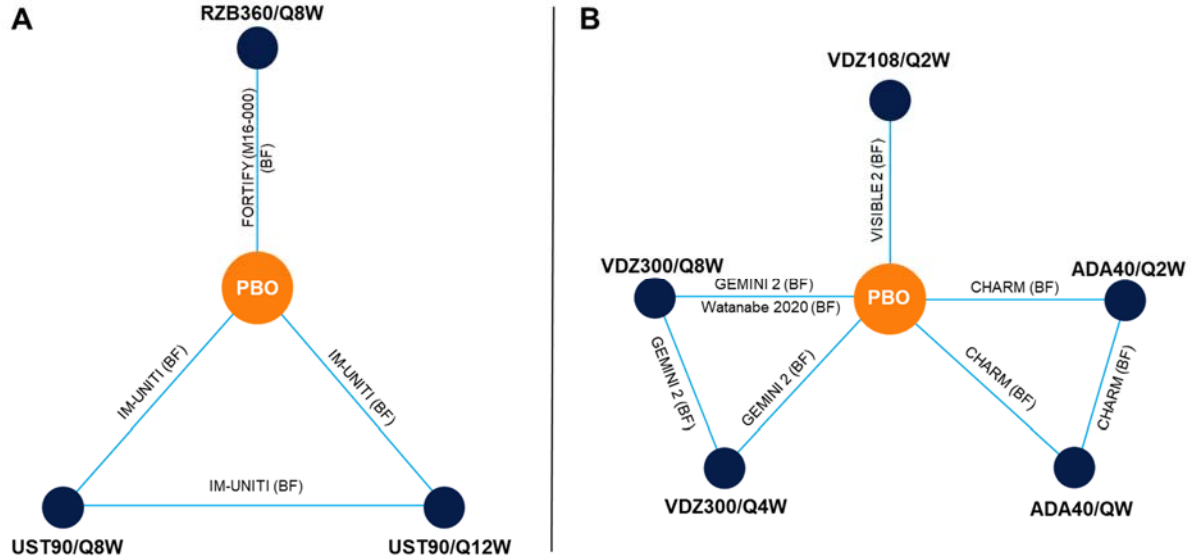
The BF population network diagrams for the induction and maintenance phases are presented in Figure 9 and Figure 10, respectively.

Figure 9: Network diagram of included induction studies in a BF population



Abbreviations: ADA, adalimumab; BF, biologic failure; PBO, placebo; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

Figure 10: Network diagrams of included maintenance studies in a BF population: (A) risankizumab and ustekinumab; (B) adalimumab and vedolizumab



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

B.2.9.2 Results

The following sections report results from the NMA for CDAI outcomes which have been used to inform the economic model. The results are reported as RD with credible intervals (CrI). Please note that 'significance' in these results is defined by CrIs not crossing zero; these analyses should not be interpreted in a frequentist manner.

B.2.9.2.1 Base case analysis – induction CDAI clinical remission

B.2.9.2.1.1 CCF population

Table 36 presents the base case NMA CDAI clinical remission results for induction risankizumab versus comparators in a CCF population.

The results show that the RD for risankizumab versus placebo is significant ([redacted]) and comparable with the rest of the comparators (adalimumab 80/40, vedolizumab IV, ustekinumab, adalimumab 160/80, infliximab) as the CrIs cross zero; the second column of the league table shows these results. A positive value indicates a comparison in favour of risankizumab, e.g., an RD of [redacted] for the comparison versus placebo means there is a [redacted] greater absolute probability of remission in patients on risankizumab versus placebo. Darker colours indicate a larger RD.

Table 36: Results for CDAI clinical remission in CCF induction NMA (FE model)

[redacted]

B.2.9.2.1.2 BF population

Table 37 presents the base case NMA CDAI clinical remission results for induction risankizumab versus comparators in a BF population.

The results show that the RDs for risankizumab versus placebo, vedolizumab IV and ustekinumab are significant (vs placebo: [redacted]; vs vedolizumab IV: [redacted]; vs ustekinumab: [redacted]) and comparable for the rest of the comparators (adalimumab 80/40 and adalimumab 160/80) as the CrIs cross zero; the first column of the league table shows these results. A positive value indicates a comparison in favour of risankizumab, e.g., an RD of [redacted] for the comparison versus placebo means there is a [redacted] greater absolute probability of remission in patients on risankizumab versus placebo. Darker colours indicate a larger RD.

Table 37: Results for CDAI clinical remission in BF induction NMA (FE model)

[redacted]

B.2.9.2.2 Base case analysis – induction CDAI-100 clinical response

B.2.9.2.2.1 CCF population

Table 38 presents the base case NMA CDAI-100 clinical response results for induction risankizumab versus comparators in a CCF population.

The results show that the RD for risankizumab versus placebo is significant ([redacted]) and comparable with the rest of the comparators (vedolizumab IV, adalimumab 80/40, adalimumab 160/80, ustekinumab, infliximab) as the CrIs cross

zero; the fourth column of the league table shows these results. A positive value indicates a comparison in favour of risankizumab, e.g., an RD of [redacted] for the comparison versus placebo means there is a [redacted] greater absolute probability of remission in patients on risankizumab versus placebo. Darker colours indicate a larger RD.

Table 38: Results for CDAI-100 clinical response in CCF induction NMA (FE model)

[redacted]

B.2.9.2.2.2 BF population

Table 39 presents the base case NMA CDAI-100 clinical response results for induction risankizumab versus comparators in a BF population.

The results show that the RDs for risankizumab versus placebo, vedolizumab IV, ustekinumab and adalimumab 160/80 are significant (vs placebo: [redacted]; vs vedolizumab: [redacted]; vs ustekinumab [redacted]; vs adalimumab 160/80: [redacted]) and comparable with adalimumab 80/40 as the CrIs cross zero; the first column of the league table shows these results. A positive value indicates a comparison in favour of risankizumab, e.g., an RD of [redacted] for the comparison versus placebo means there is a [redacted] greater absolute probability of remission in patients on risankizumab versus placebo. Darker colours indicate a larger RD.

Table 39: Results for CDAI-100 response in BF induction NMA (FE model)

[redacted]

B.2.9.2.3 Base-case analysis – maintenance CDAI clinical remission

B.2.9.2.3.1 CCF population (risankizumab and ustekinumab)

Table 40 presents the base case NMA CDAI clinical remission results for maintenance risankizumab versus comparators (ustekinumab) in a CCF population.

The results show that the efficacy of risankizumab is comparable with the rest of the comparators (placebo, ustekinumab (Q12W, ustekinumab Q8W) as the CrIs cross zero; the third column of the league table shows these results. A positive value indicates a comparison in favour of risankizumab, e.g., an RD of [redacted] for the comparison versus placebo means there is a [redacted] greater absolute probability of remission in patients on risankizumab versus placebo. Darker colours indicate a larger RD.

Table 40: Results for CDAI clinical remission in CCF maintenance NMA (risankizumab and ustekinumab network) (FE model)

[redacted]

B.2.9.2.3.2 CCF population (infliximab, adalimumab and vedolizumab)

[redacted] presents the base case NMA CDAI clinical remission results for the maintenance network containing infliximab, adalimumab and vedolizumab in a CCF population. Most treatments were superior to placebo with the exception of VDZ300/Q4W and VDZ108/Q2W, for which the credible intervals for each comparison crossed zero. The rest of the comparisons did not indicate superiority of any one treatment with the exception of ADA40/QW which appeared to have a significantly greater probability of remission than VDZ108/Q2W ([redacted]), VDZ300/Q4W ([redacted]) and IFX5/Q8W ([redacted]).

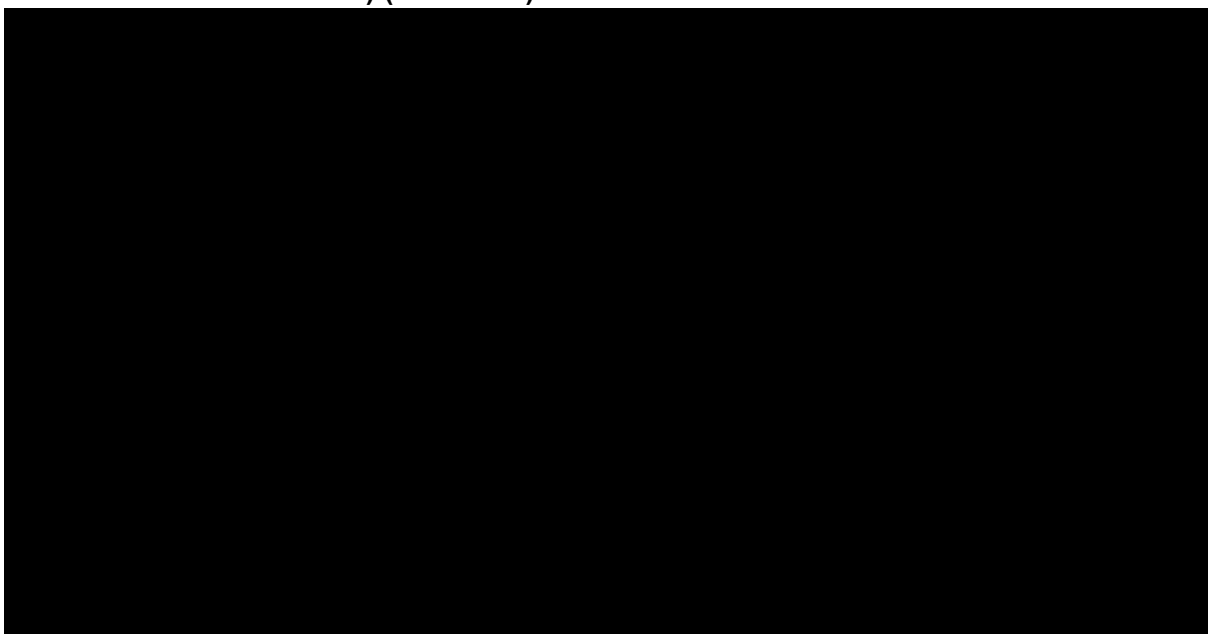
Table 41: Results for CDAI clinical remission in CCF maintenance NMA (infliximab, adalimumab and vedolizumab network) (FE model)

B.2.9.2.3.3 BF population (risankizumab and ustekinumab)

Table 42 presents the base case NMA CDAI clinical remission results for maintenance risankizumab versus comparators (ustekinumab) in a BF population.

The results show that the risk difference for risankizumab versus placebo is significant (vs placebo: [redacted]) and comparable with the rest of the comparators (UST90/Q12W, UST90/Q8W) as the credible intervals cross zero; the second column of the league table shows these results. A positive value indicates a comparison in favour of risankizumab, e.g., a risk difference of [redacted] for the comparison versus placebo means there is a [redacted] greater absolute probability of remission in patients on risankizumab versus placebo. Darker colours indicate a larger risk difference.

Table 42: Results for CDAI clinical remission in BF maintenance NMA (risankizumab and ustekinumab network) (FE model)



B.2.9.2.3.4 BF population (infliximab, adalimumab and vedolizumab)

Table 43 presents the base case NMA CDAI clinical remission results for the maintenance network containing adalimumab and vedolizumab in a BF population. All treatments were superior to placebo. All comparators (with the exception of placebo) were comparable in efficacy to one another.

Table 43: Results for CDAI clinical remission in BF maintenance NMA (adalimumab and vedolizumab network) (FE model)

B.2.9.2.4 RE model results

Results for the NMAs conducted using a RE model are presented in Appendix P. Overall, the RE NMA results were similar to the FE models although there were larger CrIs across most comparisons, which is to be expected as the RE NMA incorporates between-study differences in its efficacy estimates.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

B.2.9.3.1 RD NMA method

The NMAs used in this submission utilised the RD method, which was used in this instance as it is recommended where baseline risk-adjusted models are deemed inappropriate due to lack of convergence or face validity (122).

Like baseline risk adjustment, RD NMA is also recognised as valid framework by NICE (DSU TSD2, Section 3.7 (122)). It has been used in publications and prior submissions to NICE (125, 126). Cameron et al. (2018) (127) found that the use of an NMA on the RD scale represents a viable alternative approach to account for the presence of cross-study differences in placebo response rates. Per NICE DSU TSD2 (123, 128), RD NMA could be used as an alternative method to log-odds NMA when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network. The RD model code utilised was adapted from Dias et al. (2018) (123), which was based on modelling frameworks by Warn et al. (2002) (129).

In TA521, RD was used to adjust for cross-trial differences (125). Rather than calculating relative effects as ratios (such as odds ratios produced by traditional logit-link NMA frameworks), absolute probabilities of treatment response were subtracted across interventions in RD models, minimising potential impacts of overly low or high placebo efficacy. This may help minimise bias when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network. TA521 concluded that baseline-risk adjusted models and risk difference NMAs should yield less biased estimates of effect than the unadjusted NMA analyses on the relative scale.

Due to the general paucity of data in the relevant CD evidence networks leading to poor performance of baseline-risk adjusted logit-link NMAs, RD NMAs provided an

attractive option to minimise impacts of placebo heterogeneity on NMA-produced treatment effect estimates.

Criticism of RD models stems from potential model instability, leading to lack of convergence and sensitivity to starting values (127). However, the RD models in the CD NMA analysis in this submission converged and had appropriate fit. Appropriate vague prior distributions were utilised which corresponded to the RD scale. Starting values were utilised which are dispersed across the probability space.

In summary, the RD models addressed placebo rate variation of the sort observed in the biologic CD trials, yielded reasonable estimates, passed diagnostic tests based on their convergence and fit, are accepted by NICE, have been used in prior submissions, and have appeared in the published academic literature.

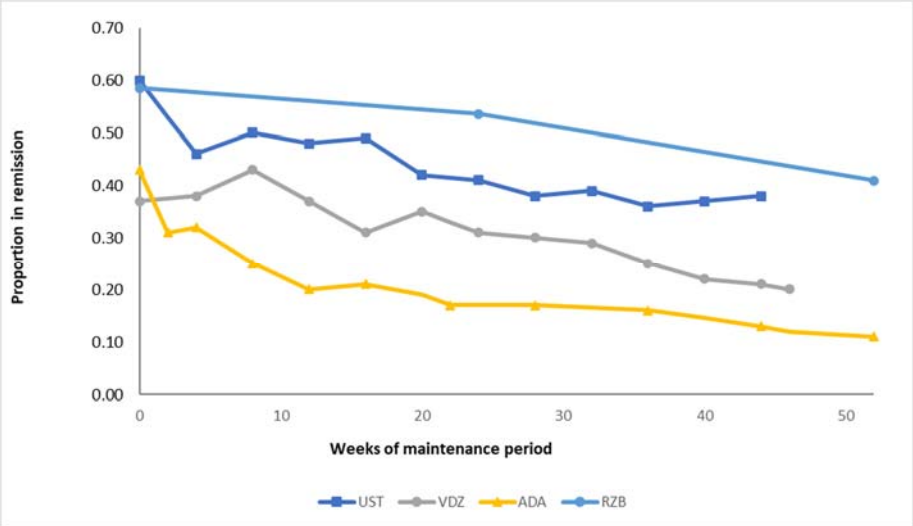
B.2.9.3.2 Use of two separate networks for the maintenance NMA

Two separate networks for the maintenance NMAs were used in order to reduce the heterogeneity in the placebo arms of the maintenance studies. Risankizumab and ustekinumab were grouped in one network (rather than a single network with adalimumab, infliximab and vedolizumab) as both are IL inhibitors and have longer half-lives. This mitigates the maintenance placebo heterogeneity issue as placebo heterogeneity is greatly reduced in the IL inhibitor network and the direct comparability of risankizumab and ustekinumab greatly improves. There was a clear differentiation in placebo efficacy in maintenance trials, with risankizumab and ustekinumab having placebo remission rates sustained notably longer than other comparators in the NMA, likely due to differences in half-lives and the long-term effects on the pathological process of ustekinumab and risankizumab when compared with the other comparators in the NMA. Placebo arms in the maintenance studies are not comparable because subjects who entered the maintenance phase were initially selected for their ability to respond to the intervention in the induction phase. Due to the long half-lives of risankizumab and ustekinumab, it is likely that their residual treatment effect (carried over from the induction phase) during the maintenance trials impacted the placebo group for longer than the other comparators. This is illustrated in Figure 11[g], where

[g] A figure originally presented in the ustekinumab NICE submission TA456 (46) updated to include risankizumab data.

the proportion of subjects receiving placebo in the maintenance period and achieving remission is prolonged for risankizumab and ustekinumab when compared with adalimumab and vedolizumab.

Figure 11: Proportion of subjects receiving placebo during maintenance phase in CDAI clinical remission



Abbreviations: ADA, adalimumab; CDAI, Crohn's Disease Activity Index; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

In addition, the induction periods varied across the different treatments with ustekinumab and risankizumab having the longest (8 weeks and 12 weeks, respectively), further contributing to the residual treatment effect in the maintenance phase. Therefore, adalimumab, infliximab and vedolizumab were grouped together in a separate network to risankizumab and ustekinumab.

B.2.9.3.3 Potential for network inconsistency

In the network diagrams contained in B.2.9.1.5, there are loops that can show inconsistency in the following populations, phases and efficacy outcomes:

- BF induction CDAI clinical remission, formed by GAIN (110) and Watanabe et al. (2012) (120) for ADA160/80, ADA80/40 and PBO
- CCF maintenance CDAI clinical remission (non-IL-23 comparators), formed by GEMINI 2 (105) and Watanabe et al. (2020) (121) for VDZ300/Q8W, VDZ300/Q4W and PBO

- BF maintenance CDAI clinical remission (non-IL-23 comparators), formed by GEMINI 2 (105) and Watanabe et al. (2020) (121) for VDZ300/Q8W, VDZ300/Q4W and PBO

The test of the consistency assumption was conducted on each outcome's unadjusted logit-link selected model using the FE or RE unrelated mean effects (UME) model. The presence of inconsistency in each network was assessed by comparing the model fit and heterogeneity between each set of consistency (unadjusted logit-link NMA) and inconsistency (UME) models, which are summarised in Table 44 and Table 45.

Table 44: Model fit between consistency and inconsistency models, induction

Outcome	Population	Tested model	NMA Dbar	UME Dbar	NMA DIC	UME DIC
CDAI clinical remission	BF	FE	15.61	15.70	28.75	28.93
	CCF	No loop				
CR-100 clinical response	BF	FE	17.34	17.28	30.45	30.34
	CCF	No loop				

Abbreviations: BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CR, clinical response, Dbar, overall residual deviance; DIC, deviance information criteria; FE, fixed effects model; NMA, network meta-analysis; UME, unrelated mean effects model.

Table 45: Model fit between consistency and inconsistency models, maintenance

Outcome	Population	Tested model	NMA Dbar	UME Dbar	NMA DIC	UME DIC
CDAI clinical remission (RZB and UST network)	No loop					
CDAI clinical remission (ADA, IFX and VDZ network)	BF	FE	11.30	11.30	20.37	20.36
	CCF	FE	12.25	12.23	24.44	24.41

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; Dbar, overall residual deviance; DIC, deviance information criteria; FE, fixed effects model; IFX, infliximab; NMA, network meta-analysis; RZB, risankizumab; UME, unrelated mean effects model; UST, ustekinumab; VDZ, vedolizumab

In all assessed networks, the posterior means of the residual deviance (Dbar) and the DIC were very similar between the NMA and UME models (Table 44 and Table 45), suggesting lack of evidence for inconsistency in these networks. A difference in DIC values of ≥4 suggests there is no evidence of difference in model appropriateness (130).

B.2.9.4 Conclusion

Risankizumab was found to have broadly comparable efficacy with the rest of the comparators in the NMA, with the exception of placebo, where risankizumab was superior. The NMA results for the CCF population generally show comparable efficacy

for risankizumab versus other comparators, while the results for the BF population generally favour risankizumab. The results of the NMA remained consistent regardless of the NMA model type used (i.e., FE or RE model).

B.2.10 Adverse reactions

Summary

- In ADVANCE and MOTIVATE, induction with risankizumab 600 mg IV for 12 weeks was generally well tolerated
  - The overall incidence of treatment-emergent adverse events (TEAEs) during the 12-week induction period was similar between the risankizumab 600 mg IV and placebo IV treatment arms (56.3% vs 56.5% in ADVANCE and 47.6% vs 66.2% in MOTIVATE)
  - The rates of serious AEs (SAEs), severe AEs and AEs leading to discontinuation were numerically higher in the placebo IV arm than the risankizumab 600 mg IV arm†
  - Two deaths occurred during induction (ADVANCE), both of which were in the placebo IV arm. No deaths occurred in the risankizumab 600 mg IV arm.
- In FORTIFY, risankizumab 360 mg SC as maintenance treatment for 1 year was generally well tolerated
  - The incidence of TEAEs was 72.1% in the risankizumab 360 mg SC arm and 73.4% in the placebo SC (withdrawal) arm
  - The percentage of subjects with SAEs, severe AEs and AEs leading to discontinuation were comparable in risankizumab 360 mg SC and placebo SC (withdrawal) arms
  - There were no deaths reported during the maintenance study
- Across the induction and maintenance studies, no new safety risks were identified, and the overall safety profile was consistent with the known safety profile of risankizumab in the management of psoriasis

† The rates of SAEs, severe AEs and AEs leading to discontinuation were numerically higher in the placebo IV arm, with most events related to underlying CD.

The primary data for risankizumab CD in this submission is taken from clinical study reports (CSRs) and published manuscripts. At the time of submission, only data from the CSRs were deemed commercial in confidence.

All AEs described were considered treatment-emergent and summarised using Medical Dictionary for Regulatory Activities (MedDRA®), Version 23.1 primary system organ class and preferred term.

B.2.10.1 ADVANCE and MOTIVATE

B.2.10.1.1 Treatment-emergent adverse events

An overview of treatment-emergent adverse events (TEAEs) is provided for the SA1 population (which included all subjects who received at least 1 dose of risankizumab during Induction Period 1 of ADVANCE and MOTIVATE) in Table 46. As mentioned in Section B.2.6, results are presented for the anticipated licensed doses of risankizumab only. A summary of TEAEs occurring in ≥5% of subjects in either the risankizumab 600 mg IV treatment group or the placebo IV treatment group is presented in Table 47.

Table 46: Overview of TEAEs and deaths during Induction Period 1 by n (%) of subjects – ADVANCE and MOTIVATE SA1 population

	ADVANCE		MOTIVATE	
	RZB 600 mg IV N=373	PBO IV N=186	RZB 600 mg IV N=206	PBO IV N=207
Any TEAE	210 (56.3)	105 (56.5)	98 (47.6)	137 (66.2)
TEAE related to COVID-19	1 (0.3)	2 (1.1)	0	1 (0.5)
TEAE related to study drug according to the investigator	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	22 (5.9)	18 (9.7)	7 (3.4)	25 (12.1)
Serious TEAE	27 (7.2)	28 (15.1)	10 (4.9)	26 (12.6)
TEAE leading to discontinuation of study drug	9 (2.4)	14 (7.5)	2 (1.0)	17 (8.2)
TEAE leading to death	0	2 (1.1)	0	0
Deaths occurring ≤140 days after last dose of study drug	[redacted]	[redacted]	[redacted]	[redacted]
Deaths occurring >140 days after last dose of study drug	[redacted]	[redacted]	[redacted]	[redacted]
Deaths related to COVID-19	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV, intravenous; PBO, placebo; RZB, risankizumab; SA, safety analysis; SC, subcutaneous; SF, stool frequency; SS, sub study; TEAE, treatment-emergent adverse event.
Source: ADVANCE CSR (38), MOTIVATE CSR (39), D'Haens et al (2022) (106).
Note: TEAEs for the 12-Week Induction Period are defined as events that begin either on or after the first dose of the study drug in the 12-Week Induction Period and until the first dose of study drug in the FORTIFY study if the subject is enrolled into FORTIFY or until first dose of study drug in Induction Period 2 if the subject is enrolled into

Induction Period 2, or within 140 days after the last dose administration of the study drug in 12-Week Induction Period if the subject does not participate in FORTIFY or the Induction Period 2.

Table 47: TEAEs reported in ≥5% of subjects in either treatment group or during Induction Period 1, by n (%) of subjects – ADVANCE and MOTIVATE SA1 population

	ADVANCE		MOTIVATE	
MedDRA 23.1 Preferred Term	**RZB 600 mg IV N=373**	**PBO IV N=186**	**RZB 600 mg IV N=206**	**PBO IV N= 207**
Subjects with any TEAE, n (%)	210 (56.3)	105 (56.5)	98 (47.6)	137 (66.2)
Headache	24 (6.4)	8 (4.3)	11 (5.3)	11 (5.3)
Nasopharyngitis	22 (5.9)	5 (2.7)	8 (3.9)	11 (5.3)
Nausea	17 (4.6)	10 (5.4)	5 (2.4)	11 (5.3)
Abdominal pain	8 (2.1)	10 (5.4)	5 (2.4)	11 (5.3)
Crohn's disease	10 (2.7)	25 (13.4)	8 (3.9)	33 (15.9)
Anaemia	NA	NA	5 (2.4)	11 (5.3)

Abbreviations: AE, adverse event; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; NA, not applicable; PBO, placebo; RZB, risankizumab; SA, safety analysis; SC, subcutaneous; TEAE, treatment-emergent adverse event.
Source: D'Haens et al (2022) (106).
Note: TEAEs for the 12-Week Induction Period are defined as events that begin either on or after the first dose of the study drug in the 12-Week Induction Period and until the first dose of study drug in the FORTIFY study if the subject is enrolled into FORTIFY or until first dose of study drug in Induction Period 2 if the subject is enrolled into Induction Period 2, or within 140 days after the last dose administration of the study drug in 12-Week Induction Period if the subject does not participate in FORTIFY or the Induction Period 2.

B.2.10.1.2 AEs of special interest

A summary of AEs of special interest that were reported during Induction Period 1 of ADVANCE and MOTIVATE (SA1 population) is presented in Table 48.

Table 48: Overview of TEAEs of special interest during Induction Period 1 by n (%) of subjects – ADVANCE and MOTIVATE SA1 population

	ADVANCE		MOTIVATE	
Any treatment emergent	**RZB 600 mg IV N=373**	**PBO IV N=186**	**RZB 600 mg IV N=206**	**PBO IV N= 207**
Serious infections	3 (0.8)	7 (3.8)	1 (0.5)	5 (2.4)
Active tuberculosis	1 (0.3)	1 (0.5)	0	0
Hypersensitivity	19 (5.1)	6 (3.2)	8 (3.9)	10 (4.8)
Injection site reactions	4 (1.1)	1 (0.5)	1 (0.5)	3 (1.4)
Lymphoma	0	0	0	0

Abbreviations: IV, intravenous; TEAE, treatment-emergent adverse event.
Source: D'Haens et al (2022) (106).
Note: For n (%), subjects are counted once in each row, regardless of the number of events they may have had. AEs of special interest were defined based on prevalence in the moderately to severely active CD population, customary concerns with injected immunoglobulin products, the immunomodulatory activity of risankizumab, or

regulatory interest. These AEs of special interest were identified using standard MedDRA queries (SMQ) and company MedDRA queries (CMQ).

B.2.10.2 FORTIFY

B.2.10.2.1 Treatment-emergent adverse events

An overview of TEAEs is provided for the SA1 population of Sub-study 1[h] (which included all subjects who received at least 1 dose of risankizumab during FORTIFY) in Table 49. In FORTIFY, TEAEs were defined as events that begin either on or after the first dose of the study drug in Sub-Study 1 and within 140 days after the last dose administration of the study drug or until the first dose of study drug in Sub-study 3[i] if the subject was enrolled into Sub-Study 3. As mentioned in Section B.2.6, results are presented for the anticipated licensed doses of risankizumab only. A summary of TEAEs occurring in ≥5% of subjects in either the risankizumab 360 mg SC treatment group or the placebo SC treatment group is presented in Table 50.

Table 49: Overview of TEAEs and all deaths, by n (%) of subjects – randomised subjects, FORTIFY SA1 population

	FORTIFY†	
	RZB 360 mg SC N=179	**PBO SC‡ N=184**
Any TEAE	129 (72.1)	135 (73.4)
TEAE related to COVID-19	4 (2.2)	1 (0.5)
TEAE related to study drug according to the investigator	[redacted]	[redacted]
Severe TEAE	21 (11.7)	23 (12.5)
Serious TEAE	24 (13.4)	23 (12.5)
TEAE leading to discontinuation of study drug	6 (3.4)	6 (3.3)
TEAE leading to death	[redacted]	[redacted]
Deaths occurring ≤140 days after last dose of study drug	[redacted]	[redacted]
Deaths occurring >140 days after last dose of study drug	[redacted]	[redacted]
Deaths related to COVID-19	[redacted]	[redacted]

Abbreviations: PBO, placebo; RZB, risankizumab; SC, subcutaneous; TEAE, treatment-emergent adverse event.
Source: FORTIFY CSR (40), Ferrante et al (2022) (107).
† Data reported for randomised subjects only from FORTIFY SS1; ‡ The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy in ADVANCE or MOTIVATE and were randomised to receive placebo in FORTIFY.

[h] FORTIFY consists of 3 sub-studies. This submission presents the results from FORTIFY Sub-study 1 (SS1), which was a 52-week randomised, double-blind, placebo-controlled maintenance study.
[i] Sub-study 3 is an OL long-term extension for which data collection is still ongoing.

Table 50: TEAEs reported in ≥5% of subjects in either treatment group – randomised subjects, FORTIFY SA1 population

	FORTIFY†	
MedDRA 23.1 Preferred Term	**RZB 360 mg SC (N=179)**	**PBO SC‡ (N=184)**
Subjects with any TEAE, n (%)	129 (72.1)	135 (73.4)
Headache	11 (6.1)	11 (6.0)
Nasopharyngitis	17 (9.5)	25 (13.6)
Nausea	4 (2.2)	13 (7.1)
Abdominal pain	9 (5.0)	13 (7.1)
Crohn's disease	21 (11.7)	32 (17.4)
Arthralgia	17 (9.5)	20 (10.9)
Diarrhoea	4 (2.2)	10 (5.4)

Abbreviations: AE, adverse event; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; NA, not applicable; PBO, placebo; RZB, risankizumab; SA, safety analysis; SC, subcutaneous; TEAE, treatment-emergent adverse event. †Data reported for randomised subjects only from FORTIFY SS1; ‡ The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy in ADVANCE or MOTIVATE and were randomised to receive placebo in FORTIFY.
Source: Ferrante et al (2022) (107). Note: Cells that are marked NA indicate that this AE was not reported in ≥5% of subjects in either arm of that trial. Note: Subjects are counted once in each row, regardless of the number of events they may have had. For subjects receiving risankizumab rescue therapy (see Section B.2.3.1.2), all events happening after receiving risankizumab rescue therapy are presented regardless of the previous treatments. Adverse events happening before receiving risankizumab rescue therapy are presented in their original treatment arm.

B.2.10.2.2 AEs of special interest

A summary of AEs of special interest that were reported during FORTIFY (SA1 population) is presented in Table 51.

Table 51: Overview of TEAEs of special interest by n (%) of subjects – randomised subjects FORTIFY SA1 population

FORTIFY	**RZB 360 mg SC (N=179)**	**PBO SC‡ (N=184)**
Serious infections	8 (4.5)	7 (3.8)
Active tuberculosis	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
Injection site reactions	11 (6.1)	9 (4.9)
Lymphoma	[redacted]	[redacted]

Abbreviations: CMQ, Company MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; RZB, risankizumab; SA, safety analysis; SC, subcutaneous; SMQ, Standardized MedDRA query; TEAE, treatment-emergent adverse event. The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy in ADVANCE or MOTIVATE and were randomised to receive placebo in FORTIFY. Source: FORTIFY CSR (40), Ferrante et al (2022) (107).
Note: Subjects are counted once in each row, regardless of the number of events they may have had. For subjects receiving risankizumab rescue therapy (see Section B.2.3.1.2), all events happening after receiving risankizumab rescue therapy are presented regardless of the previous treatments. Adverse events happening before receiving risankizumab rescue therapy are presented in their original treatment arm.
AEs of special interest were defined based on prevalence in the moderately to severely active CD population, customary concerns with injected immunoglobulin products, the immunomodulatory activity of risankizumab, or regulatory interest. These AEs of special interest were identified using standard MedDRA queries (SMQ) and company MedDRA queries (CMQ).

B.2.10.3 Additional studies

For the pooled safety analysis provided in Section B.2.10.4.1.1, data from a Phase 2 induction trial of risankizumab in subjects with moderate-to-severe CD were pooled with safety data from the risankizumab Phase 3 induction trials (ADVANCE, MOTIVATE). The Phase 2 induction study (M15-993 [NCT02031276]) was a randomised, double-blind, placebo-controlled phase 2 study which enrolled subjects with moderate-to-severe CD at 36 referral sites in North America, Europe and south-east Asia (131).

Eligible subjects were aged 18–75 years, with a diagnosis of CD for at least 3 months, assessed as moderate-to-severe CD at screening, defined as a CDAI of 220-450, with mucosal ulcers in the ileum or colon, or both, and a Crohn's Disease Endoscopic Index of Severity (CDEIS) of at least 7 (≥4 for subjects with isolated ileitis) on ileocolonoscopy scored by a masked central reader. Subjects could have had previous treatment with one or more TNF-alpha inhibitors or vedolizumab. Subjects previously treated with ustekinumab were excluded, as were subjects who had received any other biologic agent (including agents targeting integrins) within 8 weeks or five half-lives before randomisation. Subjects continued stable doses of oral corticosteroids, oral 5-aminosalicylates, azathioprine, mercaptopurine, methotrexate and antibiotics throughout the trial if they were on these at the start. Subjects were randomised 1:1:1 to receive risankizumab 200 mg IV (n=41), risankizumab 600 mg IV (n=41), or placebo IV (n=39) via an interactive response system to a double-blind investigational product and stratified by previous exposure to TNF-alpha inhibitors (yes vs no). Subjects received their assigned treatment by intravenous infusion at weeks 0, 4 and 8. Subjects were followed through Week 12 every 4 weeks. The primary outcome was clinical remission in the pooled risankizumab dose groups, defined by a CDAI <150 at Week 12. Secondary outcomes (all evaluated at Week 12) including clinical response (defined by either CDAI <150 or a CDAI reduction from baseline of ≥100), endoscopic remission (CDEIS score of ≤4; ≤2 for subjects with isolated ileitis), endoscopic response (>50% CDEIS reduction from baseline), mucosal healing (absence of mucosal ulceration), and deep remission (clinical remission and endoscopic remission).

Comparing the placebo IV and risankizumab 600 mg IV groups, AEs (82% vs 76%, respectively), severe AEs (23% vs 7%), AEs leading to discontinuation (15% vs 2%) and SAEs (31% vs 7%) were higher in the placebo IV arm. The most common AE was nausea and most common SAE was worsening of underlying CD. No deaths occurred.

B.2.10.4 Overview of safety from the pivotal induction and maintenance trials

Induction with risankizumab 600 mg IV for 12 weeks was generally well tolerated. In both ADVANCE and MOTIVATE, the overall incidence of AEs during the 12-week induction period was similar among all treatment arms. The rates of SAEs, severe AEs and AEs leading to discontinuation were numerically higher in the placebo IV arm, with most events related to underlying CD. Across both studies, the most frequently reported AEs in ≥5.0% of subjects in the risankizumab arm were headache and nasopharyngitis, whereas the most common AEs in the placebo IV arm were CD (worsening of CD), abdominal pain, nausea and headache.

Additionally, risankizumab 360 mg SC as maintenance treatment for 1 year was generally well tolerated. The most common AEs (≥5.0%) in the risankizumab 360 mg SC arm was CD (worsening of CD), nasopharyngitis, arthralgia, headache, abdominal pain and nausea. The percentage of subjects with SAEs and AEs leading to discontinuation were comparable in risankizumab 360 mg SC and placebo SC (withdrawal) arms. Across the induction and maintenance studies, no new safety risks were identified and the overall safety profile was consistent with the known safety profile of risankizumab in the management of psoriasis (132). For the risankizumab doses presented in this submission (600 mg IV and 360 mg SC [i.e., in line with anticipated licensing]), two deaths occurred during induction (ADVANCE); both of these were in the placebo IV arm. One death was reported in the risankizumab 1,200 mg IV arm in ADVANCE (data for this arm have not been reported in the submission as this is a non-licensed dose) and was caused by acute respiratory failure due to invasive squamous cell carcinoma of the left lung. This event was considered by the investigator to be unrelated to the study drug. There were no deaths reported during maintenance study.

B.2.10.4.1.1 Pooled safety data

The Placebo-Controlled 12-Week Induction Period Safety Analysis Set provides an integrated safety assessment across the placebo-controlled 12-Week Induction Periods of the Phase 2 (M15-993 [NCT02031276]) and Phase 3 studies (ADVANCE, MOTIVATE) (132). This analysis set provides a robust assessment of risankizumab 600 mg IV induction treatment. As there is only one maintenance trial for risankizumab safety data, FORTIFY (Sub-Study 1); there are no pooled results to present for maintenance risankizumab. Results of the main safety population for maintenance risankizumab is presented in Section B.2.10.2.

In the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set), the percentage of subjects with AEs was lower in the risankizumab 600 mg IV group compared to the placebo IV group ([redacted] vs [redacted], respectively) (Table 52). The rates of SAEs, severe AEs, and AEs leading to study drug discontinuation were lower in the risankizumab 600 mg IV groups compared with the placebo IV group. One death was reported in the risankizumab 1,200 mg IV group, and 2 deaths were reported in the placebo group (deaths previously summarised in Section B.2.10.4). Overall, there was no apparent dose-relationship on AE rates between the 600 mg risankizumab IV doses.

Table 52: Overview of most frequent treatment-emergent adverse - Placebo-Controlled 12-Week Induction Period Safety Analysis Set

n (%) [SSA %]	RZB 600 mg IV N=620	Placebo IV N=432
Any TEAE	[redacted]	[redacted]
TEAE related to COVID-19	[redacted]	[redacted]
TEAE related to study drug according to the investigator	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
TEAE leading to discontinuation of study drug	[redacted]	[redacted]
TEAE leading to death	[redacted]	[redacted]
All deaths	[redacted]	[redacted]
Deaths occurring ≤140 days after last dose of study drug	[redacted]	[redacted]
Deaths occurring >140 days after last dose of study drug	[redacted]	[redacted]
Deaths related to COVID-19	[redacted]	[redacted]

Abbreviations: IV, intravenous; RZB, risankizumab; SSA, study size adjusted; TEAE, treatment-emergent adverse event. Source: Risankizumab Summary of Clinical Safety (132).

In the induction period using the same safety analysis set, the most common AEs (≥5.0%) in the risankizumab 600 mg IV group were headache and nasopharyngitis, whereas the most common AEs in the placebo IV group were CD, abdominal pain, nausea and headache (Table 53). Overall, CD (worsening of CD) was the most common AE in the placebo IV group and occurred more frequently than in the risankizumab 600 mg IV group.

Table 53: Most frequent adverse events reported in ≥5% of subjects - Placebo-Controlled 12-Week Induction Period Safety Analysis Set

MedDRA 23.1 Preferred Term	RZB 600 mg IV N=620	Placebo IV N=432
Subjects with any TEAE, n (%) [SSA %]		
Headache	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
CD	[redacted]	[redacted]

Abbreviations: IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; RZB, risankizumab; SSA, study size adjusted; TEAE, treatment-emergent adverse event.
Source: Risankizumab Summary of Clinical Safety (132).

AEs of special interest

Pooled analysis of AESIs, namely serious infections, active tuberculosis, lymphoma, hypersensitivity and skin reactions, for the induction trials are presented in Table 54.

As there is only one maintenance trial for risankizumab safety data, FORTIFY (Sub-Study 1), there are no pooled AESI results to present for maintenance risankizumab. AESIs for the main safety population for maintenance risankizumab is presented in Section B.2.10.2.2, Table 51.

During the induction period (Placebo-Controlled 12-Week Induction Period Safety Analysis Set) and the maintenance period (FORTIFY Safety Population), percentages and rates AESIs were generally comparable between the risankizumab induction (risankizumab 600 mg IV) and maintenance (risankizumab 360 mg SC) groups and placebo groups (Table 54 and Table 51). Notable differences include a higher rate of serious infection reported in the placebo group versus the risankizumab 600 mg IV

group during the induction period ([redacted]% vs [redacted]%). For the maintenance phase, the rate of serious infections was similar between the risankizumab 360 mg SC and placebo SC groups.

Table 54: Overview of treatment-emergent adverse events of special interest - Placebo-Controlled 12-Week Induction Period Safety Analysis Set

n (%) [SSA %]	RZB 600 mg IV N=620	Placebo IV N=432
Serious infections	[redacted]	[redacted]
Active tuberculosis	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
Injection site reactions†	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]

Abbreviations: IV, intravenous; RZB, risankizumab; SSA, study size adjusted.
Source: Risankizumab Summary of Clinical Safety (132).
† Injection site reaction area of safety interest category contains infusion-related PTs.

B.2.11 Ongoing studies

In addition to the Phase III pivotal trials (ADVANCE, MOTIVATE, FORTIFY), a further OL head-to-head study is underway (SEQUENCE, M20-259; the estimated primary completion date is September 2023) to demonstrate the clinical effectiveness of risankizumab versus ustekinumab when sequenced after TNF-alpha inhibitor therapy for the treatment of CD (133).

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Approximately 50% of people with moderate-to-severe CD do not respond to, or cannot tolerate conventional treatment (46). Biologic therapies offer an option for treating these individuals; however, these treatments may be associated with a loss of response. Up to 30% of individuals do not respond to TNF-alpha inhibitor therapy (primary non-responders) and almost half of individuals who experience a benefit with these drugs will lose clinical benefits within the first year, requiring dose escalation or therapy change (secondary loss of response) (83). Other biologic therapies with different mechanisms of action are also associated with a primary loss of response,

with a loss of response rate of approximately 30% at 52 weeks reported for vedolizumab (integrin α4β7 inhibitor) and ustekinumab (IL-12/23 inhibitor) (92, 94).

From a safety perspective, TNF-alpha inhibitors are associated with an increased risk of malignancy and infection, including tuberculous infection (83, 89, 92). In order to prevent immunogenicity, a high percentage of individuals treated with TNF-alpha inhibitors are on combination therapy, often for long periods of time (e.g., IMM and corticosteroids), leading to an increased risk of developing severe infections and cancer, including lymphoma and non-melanoma skin cancer (101, 134-136). These issues highlight the need for the development of new treatment modalities for people with moderately to severely active CD, both with and without prior biologic treatment failure.

Risankizumab is a new class of biologic with a novel mode of action that selectively targets IL-23 which provides an additional biologic therapy option for the management of individuals with CD. Based on the innovative nature of risankizumab and potential to address an unmet clinical need for patients it was granted a Promising Innovative Medicine (PIM) designation by the MHRA in November 2021. Risankizumab subsequently received an Early Access to Medicines Scheme (EAMS) positive final scientific opinion from the MHRA in April 2022 for the treatment of moderately to severely active CD in both adult patients and adolescent patients (aged 16-17 years) who have had an inadequate response, lost response or are not suitable for currently licensed treatments.

Efficacy of risankizumab

The clinical benefits of risankizumab versus placebo have been demonstrated in two pivotal induction studies (ADVANCE and MOTIVATE) and one pivotal maintenance study (FORTIFY). The risankizumab CD studies are the first Phase 3 induction trials completed in CD to include the novel and stringent co-primary endpoints of clinical remission, using both the traditional CDAI score and the newer patient reported outcomes of SF and APS, and endoscopic response. Co-primary endpoints are novel to IBD; they represent a stringent combination of clinical symptom and endoscopic endpoints which ensure that clinical improvement is accompanied by an objective improvement of the gut mucosa which is important to achieve in CD and is associated

with improved long-term outcomes (e.g., reduced risk of relapse, decreased hospitalisations rates, steroid-free remission, and fewer bowel resections) (77, 78, 137). However, co-primary endpoints are a more difficult target to achieve when compared with a single primary outcome.

These endpoints reflect a paradigm shift in CD treatment where demonstrable healing of the mucosa, as assessed through endoscopy is associated with improved long-term outcomes (previously described), is now considered a major treatment objective in clinical trials and clinical practice (29, 138, 139). In addition, current guidance by the BSG recognises the importance of different treatment goals, with a recent focus on endoscopic outcomes, such as mucosal healing (absence of macroscopic mucosal inflammation or ulceration), in addition to controlling clinical symptoms (35). The endpoints assessed within and the subsequent results obtained from ADVANCE, MOTIVATE and FORTIFY align with these emerging treatment goals.

The results from the ADVANCE and MOTIVATE induction studies support the use of risankizumab 600 mg IV as either a biologic therapy for people with moderate-to-severe CD who have failed or are unsuitable for conventional care, or those that have already failed one or more biologics. Overall, risankizumab 600 mg IV was superior to placebo for the co-primary endpoints of CDAI clinical remission and endoscopic response for both the US and OUS protocols.

The majority of key secondary endpoints were statistically significant for risankizumab 600 mg IV versus placebo, symptomatic improvements seen as early as Week 4 and mucosal improvement measured by SES-CD observed at Week 12. Clinical response and clinical remission (defined by CDAI) were seen at Week 4, with statistically significant differences observed for the risankizumab 600 mg IV versus placebo. Continued improvements in CDAI clinical response were seen at Week 12, with greater efficacy and treatment differences relative to those at Week 4. Endoscopic remission at Week 12 was statistically significant in the risankizumab 600 mg IV arm versus placebo. As early as Week 12, approximately 1 in 5 subjects treated with risankizumab achieved the stringent endpoint of endoscopic remission; these results are indicative of the early endoscopic improvement associated with risankizumab treatment.

The results from the maintenance study (FORTIFY) support continued maintenance treatment with risankizumab 360 mg SC in subjects with clinical response to risankizumab IV induction treatment. The co-primary endpoints of CDAI clinical remission and endoscopic response met statistical significance for the risankizumab 360 mg SC arm.

Importantly, approximately 29% of subjects achieved the composite endpoint of deep remission (CDAI clinical remission [CDAI <150] and endoscopic remission [SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer]) after maintenance treatment with risankizumab compared with placebo (10%). Control of clinical symptoms and endoscopic outcomes, such as mucosal healing, are recognised as important targets for treatment of CD by the BSG (35). These outcomes are associated with improved long-term outcomes, including reduced risk of disease progression, surgery or hospitalisation (77, 78, 137). Additionally, maintenance with risankizumab 360 mg SC was associated with a greater rate of steroid-free clinical remission and steroid-free endoscopic remission and response when compared with the placebo SC arm at Week 52 (Appendix M). These results suggest that risankizumab may facilitate reduced corticosteroid use which may be beneficial to individuals with CD given the harmful side effects of long-term corticosteroid use (140).

Durable treatment effect

Evidence from across the pivotal CD trials indicates that risankizumab has a durable treatment effect in subjects with biologic inadequate response/intolerance (Bio-IR) or inadequate response/intolerance to conventional therapy (non-Bio-IR).

A substantial proportion of the subjects enrolled in the ADVANCE and MOTIVATE induction studies were treatment refractory, with 30% and 52% of subjects, respectively, having failed more than one previous biologic therapy. The risankizumab studies enrolled a more refractory population when compared with the other recently licensed biologic therapies, ustekinumab and vedolizumab.

Furthermore, the average disease duration was 9 and 12 years in ADVANCE and MOTIVATE, respectively. As CD is a progressive disease and disease duration

correlates with accumulated bowel damage, the disease duration of subjects in the risankizumab studies further indicates the refractory nature of the populations enrolled (141). In addition, the use of centrally read endoscopic criteria for subject inclusion in the risankizumab studies (as compared with reliance on only clinical criteria for study entry [e.g., CDAI]) may have resulted in the inclusion of subjects with greater disease severity.

For induction (ADVANCE) and maintenance (FORTIFY) treatment with risankizumab, treatment effects were observed in Bio-IR and non-Bio-IR subjects, with treatment effects higher in the non-Bio-IR population as expected due to the treatment-refractory nature of the Bio-IR population (e.g., in ADVANCE, 42.5% and 48.9% of Bio-IR and non-Bio-IR subjects, respectively, achieved primary endpoint of CDAI clinical remission and endoscopic response). Another key feature of the risankizumab CD studies was the enrolment of subjects aged 16–17 years. This populations' current choice of biologic therapies is limited to TNF-alpha therapies. Although the proportion of subjects aged 16–17 years enrolled across the studies was low at approximately 1%, this is broadly reflective of the proportion seen in UK clinical practice, according to expert clinical opinion (80). The evidence from the risankizumab CD studies has exhibited signs of efficacy and safety in subjects aged 16–17 years, and based on expert clinical opinion (80), the 16–17-year-old population was expected to have similar treatment response to an adult population if both populations have the same treatment history (i.e., bio-naïve or treatment refractory). Consequently, it can be expected that risankizumab will have similar clinical outcomes in the 16–17-year-old population as the adult population. Currently, only TNF-alpha inhibitors are licensed for use in 16–17-year-old population; a different class of biologic therapy for these individuals would provide an important treatment option. An epidemiology study in the UK indicated that the incidence of CD is increasing in people aged <17 years of age, which further underlines the need for additional treatment options in this population (48).

Safety of risankizumab

Induction with risankizumab 600 mg IV for 12 weeks (Induction Period 1) was generally well tolerated. In both ADVANCE and MOTIVATE, the overall incidence of AEs during

the 12-week induction period was similar among all treatment arms. The rates of SAEs, severe AEs and AEs leading to discontinuation were numerically higher in the placebo IV arm, with most events related to underlying CD. These results are due to the impact of uncontrolled disease as a result of subjects not receiving any active treatment (other than the permitted background treatments [which includes immunomodulator therapies], see Section B.2.3). Across both studies, the most frequently reported AEs in ≥5.0% of subjects in the risankizumab 600 mg IV arm were headache and nasopharyngitis, whereas the most common AEs in the placebo IV arm were CD (worsening of CD), abdominal pain, nausea, and headache.

Additionally, risankizumab 360 mg SC as maintenance treatment for 1 year was generally well tolerated. The most common AEs (≥5.0%) in the risankizumab 360 mg SC arm was CD (worsening of CD), nasopharyngitis, arthralgia, headache, abdominal pain, and nausea. The percentage of subjects with SAEs and AEs leading to discontinuation were comparable in risankizumab 360 mg SC and placebo SC (withdrawal) arms. Across the induction and maintenance studies, no new safety risks were identified, and the overall safety profile was consistent with the known safety profile of risankizumab.

Based on the limited number of anti-drug antibody-positive subjects, no apparent impact of immunogenicity on risankizumab exposure was observed (see Appendix M). The occurrence of anti-drug antibody-positive subjects in individuals treated with risankizumab 360 mg SC maintenance therapy was 0.9%. The anti-drug antibodies associated with risankizumab were not associated with changes to clinical response, similar to that observed for ustekinumab (90). This compares favourably with vedolizumab, where anti-drug antibodies are associated with increased clearance of vedolizumab and lower rates of clinical remission, and TNF-alpha inhibitors, where anti-drug antibodies are associated with a loss of response (89, 97). The rates of anti-drug antibody development with TNF-alpha inhibitors are high and, consequently, are often given in combination with immunosuppression (e.g., thiopurines) to prevent anti-drug antibody formation (98). TNF-alpha inhibitor anti-drug antibody rates of 28.5% and 62.8% have been reported for adalimumab and infliximab, respectively (98). Additionally, the use of thiopurines is associated with a risk for the development of lymphoma, non-melanoma skin cancer and severe infections (98). Furthermore,

combination therapy of TNF-alpha inhibitors and IMMs alters the safety profile of therapy and is associated with a higher risk of opportunistic infection and neoplasms such as lymphoma and non-melanoma skin cancer (142).

For AEs of special interest (serious infections, active tuberculosis, lymphoma, hypersensitivity, and injection site reaction), rates were generally comparable for the risankizumab induction (risankizumab 600 mg IV) and maintenance doses (risankizumab 360 mg SC) versus placebo. Notable differences include a higher rate of serious infection reported in the placebo group versus the risankizumab 600 mg IV group in the during the induction period ([redacted]% vs [redacted]%). For the maintenance phase, the rate of serious infections was similar between the risankizumab 360 mg SC and placebo SC groups (4.5% vs 3.8%). There were no cases of lymphoma recorded in the risankizumab induction or maintenance phase.

Indirect and mixed treatment comparisons

In the absence of head-to-head RCT between all comparators specified in the NICE scope, a series of NMAs were performed to assess the relative efficacy of risankizumab compared with relevant comparators (adalimumab, infliximab, ustekinumab, vedolizumab) in people with moderate-to-severe CD in CCF and BF populations. Risankizumab was found to have broadly comparable efficacy with the rest of the comparators in the NMA, with the exception of placebo, where risankizumab was superior. The NMA results for the CCF population generally show comparable efficacy for risankizumab versus other comparators, and the results for the BF population generally favour risankizumab. The results of the NMA remained consistent regardless of the NMA model type used (i.e., FE or RE model). (Note that the comparison with vedolizumab was not a head-to-head as this NMA was performed as two separate networks as explained in Section B.2.9.1).

Overall, the NMA results suggest that risankizumab is comparable with other biologics across most clinically relevant outcomes, in both CCF and BF patients.

Conclusion

Based on the evidence presented, risankizumab for the treatment of moderate-to-severe CD fulfils unmet medical needs in CD by providing a novel class of biologic

treatment for people with moderately to severely active CD with or without prior biologic therapy failure. Risankizumab is associated with significant symptomatic, clinical and mucosal improvements from as early as Week 4 versus placebo, with similar improvements observed over the 52-week SC maintenance phase. Across the induction and maintenance studies, risankizumab was well tolerated and no new safety risks were identified. In addition, the overall safety profile was consistent with the known safety profile of risankizumab.

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

B.2.12.2.1 Internal validity

ADVANCE, MOTIVATE and FORTIFY were large, multinational, placebo-controlled, well-conducted and methodologically robust studies. The study entry criteria were relevant and appropriate. The risankizumab CD study programme enrolled a total of [redacted] subjects at [redacted] UK centres, with UK subjects representing [redacted]%, [redacted]% and [redacted]% of the study populations in ADVANCE, MOTIVATE and FORTIFY, respectively.

The studies were placebo-controlled, as mandated by the Food and Drug Administration and EMA. The placebo design is similar to other recently approved biologics for moderate-to-severe CD, and this design facilitates indirect treatment comparison with multiple other comparator treatments through the placebo arms. Additionally, conventional care (i.e., immunomodulators, corticosteroids) was permitted in both the risankizumab and placebo treatment arms in the risankizumab CD trials, in line with the expected use of risankizumab in UK clinical practice. In line with anticipated licensing, risankizumab may be used in addition to conventional care; therefore, a placebo arm was used to estimate the added benefit of risankizumab on top of conventional care for moderate-to-severe CD.

The baseline demographics and clinical characteristics of subjects were well balanced between the treatment groups in each trial and were generally similar across studies. Across studies, the disease severity baseline characteristics were reflective of moderately to severely active CD (based on CDAI, SES-CD, SF, and AP scores).

The co-primary efficacy endpoints included endoscopic response. The risankizumab CD studies are the first Phase 3 induction trials completed in CD to include the co-primary endpoints of clinical remission, using both the traditional CDAI score and the newer patient reported outcomes of SF and APS, and endoscopic response. These endpoints reflect a paradigm shift in CD treatment where endoscopic healing, a target associated with improved long-term outcomes, is now a primary treatment objective (35, 74, 75).

A limitation of the FORTIFY maintenance study is the re-randomised responder-withdrawal design (which was also a limitation of pivotal maintenance trials for other biologic therapies approved for CD (104, 105)), where subjects with previous exposure to risankizumab in the induction studies could be randomised to the placebo SC arm in FORTIFY.

Due to the long elimination half-life of risankizumab, placebo SC (withdrawal) subjects in the maintenance study showed measurable declining risankizumab serum exposures from the previous IV induction treatment at Week 16 (drug serum concentrations at Week 16: risankizumab 360 mg SC [7.75 µg/mL] vs placebo SC withdrawal [2.07 µg/mL]) (107). As a consequence, the maintenance placebo SC (withdrawal) arm contains subjects who achieved clinical response to risankizumab IV induction but were subsequently treated with placebo plus permitted conventional therapies in FORTIFY. Consequently, there was prolonged efficacy observed in the placebo SC (withdrawal) arm for symptomatic endpoints in the maintenance study, with approximately 40% of subjects meeting the clinical remission (per CDAI or SF/APS) endpoints at Week 52. However, fewer subjects in the placebo SC (withdrawal) arm met the objective endoscopic (SES-CD scores) and biomarker endpoints (i.e., high-sensitivity C-reactive protein [hs-CRP] and fecal calprotectin [FCP]) at Week 52 compared with subjects in the risankizumab 360 mg SC arm. This is further supported by IL-22 concentrations (a potential pharmacodynamic biomarker of IL-23 activity, with lower levels of serum IL-22 indicative of IL-23 activity (143)) at Week 52, which remained below those at induction baseline indicating a residual pharmacodynamic effect. In addition, SES-CD scores and hs-CRP and FCP levels increased over time (from Week 0 to Week 52) for the placebo SC (withdrawal) arm,

whereas subjects who continued to receive risankizumab 360 mg SC maintenance therapy experienced decreases in these objective markers (Appendix M).

These results indicate that prior exposure to risankizumab during the induction study was a likely contributor to treatment response in the placebo SC (withdrawal) arm during the maintenance study and is supported by the observed increase in endoscopic inflammation and inflammatory biomarkers over time in the placebo SC (withdrawal) arm.

Another limitation of the maintenance study design is that subjects randomised to receive maintenance treatment could have received risankizumab 1,200 mg IV in the induction studies; this dose will not be licenced based on the current anticipated licencing for risankizumab (proposed induction dose is risankizumab 600 mg IV).

B.2.12.2.2 External validity

The evidence base for risankizumab reflects the proposed licensed indication and anticipated use in clinical practice in the UK.

The overall subject populations of the induction (ADVANCE, MOTIVATE) and maintenance (FORTIFY) studies were similar with regard to demographic and key disease characteristics and considered to reflect UK clinical practice according to expert clinical opinion (80). While there were some populations with certain disease characteristics which were excluded from the trial (i.e., subjects with stomas), exclusion of such populations is common in CD clinical trials.

A limitation of the co-primary endpoints is that the measures of clinical response (either CDAI or PRO [SF/APS]) are not commonly used in UK clinical practice. However, these measures were chosen as they are commonly used in clinical trials for CD and permit indirect treatment comparisons (i.e., NMA) with trials of other biologic therapies for CD. In the UK, different measures of response are used (i.e., the Harvey Bradshaw Index [HBI]) as they are more suited to clinical practice (47, 92, 97, 114). While not commonly used in UK clinical practice, both the CDAI and PRO (SF/APS) measures utilise similar items for disease assessment when compared with the HBI. The HBI is based on a simplified version of the CDAI, and shares several common items for

disease measurement (32). In addition, both of the items required for PRO (SF/APS) (stool frequency and abdominal pain) are items assessed in the HBI (34).

The risankizumab CD trials included treatment arms with different doses of risankizumab, however, only results for the risankizumab doses which are expected to be licenced for use in UK clinical practice (RISA 600 mg IV and RISA 360 mg SC) are presented in this submission. Additionally, it should be noted that subjects in the maintenance study FORTIFY could have received a non-licensed RISA dose (1,200 mg IV) during the induction studies.

A key strength of the risankizumab CD studies included the enrolment of subjects which were representative of people with moderate-to-severe CD seen in current UK clinical practice in terms of concomitant medication use and prior biologic therapy failure. To date, all approved biologics have been studied in a conventional therapy failure population and/or a single or multiple TNF-alpha inhibitor failure population (89, 92, 113, 114). The ADVANCE, MOTIVATE, and FORTIFY studies differentiated from these studies by also including subjects who may have failed ustekinumab and/or vedolizumab, or conventional therapy (corticosteroids and immunosuppressants) only. Subjects in the risankizumab CD studies could have failed multiple biologics with different modes of action (subjects would have been grouped in the Bio-IR population). Based on expert clinical opinion (80), the enrolled subjects are reflective of people with moderate-to-severe CD observed in current clinical practice. These subjects would have comprised the Bio-IR populations in risankizumab CD studies. As a consequence of the eligibility criteria, the risankizumab CD studies enrolled a substantial number of treatment refractory subjects (subjects with >1 prior biologic failure, Section B.2.3.3) which are recognised as a hard-to-treat population and have reduced biologic therapy options due to prior failure.

Additionally, based on expert clinical opinion (80), the two main subpopulations in the risankizumab CD studies, Bio-IR and non-Bio-IR, are broadly representative of populations seen in UK clinical practice, namely those with prior biologic therapy experience (BF population) and those with no prior biologic therapy experience (CCF population), respectively.

Both generic (EQ-5D-5L) and disease-specific measures of HRQoL were used (IBDQ Total Score) in the risankizumab CD studies. However, only EQ-5D outcomes were used in the cost-effectiveness model. While this measure is not designed to be disease specific and thus may not capture nuanced disease effects on QoL, it does provide direct trial data which can be imputed directly into the model (i.e., mapping would be required to get scores from other disease-specific QoL measures before imputation into the model) and follows the recommended approach of NICE methods guide (144).

It must be noted that the percent of subjects with exposure, including intolerance or inadequate response, to ustekinumab was planned to be no more than 20% in the risankizumab induction studies (ADVANCE and MOTIVATE). Despite this limit, the biologic therapy history of the subjects enrolled in the risankizumab induction and maintenance trials was consistent with that seen in UK clinical practice, as determined by expert clinical opinion (80).

As the risankizumab CD studies were placebo-controlled rather than active-controlled, there is no direct comparative evidence for risankizumab versus other biologic therapies for moderate-to-severe CD. Consequently, indirect treatment comparisons are required using an NMA. While NMA is a common method for simultaneous comparison of interventions that have not been directly compared in a head-to-head study, there are certain limitations including heterogeneity in the studies being compared. For the NMA presented in this submission, heterogeneity across the included studies included induction duration, prior biologic therapy exposure (i.e., fewer biologic therapy options were available when earlier trials were conducted), outcomes measures used, and reporting of efficacy and safety outcomes (specifically the use of pooled results for different biologic therapy doses and pooled results for safety estimates). Additionally, there was a sparse network of trials for the analyses in the NMA, specifically for efficacy outcomes.

A limitation of the maintenance NMA results is the different placebo rates observed in the comparator trials. The pharmacodynamics and pharmacokinetics of these biologic therapies, including their half-life and long-term effects on the pathological process, are different, as can be clearly observed by the responders who were randomised to placebo in the maintenance studies (Section B.2.9.3.2). To address this problem, the

risankizumab NMA separated the maintenance network into two networks, grouping risankizumab and ustekinumab together based on criteria used for subject entry to the maintenance trials and observed placebo effects in maintenance trials. The other biologic therapies (adalimumab, infliximab, vedolizumab) were analysed in a separate network. This approach was taken as this analysis is superior to an unadjusted NMA or an analysis of unadjusted raw treatment effects and has more face validity over methods which rely heavily on imputation or modelling of RCT data inputs. Of note, the latter methods cited were used and criticised in a previous NICE submission of an approved biologic therapy for the management of moderate-to-severe CD and this determined the approach taken for the risankizumab maintenance NMA.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted on 02 February 2022 to identify and assess health economic evaluations, appraise cost-effectiveness evaluations, and examine cost and resource use in CD. The SLR was conducted as per guidance from the Cochrane Handbook for Systematic Reviews of Interventions, Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Healthcare, and Methods for the Development of NICE Public Health Guidance (145). Full details of the SLR search strategy, study selection process and results are presented in Appendix G. In total, 7 records were identified which reported cost-effectiveness analyses conducted from a UK healthcare system perspective and are therefore considered to be relevant to clinical practice in England. These studies are presented in Table 55.

Table 55: Summary of published UK-based cost-effectiveness studies

Study, year (reference)	Summary of model	Population (mean age, years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Bodger et al. (2009) (146)	CEA (Markov model) • Comparison 1: IFX (1-year) vs CC • Comparison 2: IFX (2-year) vs CC • Comparison 3: ADA (1-year) vs CC • Comparison 4: ADA (2-year) vs CC Country: UK Currency (cost year): GBP (2006/2007) Perspective: UK NHS perspective Time horizon: Lifetime	Adults with moderately to severely luminal active CD	Mean QALYs (SD): • **Comparison 1**: 14.568 (0.076) vs 14.209 (0.105) • **Comparison 2**: 14.901 (0.075) vs 14.209 (0.105) • **Comparison 3**: 14.682 (0.074) vs 14.209 (0.105) • **Comparison 4**: 15.156 (0.075) vs 14.209 (0.105)	Mean costs (SD): • **Comparison 1:** £50,330 (£3,450) vs £43,490 (£4,980) • **Comparison 2:** £58,230 (£3,530) vs £43,490 (£4,980) • **Comparison 3:** £46,730 (£3,410) vs £43,490 (£4,980) • **Comparison 4:** £53,090 (£3,560) vs £43,490 (£4,980)	• **Comparison 1**: £19,050 / QALY gained • **Comparison 2**: £21,300 / QALY gained (£7,900 / 0.333 QALY) • **Comparison 3**: £7,190 / QALY gained • **Comparison 4**: £10,310 / QALY gained (£6,360 / 0.474 QALY) WTP threshold: £30,000 / QALY
Catt et al. (2019) (147)	CEA (decision-analytic model) • IFX (biosimilar) vs IFX Country: UK Currency (cost year): GBP (2019) Perspective: UK NHS perspective Time horizon: 1 year	People with moderate-to-severe CD who were biologic-naïve	Expected QALYs: 0.803 vs 0.803 QALYs	Expected costs: £18,087 vs £19,176	Inflectra™ vs Remicade®: Dominant WTP threshold: £30,000/QALY
Lindsay et al. (2008) (148)	CEA (Markov model) • IFX vs CC Country: UK Currency (cost year): GBP (2005/2006) Perspective: UK NHS perspective Time horizon: 5 years	People with severe active luminal CD/ fistulising CD with single/multiple draining fistulae, incl. perianal and enterocutaneous fistulae, for ≥3 months	**Severe luminal active CD:** • 2.145 vs 1.959 QALYs **Fistulising CD:** • 2.449 vs 2.247 QALYs	**Severe luminal active CD:** • £31,499 vs £26,627 **Fistulising CD:** • £37,488 vs £31,490	**Severe luminal active CD:** • £26,128/ QALY gained **Fistulising CD:** • £29,752/ QALY gained WTP threshold: £30,000/QALY
Loftus et al. (2009) (149)	CEA • ADA vs non-biologic therapy Country: UK Currency (cost year): GBP (2006) Perspective: UK NHS perspective Time horizon: Lifetime	People with moderate-to-severe CD	**Moderate-to-severe CD:** • 0.8647 vs 0.7743 QALYs **Severe CD:** • 0.8516 vs 0.7339 QALYs **Remission**: 35.5% vs 6.6% **Moderate disease**: 39.7% vs 39.2%	**Moderate-to-severe CD:** • £9,696 vs £6,649 **Severe CD:** • £10,882 vs £8,992	**Moderate-to-severe CD:** • £33,731/ QALY gained • DSA: £17,873 - £57,571/ QALY gained **Severe CD**: • £16,064/ QALY gained • DSA: £5,250 - £34,230/ QALY gained

Study, year (reference)	Summary of model	Population (mean age, years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			Severe disease: 24.2% vs 44.6% **Very severe disease**: 0.6% vs 9.6%		WTP threshold: £30,000/QALY
Robson et al. (2018) (150)	CEA (decision-analytic model) • VDZ vs CC Country: UK Currency (cost year): GBP (2018) Perspective: NHS and PSS perspective Time horizon: lifetime	People with moderate-to-severe active CD who have failed on an TNFi	Confidential vs 13.064 QALYs	NR	**Base case ICER:** • £21,620/ QALY gained **Average probabilistic ICER (95% CI):** • £27,428/ QALY (-£7,883 to £82,947) WTP threshold: £30,000/QALY
Saito et al. (2013) (151)	CEA (decision-analytic model) • IFX + AZA vs IFX Country: UK Currency (cost year): GBP (2008) Perspective: UK NHS perspective Time horizon: 1 year	People aged 25 years old with moderate-to-severe CD who were biologic-naïve and refractory to conventional TNFi therapy	0.668 vs 0.064 QALYs	£8,573.04 vs £6,979.68	£24,917/QALY gained DSA: £17,147 – £45,564/QALY gained WTP threshold: £30,000/QALY
Wilson et al. (2018) (152)	CEA (two-part decision-analytic model (1-year decision tree model + post-1-year Markov model)) • VDZ vs UST Country: UK Currency (cost year): GBP (2017) Perspective: NR Time horizon: 5, 10, 30 years	People with moderate-to-severe active CD who have previously failed TNFi	**5 years:** • 2.348 vs 2.341 QALYs **10 years:** • 3.997 vs 3.980 QALYs **30 years:** • 8.111 vs 8.091 QALYs	Incremental cost savings: • £643 - £1,253	Dominant PSA: Dominant WTP threshold: NR

Abbreviations: ADA, adalimumab; AZA, azathioprine; CC, conventional care; CD, Crohn's disease; CEA, cost-effectiveness analysis; CI, confidence interval; DSA, deterministic sensitivity analysis; GBP, British Pound Sterling; ICER, incremental cost-effectiveness ratio; IFX, infliximab; NHS, National Health Service; NR, not reported; PSA, probabilistic sensitivity analysis; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VDZ, vedolizumab; WTP, willingness to pay.

B.3.2 Economic analysis

The economic SLR (Appendix G) did not identify any cost-effectiveness analyses (CEAs) that included risankizumab as a comparator in CD. Therefore, in this submission, it was necessary to develop a *de novo* economic model to determine the cost-effectiveness of risankizumab versus relevant comparators for the treatment of people with moderate-to-severe CD from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS). To inform the model structure, functionality, assumptions and data sources, previous NICE technology appraisals (TAs) for the treatment of moderate-to-severe CD (i.e., TA352 (47) and TA456 (46)) were used.

B.3.2.1 Patient population

In line with the anticipated positioning of risankizumab based on the treatment pathway of CD in the UK (Section B.1.3.5), the base-case population included [redacted]. The patient populations included in the economic model are aligned with the eligibility criteria for the risankizumab CD pivotal clinical trials ADVANCE, MOTIVATE and FORTIFY (see Section B.2 for more information). The populations were divided into two subgroups:

Conventional care failure (CCF): Patients who had an inadequate response or intolerance to conventional therapy (defined as one or more of the following: aminosalicylates, oral locally acting steroids [e.g., budesonide, beclomethasone], systemic corticosteroids [prednisone or equivalent], or immunomodulators).This population is analogous to the 'Non-Bio-IR' population used in the risankizumab CD clinical trials (see Section B.2 for more information).

Biologic failure (BF): Patients with documented IR or intolerance (either failure to respond to induction treatment, or loss of response to maintenance therapy) to one or more biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab). This population is analogous to the 'Bio-IR' population used in the risankizumab CD clinical trials (38-40).

In addition to the definitions and assumptions described above, clinicians at an expert advisory board (80) also concluded that the non-Bio-IR and Bio-IR populations in the risankizumab CD clinical trials are analogous to the CCF and BF populations, respectively.

The model utilised data from the risankizumab CD clinical trials for several model inputs. Data from the ITT1A primary efficacy analysis sets of ADVANCE/MOTIVATE (patients from Induction Period 1 for both induction studies) and FORTIFY were used throughout the cost-effectiveness model (CEM) for baseline characteristics and efficacy outcomes. Safety data were obtained from the SA1A analysis sets of ADVANCE and MOTIVATE, which included all patients who received at least 1 dose of study medication during the 12-week induction period.

B.3.2.2 Model structure

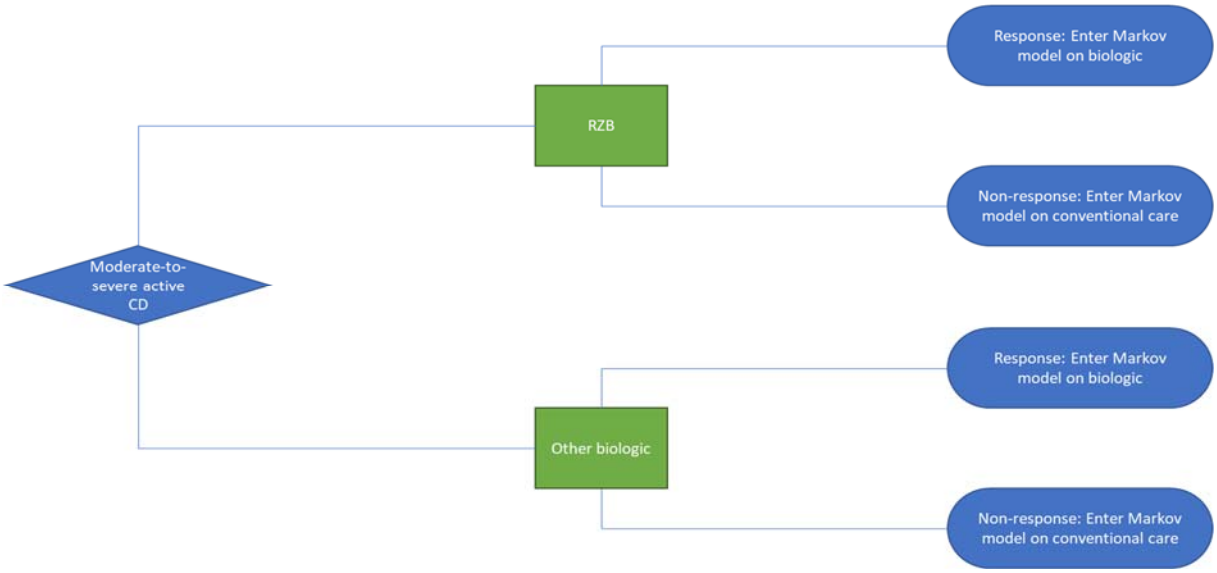
The CEM was developed in Microsoft® Excel (Microsoft, Washington, USA, 2022), using Visual Basic for Applications (VBA) functionality to determine the cost-effectiveness of risankizumab versus relevant comparator treatments in the management of moderately to severely active CD over a lifetime horizon. The modelling framework comprised two separate parts. The first part was a decision tree that reflects the induction period of treatment. The second part included four Markov model matrices that estimated the long-term course of CD including maintenance therapy and post-maintenance phases using clinical trial data (further described in Section B.3.2.2). The model parameter 'maximum treatment duration (in weeks)' determined when patients were universally discontinued from biologic therapy and occurred for long-term responders (defined as a 1-year response duration in the base-case analysis). This parameter reflects clinical practice and NICE guidance, which states that patients should be re-assessed at 12 months to determine whether continuing with biologic treatment is appropriate (53). An additional model parameter governed the duration of the 'post-maintenance response', which was residual treatment effect from previous biologic exposure after biologic discontinuation. This was defined as one year in the base case analysis; a scenario analyses explored a 6-month residual treatment effect duration.

B.3.2.2.1 Induction period decision tree

As illustrated in the decision tree schematic (Figure 12), patients with moderate-to-severe CD who were refractory to conventional care (CC) or a previous biologic treatment entered the decision tree when they were either treated with induction risankizumab or an alternative biologic (e.g., ustekinumab, vedolizumab). Efficacy outcomes were assessed at the end of induction, while costs were incurred from the start of induction. Note that induction periods differed in length based on the respective biologic therapy (e.g., 12 weeks for risankizumab

compared with 8 weeks for ustekinumab) and these differences in duration were reflected in the model.

Figure 12: Decision tree structure: Induction phase



Abbreviations: CD, Crohn's disease; RZB, risankizumab.
Note: Squares represent decision nodes, circles are chance nodes, and triangles are termini of the decision tree. The baseline of the induction trials is aligned with the model baseline, which occurs at the first square (decision node) on the left in the figure above.

At the end of induction, patients transitioned to the Markov model. Response status at the end of the induction phase was based on CR-100 (a response is determined by a ≥100-point drop in CDAI score from baseline to end of induction), with the response input for each treatment derived from the induction NMA (see Section B.2.9). Although different response criteria were used across the included trials, the model base-case analysis assumed the CR-100 criterium of response to treatment (a similar approach was taken in the ustekinumab and vedolizumab NICE submissions [the most recent submissions in CD] (46, 47)). Induction phase responders continued to be treated with a biologic maintenance regimen unless they required a dose escalation or discontinued therapy, while non-responders switched to CC. This was a simplifying assumption, as per the ustekinumab and vedolizumab NICE submissions (46, 47), and had no incremental impact on model results as it was equal for all comparators. In clinical practice, it is unlikely that patients who did not respond to a biologic therapy would receive CC, and instead would be prescribed another biologic therapy or surgery; however, no sequence data were available. In addition, the choice for which biologic will be used will depend on many factors (e.g., patient) and as such there is no 'standard' sequence. As a result, the model does not seek to model treatment sequences and instead compares biologic monotherapies.

B.3.2.2.2 Maintenance and post-maintenance Markov model

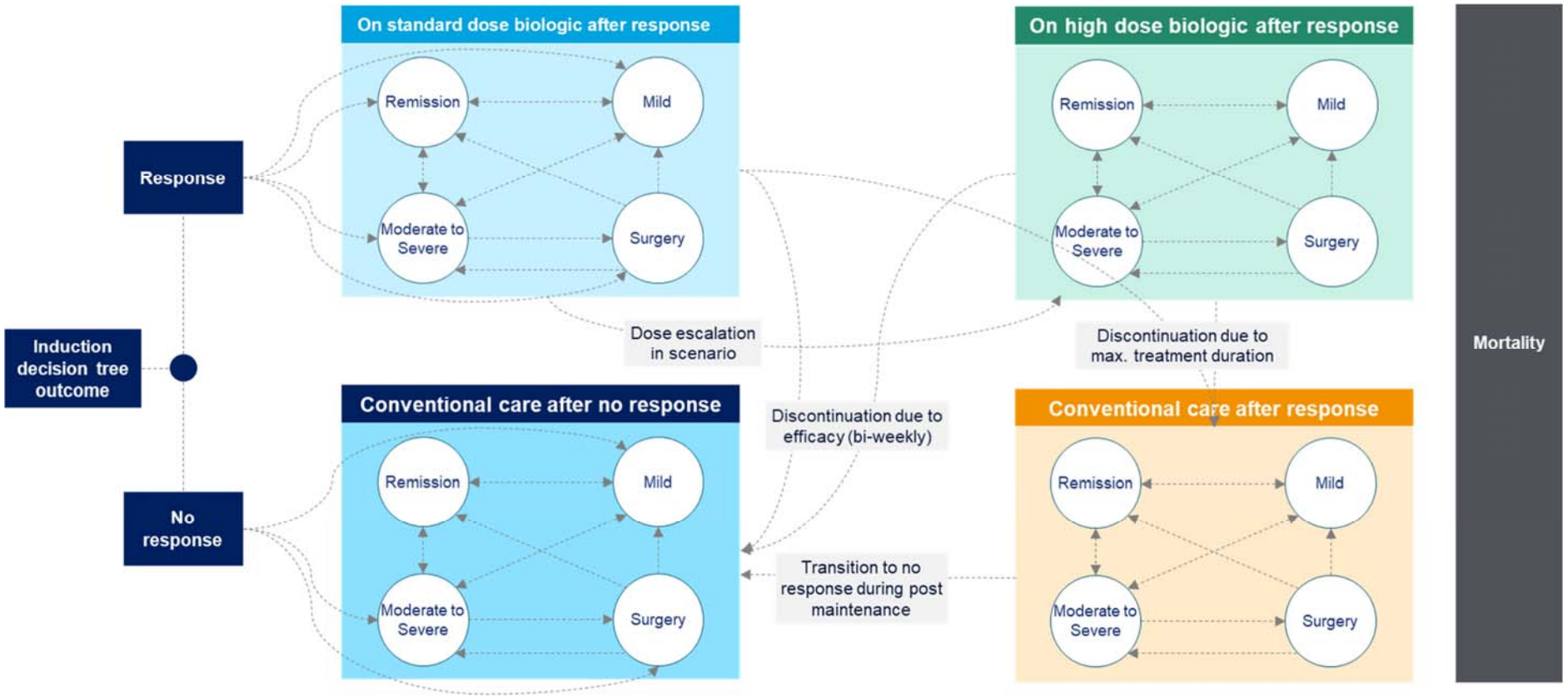
At the end of the induction decision tree, patients entered the maintenance Markov model. The length of each Markov cycle was two weeks, while the model time horizon was the expected maximum lifetime for the model cohort (60 years starting from a mean age of 38.83 for the CCF population and 38.22 for the BF population; mean age was based on risankizumab trial data [Section B.2.3.3]). Biologic treatment duration was assumed to be one year, and the model used a half-cycle correction to account for the fact that events and transitions could occur at any point during the cycle (see Section B.3.9.2 for a summary of all model assumptions).

In each cycle, patients faced one of four sets of transition probability matrices (described in Section B.3.2.2.2.1) that were based on their response status to induction therapy, biologic maintenance dose and whether they had discontinued biologic therapy (Figure 13). The maintenance phase ends and the post-maintenance phase begins when all patients, including responders, are discontinued from biologics.

The arrows in Figure 13 represent the possible transitions between health states. Within the Markov model, there were four health states and an absorbing mortality state. Three states (and 'Death') assumed no possibility of surgery and are based on CDAI scores: a) 'Remission' (CDAI <150); b) 'Mild CD' (150 ≤ CDAI < 220); and c) 'Moderate to severe CD' (220 ≤ CDAI < 600). The arrows in Figure 13 demonstrate the possible transitions between health states. Patients could transition between the CDAI-based health states in any cycle or remain in their current state. Patients could also transition to the mortality health state at any time. The model used all-cause mortality rates and did not apply different mortality rates dependent on health states.

The model assumed that only patients with moderate-to-severe CD could have undergone surgery; surgery was only possible for patients in the surgery state. After surgery, patients were assumed to stay in a 'post-surgery' tunnel state for 8 weeks (2 weeks of surgery and 6 weeks of post-surgery), where they experienced surgery-related disutilities and costs. After the 8-week period, assuming no mortality, patients transitioned back to one of the CDAI-based health states. The health-state transition model used the structure published in Bodger et al. (2009) (146), also used in the ustekinumab CD and vedolizumab CD NICE submissions (46, 47).

Figure 13: Long-term model structure: Maintenance and post-maintenance phases



Notes: Patients may remain in the health state in which they began a cycle. Surgery includes one surgical (2 weeks) and three post-surgical tunnel (6 weeks) states, such that a surgical episode lasts 8 weeks. Patients may transition to death at any time.
*Dose escalation in the base case only affects patient biologic costs; Patients do not transition to the high-dose matrix as they have failed standard-dose treatment and therefore escalate to achieve standard-dose efficacy. The same assumption was applied to those patients' requiring initiation with the high dose of ustekinumab as the higher dose is administered where a patient is expected to not respond adequately to the standard dose (80).

B.3.2.2.2.1 Overview of Markov matrices for maintenance and post-maintenance periods

Transition probabilities were a function of which of the four sets of matrices they were in, which was in turn a function of which treatment they had received and whether they had a response at the end of induction. Patients who discontinued biologics, based on the maintenance trial discontinuation rates, transitioned to the CC Markov matrix, which included CC-based transition probabilities.

Markov matrices were estimated using ordered probit models informed by primary patient data from the risankizumab CD clinical trials following the principles outlined in NICE DSU 2 (page 29 onwards) (122). The use of ordered probit models allowed for the estimation of transition matrices without having to rely on additional assumptions beyond those used in specifying the model (ordered probit models are suitable for the modelling of outcomes with natural ordering; an ordered probit model was recently used in NICE TA480 (153)). The methods used are described in detail in Section B.3.3.3.3. These matrices were calibrated for each comparator by changing the remission-mild cutpoint in the ordered probit model estimated for risankizumab so that the predicted end of maintenance remission rate for patients receiving the respective therapy matches that calculated in the maintenance NMA remission analysis. For example, the ustekinumab Q12W arm in the company model used a calibrated version of the risankizumab ordered probit model to adjust its standard dose on biologic Markov matrix so that its end-of-maintenance remission rate was equal to 61.90% (CrI: 43.41% to 80.25%; see Table 66, Section B.3.3.3) in the CCF population. The ‘maximum treatment duration (in weeks)’ determines when patients were universally discontinued from biologic therapy, and this occurred for long-term responders as described in Section B.3.2.2.

The four sets of Markov matrices patients could enter included:

Standard-dose biologic after response: Patients entered this matrix if they had a CR-100 response at the end of induction and started standard-dose biologic therapy in the maintenance phase. The transition probability matrix was based on analysis of CDAI data over time from the risankizumab 360 mg SC maintenance arm in FORTIFY to reflect

transition probability changes in health states. The transition matrix was used and calibrated using NMA estimates for each standard-dose version of biologic therapy.

High-dose biologic after response: Patients entered this matrix if they had a CR-100 response at the end of induction and started high-dose biologic therapy at the beginning of the maintenance phase. This transition matrix was based on analysis of data from the risankizumab 360 mg SC maintenance arm in FORTIFY for responders and calibrated using NMA estimates for each high-dose version of biologic therapy. In the base case, patients who dose escalate continued to have the same efficacy estimates as those in the standard-dose matrix but with increased costs of more intensive high-dose biologic therapies. The base case assumed that patients who have their dose escalated have lost response to standard-dose biologic treatment and therefore benefited only by retaining average standard-dose efficacy (i.e., an increased dose is required to achieve the same level of response) (80). Therefore, in the model, dose escalation only increased patient biologic costs and did not increase efficacy; the same assumption was applied to those patients requiring initiation with the high dose of ustekinumab (Q8W; assumption was based on expert clinical feedback) (80).

Conventional care after response: Patients entered this matrix after discontinuing biologic therapy due to the 'maximum treatment duration' parameter, which determined when biologic therapy was ended for all responders. This matrix represented patients who responded and continued to respond to biologic therapy but at a certain timepoint, therapy was stopped due to patient, physician or payer intervention. The matrix was based on analysis of CDAI data change over time for patients in the re-randomised placebo SC (withdrawal) arm in FORTIFY (i.e., patients who received risankizumab IV for induction, had a response at the end of the initial 12-week induction period [Induction Period 1] and were subsequently randomised to the placebo SC [withdrawal] arm in the maintenance study). These patients experienced the 'residual treatment effect' and were analogous to risankizumab responders who were discontinued for reasons other than intolerance, primary failure or secondary failure. Patients exited this matrix to the 'Conventional care after no response' matrix when the 'residual treatment effect' was assumed to wear off based on the 'duration of post-maintenance response' parameter (defined as one year in the base case analysis). The 'residual treatment effect' was based on the pharmacokinetic and pharmacodynamic properties of biologic therapies, which may explain the differences in

placebo arm remission rates in the maintenance phase across the different biologic therapies (see Section B.2.9.3.2 doe more details).

Conventional care after no response: Patients entered this matrix to receive CC if: a) they did not achieve a CR-100 response and subsequently started CC therapy, or b) the period in which the 'residual treatment effect' occurs has ended. This matrix was estimated using data from the 'true placebo' group from FORTIFY (IV placebo responders at Week 12 of Induction Period 1 in ADVANCE and MOTIVATE who were assigned to receive maintenance placebo SC in FORTIFY) which consisted of N=24 patients (see Section B.2.3.1 for further details). Patients in the 'true placebo' group were not part of the primary analytical dataset of risankizumab CD trials. Study outcomes for this population are available in Appendix M. Note that this arm is different from the placebo SC (withdrawal) arm in FORTIFY where responders to risankizumab IV induction treatment were re-randomised to placebo SC. This arm represents, as best as possible given the study design, long-term outcomes of patients who are exclusively on CC. One limitation was that the 'true placebo' population in FORTIFY was required to have a clinical SF/APS response, but not a CR-100 response, after induction to continue with placebo SC in the maintenance trial. Consequently, the efficacy of the 'true placebo' arm is likely overstated as it represents patients for whom CC therapy was marginally effective, resulting in achievement of clinical response but not a CR-100 response.

Table 56: Features of the economic analysis for CCF and BF populations

	Previous appraisals		**Current appraisal**	
Factor	**TA352 (47)**	**TA456 (46)**	**Chosen values**	**Justification**
Time horizon	10 years (original), lifetime (revised)	Lifetime	Lifetime (60 years from mean age of 38.83 [CCF] and 38.22 [BF])	Necessary to capture all long-term health benefits and costs of treatments
Treatment waning effect?	Not included	Not included	Not implemented	Lack of clinical rationale and approach used in TA352 and TA456 (the two most recent CD biologic TAs)
Source of utilities	GEMINI 2 and GEMINI 3 trials	UNITI-1, UNITI-2 and IM-UNITI trials mapped to EQ-5D	RZB pivotal RCTs for RZB and all comparators	Most appropriate data source as EQ-5D was assessed in risankizumab RCTs
Source of costs	**Drug costs:** BNF, 2013 **Health-state resource costs:** Bodger et al.	**Drug costs:** MIMS **Health-state resource**	**Drug costs:** BNF 2022 **Health-state resource costs**: TA456 (2017)	TA456 cost data specific to health states used in the model are the most recent data available

	Previous appraisals		Current appraisal	
Factor	**TA352 (47)**	**TA456 (46)**	**Chosen values**	**Justification**
	(2009), clinical expert survey **Surgery and AE costs:** NHS ref costs 2011/12	**costs:** Delphi panel **Surgery and AE costs:** NHS ref costs 2014/15	inflated to 2020/21 values **Surgery and AE costs:** NHS ref costs 2019/20	(46); NHS reference costs used wherever possible

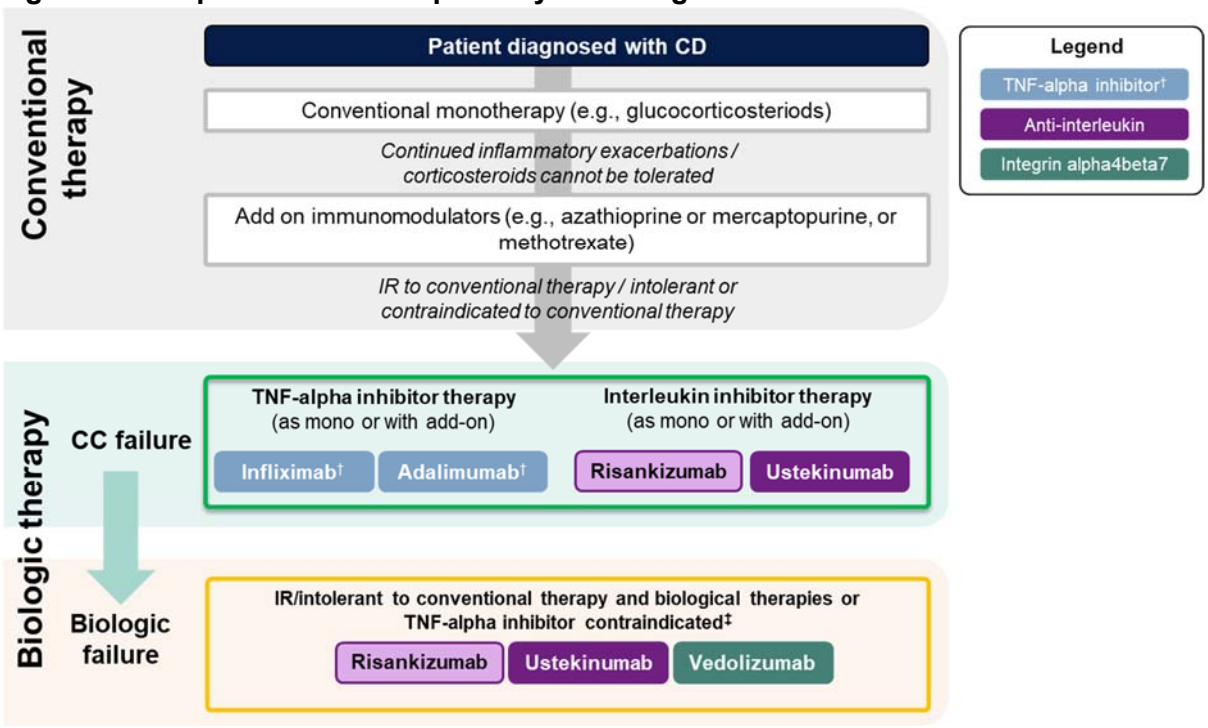
Abbreviations: AE, adverse event; BF, biologic failure; BNF, British National Formulary; CCF, conventional care failure; CD, Crohn's disease; EQ-5D, EuroQol 5 Dimensions health questionnaire; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; RCTs, randomised controlled trials; RZB, risankizumab; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

The intervention of interest was 600 mg IV risankizumab administered as induction therapy during weeks 0, 4 and 8, followed by 360 mg SC risankizumab administered Q8W in the maintenance period. This is in line with the regimen used in the pivotal risankizumab CD clinical trials and the expected licensed indication for risankizumab CD (Appendix C).

The proposed positioning for risankizumab (depicted in Figure 14) is for the treatment of [redacted] (green outline box, Figure 14) [redacted] (yellow outline box). TNF-alpha contraindicated people with CD are considered as part of the BF population in the cost-effectiveness analyses presented in this submission since the majority (69%) of the TNF-alpha contraindicated population were expected to have failed a prior biologic (81), and treatment options were equal to the BF population. This is in line with the approach taken in the previous ustekinumab in CD NICE submission (TA456) (46).

Figure 14: Proposed treatment pathway including risankizumab for CD in the UK



Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor.
Figure adapted from NICE guidance. Source: NICE. Crohn's disease: management (NG129). 2019. NHS England, Clinical Commissioning Policy. 2020. (53). † Biosimilars are also available; The only approved biologic therapy for use in children and adolescents (>6–17 years old) with moderate-to-severe CD (53). ‡ TNF-alpha contraindicated people with CD are considered as part of the biologic failure population, in line with the health economic models (this submission). The majority (69%) of the TNF-alpha contraindicated population were expected to have failed a prior biologic (81) and analyses presented are split between the CC failure and biologic failure populations. Note: For paediatric patients, enteral nutrition or steroids are generally used for mild disease. For severe disease, stronger immunosuppressive add-on therapies, such as azathioprine, are used (82).

The model included CCF and BF populations. TNF-alpha inhibitors (infliximab, adalimumab) and ustekinumab were included in the model for the CCF population. Ustekinumab and vedolizumab were included in the model for the BF population (this also includes any patients who have contraindications or intolerance to TNF-alpha inhibitors). These analyses are in line with current NICE guidance for TNF-alpha inhibitors (infliximab, adalimumab), ustekinumab and vedolizumab (53) (Figure 14).

Conventional care was defined as aminosalicylates, oral locally acting steroids [e.g., budesonide], systemic corticosteroids [prednisone or equivalent], or immunomodulators). Details of the CC therapies and their assumed usage is provided in Table 57. Assumed usage is taken from TA456 (46), which was in turn based on estimates from TA352 which used a mix of treatments comprising conventional therapy from the Royal College of Physicians UK IBD Audit (154). The dosing regimens for biologic comparator therapies are presented in Table 58.

Table 57: Conventional care therapies used in the model and their expected usage

Treatment	Usage weight	Reference
Balsalazide	5.00%	TA456† (46)
Mesalazine	5.00%	
Olsalazine	5.00%	
Sulfasalazine	5.00%	
Budesonide	6.00%	
Prednisolone	19.00%	
Azathioprine	57.00%	
Mercaptopurine	10.00%	
Methotrexate	11.00%	

Abbreviations: TA, technology appraisal.
† Based on the report from the Inflammatory Bowel Disease Audit Steering Group by the Royal College of Physicians (154).

Table 58: Intervention dosing information (UK-approved dosing)

Treatment (reference)	Induction			Maintenance	
	Induction dosing	Induction duration in model (weeks)	Response assessed (weeks)	Maintenance dosing	Maintenance dose escalation
RZB (3, 4)	600 mg IV at weeks 0, 4 and 8	12	12	360 mg SC Q8W from week 12	N/A
UST (90, 92)	6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 and <85 kg: 390 mg; >85kg: 520 mg	8	6 and 8†	90 mg SC Q12W from week 8	90 mg SC Q8W
VDZ IV (89)	300 mg IV at weeks 0, 2 and 6	10	6 and 10‡	300 mg IV Q8W from week 14	300 mg IV Q4W
VDZ SC (89, 155)	300 mg IV at weeks 0, 2 and 6	10	6 and 10‡	108 mg SC Q2W from week 14	N/A
ADA 160/80 biosimilar (113)	160 mg SC at week 0; 80 mg SC at week 2	4	4	40 mg SC Q2W from week 4	40 mg SC QW
ADA 160/80 (113)	160 mg SC at week 0; 80 mg SC at week 2	4	4	40 mg SC Q2W from week 4	40 mg SC QW
ADA 80/40 (113)	80 mg SC at week 0; 40mg SC at week 2	4	4	40 mg SC Q2W from week 4	40 mg SC QW
IFX IV (114)	5 mg/kg IV at weeks 0 and 2	6	2	5 mg/kg IV Q8W from week 14	10 mg/kg IV Q8W
IFX IV biosimilar (97)	5 mg/kg IV at weeks 0 and 2	6	2	5 mg/kg IV Q8W from week 14	10 mg/kg IV Q8W
IFX SC§ (114, 156)	5 mg/kg IV at weeks 0 and 2	6	2	120 mg SC Q2W from Week 6	N/A

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; N/A, not applicable; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; TNF, tumour necrosis factor; UST, ustekinumab; VDZ, vedolizumab.
†Janssen indicates response assessed at weeks 6 and 8, in the model week 8 is used; ‡ Takeda indicates response assessed at weeks 6 and 10, in the model week 10 is used. Note: The biologic labels allow for continued biologic therapy to patients after induction therapy, even for non-responders, for a specified period of time. § For infliximab subcutaneous, only a biosimilar formulation is available but will just be referred to as IFX SC throughout the submission.

B.3.3 Clinical parameters and variables

B.3.3.1 Patient characteristics

Baseline patient characteristics were derived from the risankizumab CD induction trials, specifically from post-hoc analysis of the ADVANCE and MOTIVATE ITT1A populations. Mean and standard deviation of patient age, sex and weight were calculated separately for the CCF and BF populations. Weight category distribution (sample size and percentage) was calculated separately for CCF and BF populations. Weight was an important parameter for weight-based dosing regimens such as ustekinumab. Age and sex determined background mortality rates. Baseline disease severity distribution across mild, moderate and severe was included. Initial health-state severity (sample size and percentage) was calculated for combined CCF and BF populations. Table 59 and Table 60 summarise the general model settings and baseline patient characteristics used in the model, respectively.

Table 59: General model settings used in the economic model

Parameter	Mean	SE	DSA (low; high)	Source/Note
Time horizon (years, until max age of 101)	60	N/A	40; 80	Base is same as TA456 (46), i.e., lifetime (starting age is ~40 years old). Low/high: ± 20 years
Discount rate (costs)	3.5%	N/A	Not used	Base: NICE reference case (157)
Discount rate (utilities)	3.5%	N/A	Not used	

Abbreviations: DSA, deterministic sensitivity analysis; N/A, not applicable; SE, standard error; TA, technology appraisal.

Table 60: Baseline patient characteristics used in the economic model

Parameter	Mean	SE	DSA (Low; high)	Source/Note
CCF baseline demographics (N=359)				
Mean patient age (years)	38.83	0.73	37.40; 40.26	Base/low/high: RZB trial data. Post-hoc analysis of ADVANCE ITT1A population
Mean percent male (%)	54.9	0.03	49.7; 60.0	
Weight (kg)	71.15	0.93	69.33; 72.97	
<55kg (%)	17.8	N/A	100.0; 0.0	Base: RZB trial data. Post-hoc analysis of ADVANCE ITT1A population. Low/high: assumption
>55kg and ≤85kg (%)	65.5	N/A	0.0; 0.0	
>85kg (%)	16.7	N/A	0.0; 100.0	
BF baseline demographics (N=1060)				
Mean patient age (years)	38.2	0.40	37.43; 39.01	Base/low/high: RZB trial data. Post-hoc analysis of ADVANCE and MOTIVATE ITT1A population
Mean percent male (%)	52.5	0.02	49.4; 55.5	
Weight (kg)	71.2	0.59	70.05; 72.35	
<55kg (%)	19.1	N/A	100.0; 0.0	Base: RZB trial data. Post-hoc analysis of ADVANCE and MOTIVATE ITT1A population. Low/high: assumption
>55kg and ≤85kg (%)	61.1	N/A	0.0; 0.0	
>85kg (%)	19.8	N/A	0.0; 100.0	

Abbreviations: BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; DSA, deterministic sensitivity analysis; ITT, intention-to-treat; N/A, not applicable; RZB, risankizumab; SE, standard error.

B.3.3.2 Efficacy inputs

In the model, the efficacy inputs included CDAI response rates (induction only), CDAI remission rates (induction and maintenance), splits between mild and moderate-to-severe CD for patients based on CDAI response at the end of induction, biologic discontinuation rates, biologic dose escalation rates, starting dose of biologic in maintenance, surgery rates, and biologic AE rates. Efficacy inputs in the model were listed for the induction, maintenance and post-maintenance periods, along with their sources. Induction CDAI response and remission rates were derived from the NMA (see Section B.2.9 and Appendix D).

B.3.3.2.1 Induction period efficacy: CDAI-100 response

Induction CR-100 response in CCF and BF populations derived from the NMA are presented in Table 61. The sensitivity analysis inputs used in the deterministic sensitivity analysis (DSA) were based on the CrIs from the NMA. CC rates based on the placebo arms of the biologic trials were also sourced from the NMA.

Table 61: Induction CDAI-100 efficacy inputs based on the NMA

Treatment	Induction dosing (reference)	Responders	CrI, % (low; high)
CCF population			
RZB	600 mg IV at weeks 0, 4 and 8 **(3)**	[redacted]	[redacted]
UST	6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 & <85 kg: 390 mg; >85kg: 520 mg **(92)**	[redacted]	[redacted]
ADA 160/80 / ADA 160/80 biosimilar†	160 mg SC at week 0; 80 mg SC at week 2 **(113)**	[redacted]	[redacted]
ADA 80/40	80 mg SC at week 0; 40mg SC at week 2 **(113)**	[redacted]	[redacted]
IFX IV / IFX IV biosimilar†	5 mg/kg IV at weeks 0 and 2, dose at week 6 for responders **(97, 114)**	[redacted]	[redacted]
IFX SC	5 mg/kg IV at weeks 0 and 2 **(114, 156)**	[redacted]	[redacted]
BF population			
RZB	600 mg IV at weeks 0, 4 and 8 **(3)**	[redacted]	[redacted]
UST	6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 & <85 kg: 390 mg; >85kg: 520 mg **(92)**	[redacted]	[redacted]
VDZ IV	300 mg IV weeks 0, 2 and 6 **(89)**	[redacted]	[redacted]
VDZ SC	300 mg IV at weeks 0, 2 and 6 **(89)**	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CrI, credible interval; DSA, deterministic sensitivity analysis; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.
† Biosimilar formulations are assumed equal to originator drug. Source: NMA described in Section B.2.9.

B.3.3.2.2 Induction period efficacy: CDAI clinical remission

The NMA-derived induction remission rates in CCF and BF populations are presented in Table 62.

Table 62: Induction remission rates (CDAI <150) based on the NMA

Treatment	Induction dosing (reference)	Responders	CrI, % (low; high)
CCF population			
RZB	600 mg IV at weeks 0, 4 and 8 (3)	[redacted]	[redacted]
UST	6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 & <85 kg: 390 mg; >85kg: 520 mg (92)	[redacted]	[redacted]
ADA 160/80 / ADA 160/80 biosimilar†	160 mg SC at week 0; 80 mg SC at week 2 (113)	[redacted]	[redacted]
ADA 80/40	80 mg SC at week 0; 40mg SC at week 2 (113)	[redacted]	[redacted]
IFX IV / IFX IV biosimilar†	5 mg/kg IV at weeks 0 and 2, dose at week 6 for responders (97, 114)	[redacted]	[redacted]
IFX SC	5 mg/kg IV at weeks 0 and 2 (114, 156)	[redacted]	[redacted]
BF population			
RZB	600 mg IV at weeks 0, 4 and 8 (3)	[redacted]	[redacted]
UST	6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 & <85 kg: 390 mg; >85kg: 520 mg (92)	[redacted]	[redacted]
VDZ IV	300 mg IV weeks 0, 2 and 6 (89)	[redacted]	[redacted]
VDZ SC	300 mg IV at weeks 0, 2 and 6 (89)	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CrI, credible interval; DSA, deterministic sensitivity analysis; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.
† Biosimilar formulations are assumed equal to originator drug. Source: NMA described in Section B.2.9.

B.3.3.3 Maintenance efficacy inputs / technical features

B.3.3.3.1 Non-remission patient allocation into mild, moderate to severe health states

At the end of induction, patients who did not achieve remission were allocated into the mild or moderate-to-severe CD health states in the model. Trial data from the risankizumab CD trials were used for risankizumab patient allocation to health states based on the patients who were in response (those in response but not remission have a higher likelihood of being in mild compared with moderate-to-severe disease) and not in response. These distributions were required to provide starting distributions for patients who had not responded following induction. However, these distributions were not reported in the comparator biologic studies. Consequently, all therapies used the distributions from the risankizumab CD trials.

Table 63 includes the proportions of patients who were in moderate-to-severe states by CCF and BF populations who were not in remission, by response status (i.e., who achieved or

did not achieve a response). The proportion of patients with mild disease was estimated using the following calculation:

$$\text{Proportion of mild patients} = 1 - (\text{estimated remission probability from the NMA}) * \text{proportion with moderate to severe disease}$$

For patients who did not achieve response, the mild proportion was estimated as follows:

$$\text{Proportion of mild patients (no response)} = 1 - (\text{proportion with moderate to severe disease})$$

Table 63: Percentage of patients in moderate-to-severe CD health states after induction who are not in remission

Parameter	Percent	SE	DSA (low; high)	Source/Note
Percent of responders remaining moderate-to-severe: CCF population				
Moderate-to-severe (CDAI 220+)	8.4	0.019	4.7; 12.1	Base: RZB trial data. Post-hoc analysis of ADVANCE ITT1A population (158). Low/high: 95% CI
Percent of responders remaining moderate-to-severe: BF population				
Moderate-to-severe (CDAI 220+)	7.8	0.011	5.5; 10.0	Base: RZB trial data. Post-hoc analysis of ADVANCE and MOTIVATE ITT1A population (158). Low/high: 95% CI
Percent of non-responders remaining moderate-to-severe: CCF population				
Moderate-to-severe (CDAI 220+)	71.8	0.042	63.6; 79.9	Base: RZB trial data. Post-hoc analysis of ADVANCE and MOTIVATE ITT1A population (158). Low/high: 95% CI
Percent of non-responders remaining moderate-to-severe: BF population				
Moderate-to-severe (CDAI 220+)	73.5	0.022	69.1; 77.8	Base: RZB trial data. Post-hoc analysis of ADVANCE and MOTIVATE ITT1A population (158). Low/high: 95% CI

Abbreviations: BF, biologic failure; CCF, conventional care failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; DSA, deterministic sensitivity analysis; ITT, intention-to-treat; RZB, risankizumab; SE, standard error.

B.3.3.3.2 Maintenance and post-maintenance period efficacy: Overview of data-driven approach

Based on NICE/ERG critique of the most recent previous CD submission, TA456 (46), the maintenance and post-maintenance analyses in this submission utilised individual level data from the risankizumab CD maintenance study (FORTIFY) to estimate maintenance phase efficacy. The analysis was then calibrated for each of the comparators for four sets of Markov matrices (see Section B.3.2.2.2.1) in order to provide data-driven inputs instead of a set of assumptions, constraints and arbitrary starting values like those used in TA456 (46). The

ordered probit model sample is shown in Section B.3.3.3.3.1 and its corresponding results are shown in Section B.3.3.3.3.2.

A regression model using risankizumab CD maintenance data (FORTIFY) was first estimated to yield a Markov matrix. To avoid having to make assumptions about health-state occupancy when using a binary outcome to estimate proportions of patients who may be in mild or moderate-to-severe health states, an ordered probit model was specified to model this relationship. The probit model outputs and the corresponding transition matrices are shown on the 'Library – oprobit' and 'Calc – Calibration' Microsoft® Excel (Microsoft, Washington, USA, 2022) worksheets of the model. The maintenance NMAs had a split network as discussed in Section B.2.9.3.2. The remaining therapies were pooled into a separate matrix. The matrix was then estimated with risankizumab CD maintenance data (FORTIFY) for each of the therapies by modifying the remission-mild cutpoint coefficient from the probit model (which corresponds directly to the efficacy outcome from the NMA) with Microsoft® Solver (Microsoft, Washington, USA, 2022) so that the remission percentage matches that from the NMA. This procedure was conducted for standard-dose biologics (Markov matrix 1) and high-dose biologics (Markov matrix 2) (see Section B.3.2.2.2).

In the post-maintenance period, for CC responders, the placebo SC (withdrawal) arm in the risankizumab CD maintenance study (FORTIFY) was used for the matrix estimation, which included patients who received risankizumab IV for induction, had a response at the end of the initial 12-week induction period (Induction Period 1) and were subsequently randomised to the placebo SC (withdrawal) arm in the maintenance study.

Afterwards, the matrix was calibrated so that the end of maintenance remission equals that of the placebo arm in the split network maintenance NMA (Markov matrix 4: Conventional care after response) (see Section B.3.2.2.2). For the 'Conventional care non-responder maintenance matrix', the 'true placebo' data (IV placebo responders at Week 12 of Induction Period 1 in ADVANCE and MOTIVATE who were assigned to receive maintenance placebo SC in FORTIFY) from the risankizumab CD maintenance study (FORTIFY) were used to estimate the effects of patients who never received biologic treatment (Markov matrix 3: Conventional care after no response) (see Section B.3.2.2.2). The following subsections describe the ordered probit regression, including the data, sample selection and estimation, the NMA inputs used, and the calibration for the four sets of Markov matrices used in the model.

B.3.3.3.3 Maintenance and post-maintenance period ordered probit models

Inputs used in the maintenance/long-term period were from post-hoc analysis of the risankizumab CD maintenance study (FORTIFY) ITT1A analysis set, calibrated to a maintenance NMA which split the comparators into two networks:

a) the ustekinumab and risankizumab network; and
b) the adalimumab, infliximab and vedolizumab network.

B.3.3.3.3.1 Ordered probit model data and sample

Risankizumab CD maintenance data (FORTIFY) were used to estimate the probability of transitioning between CDAI-based health states using an ordered probit model. Data were selected from the CDAI analysis dataset that included one or more records per subject and per time point in the trial. The patient sample was divided into three cohorts:

- Subjects in the ITT1A population who were randomised to the risankizumab 360 mg SC dose in the maintenance study (RZB group)
- Subjects in the ITT1A population who were randomised to placebo SC (withdrawal) in the maintenance trial ('residual treatment effect' group)
- Subjects in the ITT2B 'true placebo' arm, who were randomised to placebo IV induction and placebo SC maintenance, who had an SF/APS clinical response but not a CR-100 response and did not start maintenance in remission.

The first two cohorts came from the risankizumab CD maintenance study (FORTIFY) arms used in the primary efficacy analysis (ITT1A). The third cohort, the 'true placebo' group (ITT2B; analysis set not part of the primary analysis), consisted of subjects who were randomised to placebo IV induction and received placebo SC maintenance. These subjects (N=24) were required to have SF/APS clinical response in ADVANCE or MOTIVATE but did not have CR-100 response and were assigned to continue to receive blinded placebo SC in FORTIFY. As subjects in this cohort were required to have clinical response in the induction studies to enter the maintenance study, the disease trajectory of subjects in the 'true placebo' cohort were improved when compared to those who were not required to have a clinical response (i.e., the presence of a response whilst previously on placebo is likely to have favourable outcomes compared to typical CC patients). This may have contributed to better model results for the CC population than expected in clinical practice (i.e., patients in the 'true placebo' group may have had better treatment response compared with those in clinical practice on CC).

Due to sample size limitations, the cohorts were not further divided into CCF and BF populations. Baseline characteristics of the three patient cohorts are shown in Table 64.

Table 64: Baseline characteristics of ordered probit model sample

	RZB 360mg SC		PBO (withdrawal)		'True PBO'	
	Count	%	Count	%	Count	%
N	[redacted]		[redacted]		[redacted]	
Demographics						
Age (mean)	[redacted]		[redacted]		[redacted]	
Sex						
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
South/Central America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Western Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PBO, placebo; RZB, risankizumab; SC, subcutaneous.

Observations in the CDAI analysis dataset were at the subject visit level. Specifically, visits from the maintenance phase at weeks 0, 24 and 52 were included for each subject, when available. The sample excluded visits that occurred after the censor date and rescue date per the study protocol. Subjects were required to have at least two observations for inclusion in the analysis. If two or more observations were recorded for the same time point, the visit that was closest to the target date was selected as part of the sample selection criteria.

After selecting the sample, the dataset was structured as a longitudinal dataset ordered by subject and visit date with each subject contributing multiple observations. Each subject visit was classified into one of the CDAI-based health states ('Remission', 'Mild CD', 'Moderate-to-severe CD') using the value of CDAI recorded at that visit. The lag of CDAI-based health

state and subject visit were derived (a lag is the variable measurement in the prior time period). The days between visits were calculated as the subject visit date minus the lag of subject visit date.

An ordered probit model was estimated for each of the three patient cohorts, with the CDAI-based health state as the dependent variable, and the lag of CDAI-based health state and time between visits as the independent variables.

B.3.3.3.3.2 Ordered probit model results

Results from the ordered probit model for the 'Biologic' (of both low and high dose), 'Conventional care after response' and 'Conventional care after no response' Markov matrices are presented in Table 65.

Table 65: Ordered probit model results

Parameter	Estimate	SE	t-value
'Biologic' Markov transition matrix			
Lag (Mild (150 ≤ CDAI < 220))	1.071	0.192	5.567
Lag (Moderate-to-severe (CDAI 220+))	1.687	0.279	6.039
Days between trial visits	-0.007	0.002	-2.774
Remission | Mild cutpoint	-0.333	0.455	-0.732
Mild | Moderate-to-severe cutpoint	0.479	0.453	1.057
AIC	341.857		
'CC after response' Markov transition matrix			
Lag (Mild (150 ≤ CDAI < 220))	1.171	0.198	5.905
Lag (Moderate-to-severe (CDAI 220+))	1.893	0.244	7.758
Days between trial visits	-0.012	0.003	-3.980
Remission | Mild cutpoint	-1.170	0.527	-2.221
Mild | Moderate-to-severe cutpoint	-0.433	0.523	-0.829
AIC	362.131		
'CC after no response' Markov transition matrix			
Lag (Mild (150 ≤ CDAI < 220))	-0.007	0.746	-0.009
Lag (Moderate-to-severe (CDAI 220+))	0.924	0.746	1.238
Days between trial visits	-0.003	0.006	-0.580
Remission | Mild cut-point	-1.105	1.355	-0.815
Mild | Moderate-to-severe cut-point	-0.260	1.346	-0.193
AIC	65.961		

Abbreviations: AIC, Akaike information criterion; CC, conventional care; CDAI, Crohn's Disease Activity Index; RZB, risankizumab; SE, standard error. Source: RZB trial data. Post-hoc analysis of FORTIFY population.

B.3.3.3.4 Maintenance and post-maintenance Markov matrices

B.3.3.3.4.1 Uncalibrated Markov matrices

To calculate the Markov matrices, the ordered probit parameter estimates were used to estimate the marginal probabilities of remaining in the current health state or transitioning to other health states, assuming 182 days between visits (the average time between the Week 0, 24 and 52 visits in the risankizumab CD maintenance study [FORTIFY]). This resulted in uncalibrated Markov matrices with 182-day transition probabilities, which were converted into 2-week transition probabilities via standard probability-rate-probability conversions.

The uncalibrated matrices represented the basis of transition probabilities for patients who did not discontinue treatment and who had at least two CDAI observations in FORTIFY. The matrices were then calibrated for each comparator therapy based on response estimates from the NMA to inform treatment-specific Markov matrices for the CDAI response analysis. This was necessary as patient-level data were not available for comparator treatments, so the NMA results themselves had to be calibrated.

The process for calibrating Markov matrices

CDAI-based remission, mild and moderate-severe are mutually exclusive, ordered outcomes from a linear scale that have been used in prior publications and NICE submissions as health states. A categorical, or multinomial, ordered model must be used given that there are three ordered outcomes. The probit distribution was chosen given that it is one of the most commonly used distributions in multinomial ordered models; the logit and probit form the majority of these models. We chose the ordered probit model as it is based on the normal or Gaussian distribution. Normal distributions appear frequently throughout models seen in the economics literature.

The uncalibrated Markov matrices for comparators were used to calculate the remission rate at Week 52 as predicted by the ordered probit model. At Week 0 of maintenance, patients were assumed to have had a starting health-state distribution as implied by the comparator-specific induction NMA results and assumptions about the moderate-to-severe CD split for responders. Next, the uncalibrated matrices were used to predict remission rate at Week 52. After, the ordered probit model was calibrated so that the remission rate at Week 52 from the prediction is equal to that from the maintenance NMA remission rates. Specifically, Microsoft® Solver (Microsoft, Washington, USA, 2022) was used to find the value of the 'remission|mild cutpoint' from the ordered probit model which set the predicted remission

rate at Week 52 equal to the maintenance NMA remission rate. The newly calibrated matrix was then used to calculate biologic-specific transition probability matrices for use in the model. The above process was conducted for each comparator in the CCF and BF populations, for the standard-dose biologic, high-dose biologic and maintenance placebo (i.e., the 'residual treatment' effect) arms. Of note, the calibration problem only had one unique solution for any maintenance remission rate. This addressed ERG's critique to TA456, where many potential solutions might have existed to generate a given set of transition probabilities, which was a source of significant uncertainty (46). The calibration targets used in this calibration (i.e., the maintenance remission rates from the NMA) are presented in Table 66. For induction, response and remission rates are shown in Table 61 and Table 62.

Table 66: Maintenance NMA (split network) clinical remission inputs for the standard- and high-dose biologics, CCF and BF populations

Treatment	Maintenance dosing (reference)	Mean	CrI (%) (low; high)
Standard-dose maintenance: CCF population			
RZB	360 mg SC Q8W from week 12 (4)	[redacted]	[redacted]
UST	90 mg SC Q12W from week 8 (90)	[redacted]	[redacted]
ADA 160/80 (and biosimilar†)	40 mg SC Q2W from week 4 (113)	[redacted]	[redacted]
ADA 80/40	40 mg SC Q2W from week 4 (113)	[redacted]	[redacted]
IFX IV (and biosimilar†)	5 mg/kg IV Q2W from week 14 (97, 114)	[redacted]	[redacted]
IFX SC	120 mg SC Q2W from Week 6 (156)	[redacted]	[redacted]
Standard-dose maintenance: BF population – Remission (CDAI < 150)			
RZB	360 mg SC Q8W from week 12 (4)	[redacted]	[redacted]
UST	90 mg SC Q12W from week 8 (90)	[redacted]	[redacted]
VDZ IV	300 mg IV Q8W from week 14 (89)	[redacted]	[redacted]
VDZ SC	108 mg IV Q2WQ2WQ2W from week 14 (155)	[redacted]	[redacted]
High-dose maintenance: CCF population – Remission (CDAI < 150)			
UST	90 mg SC Q8W (90, 114, 156)	[redacted]	[redacted]
ADA 160/80 (and biosimilar†)	40 mg SC QW (113)	[redacted]	[redacted]
ADA 80/40	40 mg SC QW (113)	[redacted]	[redacted]
IFX IV (and biosimilar†)	10 mg/kg IV Q8W (114);(97)	[redacted]	[redacted]
IFX SC	N/A (standard dose used)	[redacted]	[redacted]
High-dose maintenance: BF population – Remission (CDAI < 150)			
UST	90 mg SC Q8W (90)	[redacted]	[redacted]
VDZ IV	300 mg IV Q4W (89)	[redacted]	[redacted]
VDZ SC	N/A (standard dose used)	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CrI, credible interval; DSA, deterministic sensitivity analysis; IFX, infliximab; IV, intravenous; N/A, not applicable;

NMA, network meta-analysis; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab. † Biosimilar formulations are assumed equal to originator drug.

An example of the calibration process in six steps appears in Figure 15 for the standard-dose risankizumab matrix in CCF. In Step 1, the ordered probit results (Table 65) were identified, and specifically the coefficient on the Remission|Mild cutpoint. This ordered probit yielded to the uncalibrated Markov matrix for standard-dose biologics. In Step 2, the remission percentage for this uncalibrated matrix was 91.5% at Week 52 – the percentage was high because the uncalibrated sample includes only patients who remained in the active treatment arm. In Step 3, the NMA remission outcome for standard-dose biologic, CCF, end of maintenance was identified; in this case 54.9% of patients on risankizumab were in remission. In Step 4, the optimisation Solver program was used in Microsoft® Excel (Microsoft, Washington, USA, 2022) to adjust the Remission|Mild cutpoint coefficient (Step 5) until a solution was found so that Week 52 remission rates equal 54.9% (Step 6). The calibrated matrix for risankizumab, standard-dose biologic in CCF, was then identified and used for that part of the model.

The efficacy representing the 'residual treatment effect' for those who responded to biologic therapies but subsequently had treatment discontinued was based on the placebo withdrawal arm in the maintenance NMA. The maintenance NMA was comprised of two split networks (one network for risankizumab and ustekinumab; and one network for infliximab, adalimumab and vedolizumab). Therefore, the 'residual treatment effect' was different per the split network. Specifically, ustekinumab and risankizumab had the same 'residual treatment effect' by application of the efficacy in the withdrawal/placebo arm from the NMA of the risankizumab and ustekinumab network, while the other biologic therapies had the same 'residual treatment effect' by applying the efficacy in the withdrawal/placebo arm from the NMA of the infliximab, adalimumab and vedolizumab network. These rates were used in the post-maintenance period to calibrate Markov matrix 4, 'Conventional care after response' (Table 67). The duration of this effect in the base case analysis was 52 weeks.

Finally, the Markov matrix for 'Conventional care after no response' was also calibrated to the remission rate at Week 52 (2/24, 8.3%) based on the analyses in the 'true placebo' group.

Table 67: Maintenance NMA (split network) clinical remission estimates from withdrawal / PBO arms for CC after response (residual treatment effect), CCF and BF populations

Treatment	Maintenance dosing (reference)	Responders	CrI (%) (low; high)
Maintenance 'CC after response': CCF population			
RZB	360 mg SC Q8W from week 12 (4)	[redacted]	[redacted]
UST	90 mg SC Q12W from week 8 (90)	[redacted]	[redacted]
ADA 160/80 / ADA 160/80 biosimilar†	40 mg SC Q2W from week 4 (113)	[redacted]	[redacted]
ADA 80/40	40 mg SC Q2W from week 4 (113)	[redacted]	[redacted]
IFX IV / IFX IV biosimilar†	5 mg/kg IV Q8W from week 14 (114);(97)	[redacted]	[redacted]
IFX SC	120 mg SC Q2W from Week 6 (156)	[redacted]	[redacted]
Maintenance 'CC after response': BF population			
RZB	360 mg SC Q8W from week 12 (4)	[redacted]	[redacted]
UST	90 mg SC Q12W from week 8 (90)	[redacted]	[redacted]
VDZ IV	300 mg IV Q8W from week 14 (89)	[redacted]	[redacted]
VDZ SC	108 mg SC Q2W from week 14 (155)	[redacted]	[redacted]

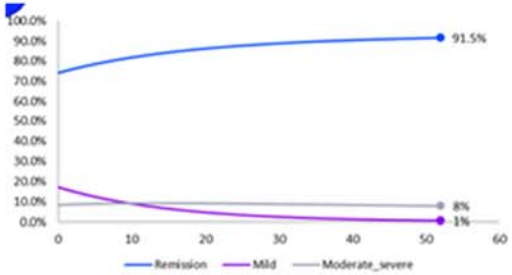
Abbreviations: ADA, adalimumab; BF, biologic failure; CC, conventional care; CCF, conventional care failure; CrI, credible interval; CDAI, Crohn's Disease Activity Index; DSA, deterministic sensitivity analysis; IFX, infliximab; IV, intravenous; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.
† Biosimilar formulations are assumed equal to originator drug. Source: NMA described in Section B.2.9.
Note: This table does not present data in the CCF population for VDZ IV or VDZ SC, nor data in the BF population for ADA 160/80, ADA 80/40 ADA 160/80 biosimilar. This is due to VDZ and ADA not being considered relevant comparators in the CCF and BF populations, respectively. All NMA results can be found in Section B.2.9.2.

Figure 15: Example of calibration process for standard-dose RZB in the CCF population*

1 **Ordinal probit estimated with FORTIFY CCF data for RZB responders who continue to receive treatment**

Parameter	Estimate	SE
Maintenance - Biologic Markov transition matrix ordered probit model		
Lag[Mild (150 ≤ CDAI < 220))	1.041	0.193
Lag[Moderate-to-severe (CDAI 220+))	1.709	0.287
Days between trial visits	-0.007	0.002
Remission|Mild cutpoint	-0.343	0.459
Mild|Moderate-to-severe cut-point	0.465	0.457
AIC		

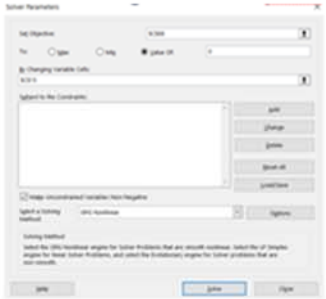
2 **Markov traces estimated with uncalibrated ordered probit model for RZB responders who continue to receive treatment**



3 **NMA absolute response rate results for RZB in CCF maintenance network**

Parameter	Mean (%)	DSA (low; high)
Maintenance - Low dose maintenance: CCF Remission (CDAI < 150) (%).		
RZB (600mg IV + 360mg SC)	54.9	32.2; 77.3
UST (6mg/kg + 90/Q12W)	61.9	43.4; 80.3

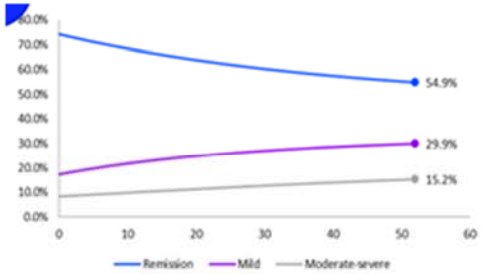
4 **Solver in MS Excel is an optimisation program that can modify the Mild|Moderate-severe cutpoint so the Week 52 remission rate equals that in the NMA, calibrating the ordered probit**



5 **Calibrated ordinal probit so the Week 52 remission rate equals that in the NMA**

Parameter	Estimate	SE
Maintenance - Biologic Markov transition matrix ordered probit model		
Lag[Mild (150 ≤ CDAI < 220))	1.041	0.193
Lag[Moderate-to-severe (CDAI 220+))	1.709	0.287
Days between trial visits	-0.007	0.002
Remission|Mild cutpoint	-0.677	0.459
Mild|Moderate-to-severe cut-point	0.465	0.457
AIC		

6 **Markov traces estimated with calibrated ordered probit model for RZB responders who continue to receive treatment**



Abbreviations: AIC, Akaike information criterion; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; DSA, deterministic sensitivity analysis; IV, intravenous; NMA, network meta-analysis; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; SE, standard error.
* Please note that all data in this example are dummy data and are not reflective of the data used in the model.

B.3.3.3.4.2 Calibrated Markov matrices

Calibrated Markov matrices for risankizumab, including for standard-dose and 'Conventional care after response' by CCF and BF, are presented in Table 68-Table 72. Note that calibrated Markov matrices for the other treatments are not presented here due to the limited space but are presented in the Microsoft® Excel (Microsoft, Washington, USA, 2022) model. The matrix for 'Conventional care after no response' is presented in Table 73. As an example, in the 'Standard-dose biologic maintenance' matrix for risankizumab in the CCF analyses, a patient on risankizumab in the maintenance period who is in remission experienced a 97.38% chance of remaining in 'remission' in the next two weeks and a 2.26% chance of transitioning to 'Mild CD'.

Table 68: Calibrated Markov transition matrix: 'Standard-dose risankizumab' in CCF population (2-week cycle)

Risankizumab CCF	Remission (CDAI <150)	Mild CD (CDAI 150 < 220)	Moderate-to-severe CD (CDAI 220+)
Remission (CDAI < 150)	0.97378	0.02269	0.00353
Mild CD (150 ≤ CDAI < 220)	0.02595	0.95054	0.02351
Moderate-to-severe CD (CDAI 220+)†	0.00985	0.03642	0.95373

Abbreviations: CCF, conventional care failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.
† The moderate-to-severe CD row excludes a 0.28% probability of transitioning to surgery.

Table 69: Calibrated Markov transition matrix: 'Conventional care after response' in CCF population (2-week cycle)

Risankizumab CCF	Remission (CDAI < 150)	Mild CD (CDAI 150 < 220)	Moderate-to-severe CD (CDAI 220+)
Remission (CDAI < 150)	0.94564	0.05069	0.00367
Mild CD (150 ≤ CDAI < 220)	0.00829	0.96398	0.02773
Moderate-to-severe CD (CDAI 220+)†	0.00182	0.03747	0.96107

Abbreviations: CCF, conventional care failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.
† The moderate-to-severe row excludes a 0.28% probability of transitioning to surgery.

Table 70: Calibrated Markov transition matrix: 'Conventional care after no response' in CCF population (2-week cycle)

Risankizumab CCF	Remission (CDAI < 150)	Mild CD (CDAI 150 < 220)	Moderate-to-severe CD (CDAI 220+)
Remission (CDAI < 150)	0.90757	0.05905	0.03338
Mild CD (150 ≤ CDAI < 220)	0.00787	0.95904	0.03309
Moderate-to-severe CD (CDAI 220+)†	0.00101	0.02452	0.97449

Abbreviations: CCF, conventional care failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.
† The moderate-to-severe row excludes a 0.28% probability of transitioning to surgery.

Table 71: Calibrated Markov transition matrix: 'Standard-dose risankizumab' in BF population (2-week cycle)

Risankizumab BF	Remission (CDAI < 150)	Mild CD (CDAI 150 < 220)	Moderate-to-severe CD (CDAI 220+)
Remission (CDAI < 150)	0.97027	0.02620	0.00353
Mild CD (150 ≤ CDAI < 220)	0.02268	0.95381	0.02351
Moderate-to-severe CD (CDAI 220+)†	0.00830	0.03862	0.95308

Abbreviations: BF, biologic failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.
† The moderate-to-severe row excludes a 0.28% probability of transitioning to surgery.

Table 72: Calibrated Markov transition matrix: 'Conventional care after response' in BF population (2-week cycle)

Risankizumab BF	Remission (CDAI < 150)	Mild CD (CDAI 150 < 220)	Moderate-to-severe CD (CDAI 220+)
Remission (CDAI < 150)	0.96076	0.03557	0.00367
Mild CD (150 ≤ CDAI < 220)	0.01376	0.95851	0.02773
Moderate-to-severe CD (CDAI 220+)†	0.00352	0.03490	0.96158

Abbreviations: BF, biologic failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.
† The moderate-to-severe row excludes a 0.28% probability of transitioning to surgery.

Table 73: Calibrated Markov transition matrix: 'Conventional care after no response' in BF population (2-week cycle)

Risankizumab BF	Remission (CDAI < 150)	Mild CD (CDAI 150 < 220)	Moderate-to-severe CD (CDAI 220+)
Remission (CDAI < 150)	0.90804	0.05858	0.03338
Mild CD (150 ≤ CDAI < 220)	0.00812	0.95879	0.03309
Moderate-to-severe CD (CDAI 220+)†	0.00105	0.02446	0.97449

Abbreviations: BF, biologic failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.
† The moderate-to-severe row excludes a 0.28% probability of transitioning to surgery.

B.3.3.4 Additional efficacy-related inputs

Additional efficacy-related inputs are presented in the following sections. Discontinuation rates were sourced from the risankizumab CD study program and from publications cited in prior TA submissions in CD, especially TA456 (46) and its underlying sources. Dose escalation rates were sourced from clinician expert opinion gathered via an advisory board (80). Surgery and post-surgery inputs were sourced from prior TA submissions in CD, namely TA456 (46) and TA352 (47) and their underlying sources.

B.3.3.4.1 Dose escalation transition probabilities

Dose escalation determined whether a patient is moved to a higher-dose regimen (either higher-dose strength or shorter-dose interval) during the maintenance phase of treatment. Clinically, dose escalation occurs when there is evidence indicating loss of response/efficacy to therapy. Dose escalation could occur at any time in the model while a patient is on any maintenance biologic therapy, except for risankizumab. There is only one maintenance dose for risankizumab (360 mg SC); thus no dose escalation rate is applied for risankizumab. Dose escalation is applied as per SmPC for each treatment only in the model. The model inputs of dose escalation rates per cycle are summarised in Table 74.

The dose escalation rates for infliximab, adalimumab, ustekinumab and vedolizumab are based on UK expert clinical opinion (80). Additionally, in clinical practice, patients who initiate ustekinumab are initiated on the high maintenance dose (i.e., Q8W treatment) if this is deemed appropriate. Based on UK expert clinical opinion, the percentage of patients initiating the ustekinumab Q8W dosing is 92.5% (80). All other treatments have 100% of patients initiating on the standard maintenance dose. Since dose escalation occurs due to an issue with achieved level of efficacy (i.e., loss of response or lack of efficacy).

Patients did not transition to the high-dose matrix after undergoing dose escalation because clinically these patients failed standard-dose treatment and receiving a higher dose would not be expected to provide higher efficacy than that of a standard-dose treatment as highlighted in the advisory board (80). In other words, patients who underwent dose escalation required a higher dose of drug to achieve the same level of response as those patients who did not need to dose-escalate. The high-dose matrix was estimated with RCT data for subjects who were randomised to a high-dose arm at the beginning of the maintenance phase without evidence of failure after receiving a standard dose. Therefore, in the model, dose escalation only increased patient biologic costs and did not increase efficacy; the same assumption was applied to those patients requiring initiation with the high dose of ustekinumab (Q8W; assumption was based on expert clinical feedback (80)).

Table 74: Maintenance dose escalation probabilities

Treatment	Maintenance dose escalation (reference)	Probability		SE	DSA (%) (low; high)	Source/ Note
		Annual (median)	Per cycle			
UST	90 mg SC Q8W (90)	92.5%	9.4%	0.0096	7.5; 11.2	Base: Clinician feedback advisory board (80) low/high value ±20.0%
ADA 160/80 / ADA 160/80 biosimilar†	40 mg SC QW (113)	50%	2.6	0.0027	2.1; 3.2	
ADA 80/40	40 mg SC QW (113)	50%	2.6	0.0027	2.1; 3.2	
IFX IV / IFX IV biosimilar†	10 mg/kg IV Q8W (97, 114)	40%	1.9	0.0020	1.6; 2.3	
IFX SC	N/A	N/A	N/A	N/A	N/A	
VDZ IV	300 mg IV Q4W (89)	30.0%	1.4%	0.0027	1.1; 1.6	
VDZ SC	N/A	N/A	N/A	N/A	N/A	

Abbreviations: ADA, adalimumab; DSA, deterministic sensitivity analysis; IFX, infliximab; IV, intravenous; N/A, not applicable; NICE, National Institute for Health and Care Excellence; QxW, every x week; SC, subcutaneous; SE, standard error; TA, technology appraisal; UST, ustekinumab; VDZ, vedolizumab. † Biosimilar formulations are assumed equal to originator drug.

B.3.3.4.2 Discontinuation from biologic treatment

Treatment discontinuation could have occurred at any time due to lack of efficacy. The model included a 2-week probability of discontinuation input that represented the rate at which patients discontinued risankizumab or other treatments due to lack of efficacy. Patients who discontinued due to this reason proceeded to the 'Conventional care after no response' matrix. The data for risankizumab were based on analysis of data from the risankizumab CD maintenance study (FORTIFY). A 2-week probability of discontinuing was calculated based on the observed 52-week rate in the trial using Equation 1.

Equation 1: Exponential formula

$$r = -[\ln(1 - P)]/T$$

Abbreviations: ln, natural logarithm; P, probability; r, rate; T, time.

Six of the 141 subjects randomised to risankizumab 360 mg SC arm discontinued the study due to lack of efficacy. Data for the other therapies were derived from the maintenance trial publications, specifically ACCENT I (infliximab), IM-UNITI (ustekinumab) and GEMINI 2 (vedolizumab). Patients on adalimumab were assumed to have discontinued due to lack of efficacy at the same rate as patients on infliximab,

as no direct data were available and adalimumab and infliximab belong to the same class of drugs. Patients using vedolizumab SC were assumed to follow the same rate as its IV formulation considering comparable efficacy and a lack of data to suggest otherwise. The same assumption was made for infliximab SC, using infliximab IV rates. Table 75 summarises the 2-week transition probabilities for discontinuation for all comparators.

Table 75: Biologic treatment discontinuation due to lack of efficacy

Treatment	Maintenance dose (reference)	Probability		SE	DSA (low; high)	Source/Note
		Annual	Per cycle			
Discontinuation due to lack of efficacy probability						
RZB	360 mg SC Q8W from week 12 (4)	4.3%	0.17%	0.0002	0.13; 0.20	Base: RZB trial data (M16-000 ITT1A population, CSR Table 14.1_2.1). Low/high: assumption, ±20.0%
UST	90 mg SC Q12W from week 8 (90)	8.0%	0.32%	0.0003	0.26; 0.38	Base: Feagan et al. (2016), supplemental material. Low/high: assumption, ±20.0%
ADA 160/80 / ADA 160/80 biosimilar†	40 mg SC Q2W from week 4 (113)	8.0%	0.32%	0.0003	0.26; 0.38	Base: NICE TA456 (46), Table 41. Assumption, equal to infliximab. Low/high: assumption, ±20.0%
ADA 80/40	40 mg SC Q2W from week 4 (113)	8.0%	0.32%	0.0003	0.26; 0.38	
IFX IV / IFX IV biosimilar†	5 mg/kg IV Q8W from week 14 (114);(97)	8.0%	0.32%	0.0003	0.26; 0.38	Base: NICE TA456 (46), Table 41. Data from ACCENT I. Low/high: assumption, ±20.0%
IFX SC	120 mg SC Q2W from Week 6 (156)	8.0%	0.32%	0.0003	0.26; 0.38	
VDZ IV	300 mg IV Q8W from week 14 (89)	41.3%	2.0%	0.0021	1.63; 2.44	Base: NICE TA456 (46), Table 41. Data from GEMINI II. Low/high: assumption, ±20.0%
VDZ SC	108 mg IV Q2W from week 14 (155)	41.3%	2.0%	0.0021	1.63; 2.44	

Abbreviations: ADA, adalimumab; CSR, clinical study report; DSA, deterministic sensitivity analysis; IFX, infliximab; ITT, intention-to-treat; IV, intravenous; NICE, National Institute for Health and Care Excellence; RZB, risankizumab; QxW, every x weeks; SC, subcutaneous; SE, standard error; TA, technology appraisal; UST, ustekinumab; VDZ, vedolizumab. † Biosimilar formulations are assumed equal to originator drug.

B.3.3.4.3 Surgery in maintenance and post-maintenance periods

Surgery rates, in terms of 2-week transition probabilities stratified by CDAI-based health state, followed inputs used in ustekinumab CD NICE submission (TA546 (46)) (Table 76). An annual 7% probability of surgery was taken from the NHS Hospital

Episode Statistics data (28) and converted into a 2-week cycle rate of 0.28% using the exponential formula shown in Equation 1 in Section B.3.3.4.2.

Following TA456, it was assumed that patients could only have surgery if they have a moderate-to-severe CDAI score. Patients undergoing surgery experienced a three-cycle tunnel state before being distributed across 'Remission', 'Mild CD', 'Moderate-to-severe CD' and (repeat) 'Surgery' states, which also follows TA456 (46).

Table 76: Surgery per 2-week cycle per CDAI level

Parameter	Percent	SE	DSA (%) (low; high)	Source/Note
Surgery per 2-week cycle				
Remission (CDAI < 150)	0.00%	N/A	0.00; 0.00	Assumption.
Mild CD (150 ≤ CDAI < 220)	0.00%	N/A	0.00; 0.00	
Moderate-to-severe CD (CDAI 220+)	0.28%	0.0021	0.22; 0.33	Base: NICE TA456 (46), Section 5.3.4. Converted from annual rate of 7% (6-8%) from NHS HES data (28). Low/high: assumption, ±20.0%

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; DSA, deterministic sensitivity analysis; HES, Hospital Episode Statistics; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SE, standard error; TA, technology appraisal.

B.3.3.4.4 Post-surgery efficacy

Upon transitioning to the 'Surgery' state, patients experienced the surgery state for one cycle and then experienced three cycles of post-surgery tunnel states. After the final post-surgery tunnel state cycle, patients had probabilities of transitioning to remission, mild or moderate-to-severe disease. For the probability of undergoing surgery, the model used the same sources as used in TA456 and TA352 (Bodger et al. (2009) (146)) as the model structure was similar in concept and utilised comparable health states. As transitions were given for 8-week cycles, an identity matrix was applied for three consecutive cycles before post-surgery transitions were implemented. Post-surgery transition probabilities stratified by CCF and BF populations are presented in Table 77.

Table 77: Post-surgery transition probabilities

Parameter	Percentage	DSA (%) (low; high)	Source
CCF population (N=199)			
Remission (CDAI < 150)	52.8%	42.2; 63.4	Base: NICE TA456 (46), Table 43. Data from Bodger et al. (2009) (146) and TA352 (47). Low/high: assumption, ±20.0%
Mild CD (150 ≤ CDAI < 220)	7.5%	6.0; 9.0	
Moderate-to-severe CD (CDAI 220+)	6.0%	4.8; 7.2	
Surgery	33.7%	26.96; 40.44	
BF population (N=78)			
Remission (CDAI < 150)	52.6%	42.1; 63.1	Base: NICE TA456 (46), Table 43. Data from Bodger et al. (2009) (146) and TA352 (47). Low/high: assumption, ±20.0%
Mild CD (150 ≤ CDAI < 220)	7.7%	6.2; 9.2	
Moderate-to-severe CD (CDAI 220+)	6.4%	5.1; 7.7	
Surgery	33.3%	26.64; 39.96	

Abbreviations: BF, biologic failure; CCF, conventional care failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; DSA, deterministic sensitivity analysis; NICE, National Institute for Health and Care Excellence; SE, standard error; TA, technology appraisal.

B.3.3.4.5 Proportion of patients starting standard-dose maintenance therapy

Ustekinumab, vedolizumab, infliximab and adalimumab have standard and high maintenance doses. Patients typically start on standard maintenance therapy after responding to induction therapy, with ustekinumab as an exception (92.5% of patients start on the high dose, according to clinical expert opinion (80)). Additionally, clinical experts stated that for infliximab, adalimumab and vedolizumab only low percentages of patients started on the high maintenance dose (10%, 5% and 0%, respectively) in clinical practice in the UK, and starting on the higher doses was not in line with their respective SmPCs. Therefore, in the model base case, all patients who entered maintenance would start the standard regimen, except for those on ustekinumab (80) (Table 78).

Table 78: Proportion of patients starting on standard-dose maintenance regimens

Treatment	Maintenance dose (reference)	%	SE	DSA (%) (low; high)	Source/Note
Proportion starting standard (vs high) dose: CCF population					
UST	90 mg SC Q12W from Wk 8 (90)	7.5	0.01	6.0; 9.0	Base: Clinical opinion and SmPC (90). Low/high: assumption, ±20.0%
ADA 160/80 (and biosimilar†)	40 mg SC Q2W from Wk 4 (113)	100	0.06	80; 100	Base: SmPC (113, 114, 156). Low/high: assumption, ±20.0%
ADA 80/40					
IFX IV (and biosimilar†)	5 mg/kg IV Q8W from Wk 14 (114);(97)	100	0.07	80; 100	
IFX SC	120 mg SC Q2W from Wk 6 (156)	100	0.05	N/A	No dose escalation
Proportion starting standard (vs high) dose: BF population					
UST	90 mg SC Q12W from Wk 8 (90)	7.5	0.01	6.0; 9.0	Base: Clinical opinion. Low/high: assumption, ±20.0%
VDZ IV	300 mg IV Q8W from Wk 14 (89)	100	0.05	80; 100	Base: SmPC (89). Low/high: assumption, ±20.0%
VDZ SC	108 mg SC Q2W from Wk 14 (155)	100	0.05	N/A	No dose escalation

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; DSA, deterministic sensitivity analysis; IFX, infliximab; IV, intravenous; N/A, not applicable; QxW, every x weeks; SC, subcutaneous; SE, standard error; SmPC, Summary of Product Characteristics; TA, technology appraisal; UST, ustekinumab; VDZ, vedolizumab. † Biosimilar formulations are assumed equal to originator drug.

B.3.3.5 Rates of treatment-related adverse events

The list of AEs in the model included serious infections, tuberculosis, lymphoma, hypersensitivity, and skin reactions, following TA456 (46) and TA352 (46). Inputs were for AEs per 2-week cycle, and were sourced from the induction and maintenance studies for risankizumab, and from publications of their respective induction and maintenance studies for the rest of the comparators, including Colombel et al. (2007) (111), Hanauer et al. (2002) (111), Rutgeerts et al. (2004) (159), Sandborn et al. (2007) (110), Sands et al.. (2014) (116), Watanabe et al. (2012) (120), and Feagan et al. (2016) (104).

The methods used to calculate per-cycle AE rate probabilities in TA456 (46) were able to be replicated for all values. The AE rates are presented in Table 79. Lymphoma was included in the AEs evaluated, and inputs were included in the model, but zero events were recorded for each treatment for this AE; consequently, it was excluded from Table 79.

Table 79: Adverse event rates by treatment per 2-week cycle

Treatment ‡ (for dosing see footnotes)	Probability (%)		SE	DSA (%) (low; high)	Source/Note
	Annual	2-week cycle			
Serious infections					
RZB	4.82	0.19	0.0002	0.15; 0.22	Base: RZB trial data. Low/high: assumption, ±20.0%
UST	8.47	0.34	0.0003	0.27; 0.41	Base: NICE TA456 (46), ERG Report Table 45. Data from UNITI-1 (118), UNITI-2 (118) and IM-UNITI (104). Low/high: assumption, ±20.0%
ADA 160/80 / ADA 160/80 biosimilar†	8.00	0.32	0.0003	0.26; 0.38	Base: NICE TA456 (2004) (159), Sandborn et al. (2007) (110), Watanabe et al. (2012) (120). Low/high: assumption, ±20.0%
ADA 80/40	8.00	0.32	0.0003	0.26; 0.38	
IFX IV / IFX IV biosimilar†	5.07	0.20	0.0002	0.16; 0.24	Base: NICE TA456 (46), ERG Report Table 45. Data from Hanauer et al. (2002) (109), Colombel et al. (2007) (111). Low/high: assumption, ±20.0%
IFX SC	5.07	0.20	0.0002	0.16; 0.24	
VDZ IV	8.00	0.32	0.0003	0.26; 0.38	Base: NICE TA456 (46), ERG Report Table 45. Data from GEMINI 2 (105), GEMINI 3 (116). Low/high: assumption, ±20.0%
VDZ SC	8.00	0.32	0.0003	0.26; 0.38	
Tuberculosis					
RZB	0.26	0.01	0.00001	0.01; 0.02	Base: RZB trial data. Low/high: assumption, ±20.0%
UST	0.00	0.00	N/A	N/A	Base: NICE TA456 (46), ERG Report Table 45. Data from UNITI-1 (118), UNITI-2 (118), IM-UNITI (104). Low/high: assumption, ±20.0%
ADA 160/80 / ADA 160/80 biosimilar†	0.00	0.00	N/A	N/A	Base: NICE TA456 (46), ERG Report Table 45. Data from Colombel et al. (2007) (111), Hanauer et al. (2002) (109), Rutgeerts et al. (2004) (159), Sandborn et al. (2007) (110), Watanabe et al. (2012) (120). Low/high: assumption, ±20.0%
ADA 80/40	0.00	0.00	N/A	N/A	
IFX IV / IFX IV biosimilar†	0.00	0.00	N/A	N/A	Base: NICE TA456 (46), ERG Report Table 45. Data from Hanauer et al. (2002) (109), Colombel et al. (2007) (111). Low/high: assumption, ±20.0%
IFX SC	0.00	0.00	N/A	N/A	
VDZ IV	0.00	0.00	N/A	N/A	Base: NICE TA456 (46), ERG Report Table 45. Data from GEMINI 2 (105), GEMINI 3 (116). Low/high: assumption, ±20.0%
VDZ SC	0.00	0.00	N/A	N/A	
Hypersensitivity					
RZB	0.26	0.01	0.00001	0.01; 0.02	Base: RZB trial data. Low/high: assumption, ±20.0%
UST	0.26	0.01	0.00001	0.01; 0.01	Base: NICE TA456 (46), ERG Report Table 45. Data from UNITI-1 (118), UNITI-2 (118), IM-UNITI (104). Low/high: assumption, ±20.0%

Treatment ‡ (for dosing see footnotes)	Probability (%)		SE	DSA (%) (low; high)	Source/Note
	Annual	2-week cycle			
ADA 160/80 / ADA 160/80 biosimilar†	0.00	0.00	N/A	N/A	Base : NICE TA456 (46), ERG Report Table 45. Data from Colombel et al. (2007) (111), Hanauer et al. (2002) (109), Rutgeerts et al. (2004) (159), Sandborn et al. (2007) (110), Watanabe et al. (2012) (120). Low/high: assumption, ±20.0%
ADA 80/40	0.00	0.00	N/A	N/A	
IFX IV / IFX IV biosimilar†	0.00	0.00	N/A	N/A	Base: NICE TA456 (46), ERG Report Table 45. Data from Hanauer et al. (2002) (109), Colombel et al. (2007) (111). Low/high: assumption, ±20.0%
IFX SC	0.00	0.00	N/A	N/A	
VDZ IV	0.00	0.00	N/A	N/A	Base: NICE TA456 (46), ERG Report Table 45. Data from GEMINI 2 (105), GEMINI 3 (116). Low/high: assumption, ±20.0%
VDZ SC	0.00	0.00	N/A	N/A	
Skin reactions					
RZB	9.19	0.37	0.0004	0.30; 0.45	Base: RZB trial data. Low/high: assumption, ±20.0%
UST	17.78	0.75	0.0008	0.60; 0.90	Base: NICE TA456 (46), ERG Report Table 45. Data from UNITI-1 (118), UNITI-2 (118), IM-UNITI (104). Low/high: assumption, ±20.0%
ADA 160/80 / ADA 160/80 biosimilar†	50.39	2.66	0.0106	2.13; 3.19	Base: Weighted average adjusted for trial duration from Colombel et al. (2007) (111), Hanauer et al. (2002) (111), Rutgeerts et al. (2004) (109), Sandborn et al. (2007) (159), Watanabe et al. (2012) (120). Low/high: assumption, ±20.0%
ADA 80/40	50.39	2.66	0.0106	2.13; 3.19	
IFX IV / IFX IV biosimilar†	17.13	0.72	0.0007	0.58; 0.86	Base: NICE TA456 (46), ERG Report Table 45. Data from Hanauer et al. (2002) (109), Colombel et al. (2007) (111). Low/high: assumption, ±20.0%
IFX SC	17.13	0.72	0.0007	0.58; 0.86	
VDZ IV	14.26	0.59	0.0006	0.47; 0.71	Base: NICE TA456 (46), ERG Report Table 45. Data from GEMINI 2 (105), GEMINI 3 (116). Low/high: assumption, ±20.0%
VDZ SC	14.26	0.59	0.0006	0.47; 0.71	

Abbreviations: ADA, adalimumab; CSR, clinical study report; DSA, deterministic sensitivity analysis; ERG, Evidence Review Group; IFX, infliximab; IV, intravenous; N/A, not applicable; NICE, National Institute for Health and Care Excellence; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; SE, standard error; TA, technology appraisal; UST, ustekinumab; VDZ, vedolizumab. † Biosimilar formulations are assumed equal to originator drug. ‡ Conventional care adverse events are not directly calculated in the model; the mean rates for all other treatments are assumed to apply to conventional care.

Dosing: RZB, induction: 600 mg IV at weeks 0, 4 and 8, maintenance: 360 mg SC Q8W from week 12 (3, 4); UST, induction: 6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 & <85 kg: 390 mg; >85kg: 520 mg (92), maintenance: 90 mg SC Q12W from week 8 (90); ADA 160/80 (and ADA 160/80 biosimilar), induction: 160 mg SC at week 0; 80 mg SC at week 2, maintenance: 40 mg SC Q2W from week 4 (113); ADA 80/40, induction: 80 mg SC at week 0; 40 mg SC at week 2, maintenance: 40 mg SC Q2W from week 4 (113); IFX IV (and IFX IV biosimilar), induction: 5 mg/kg IV at weeks 0 and 2 (114), maintenance: 5 mg/kg IV Q8W from week 14 (114); IFX SC, induction: 5 mg/kg IV at weeks 0 and 2 (114), maintenance: 120 mg SC Q2W from Week 6 ; VDZ IV, induction: 300 mg IV weeks 0, 2 and 6, maintenance: 300 mg IV Q8W from week 14 (89); VDZ SC, induction: 300 mg IV at weeks 0, 2 and 6 , maintenance: 108 mg IV Q2W from week 14 .

B.3.3.6 Rates of surgical complications

Rates of surgical complications (i.e., wound infection, prolonged ileus/bowel obstruction, intra-abdominal abscess, anastomotic leak) were estimated from published sources, which were also used in a previous NICE CD submission (TA456 (46)). Pooled data from 12 studies (McLeod et al. (2009) (160); Milsom et al. (2001) (161); Zurbuchen et al. (2013) (162); Kusunoki et al. (1998) (163); Fazio et al. (1996) (164); Irvin et al. (1973) (165); Eshuis et al. (2010) (166); Maartenese et al. (2006) (167); Ikeuchi et al. (2000) (168); Cameron et al. (1992) (169); Stocchi et al. (2008) (170); Funayama et al. (2006)) were used to estimate the 2-week rates of the included complications. Surgical complications occurred for any patient at the model time when the patient experienced a surgery. The rates varied by ±20.0%. Table 80 shows the model surgical complication inputs.

Table 80: Surgical complication rates per 2-week cycle

Parameter	Probability (%)		SE	DSA (%) (low; high)	Source/Note
	Annual	2-week cycle			
Surgical complications					
Wound infection	42.41	2.10	0.0021	1.68; 2.52	Base: Pooled estimates from various studies (McLeod et al. (2009) (160) ; Milsom et al. (2001) (161) ; Zurbuchen et al. (2013) (162) ; Kusunoki et al. (1998) (163) ; Fazio et al. (1996) (164); Irvin et al. (1973) (165); Eshuis et al. (2010); Maartenese et al. (2006) (167); Ikeuchi et al. (2000) (168) ; Cameron et al. (1992) (169) ; Stocchi et al. (2008) (170) ; Funayama et al. (2006) (171)). Low/high: assumption, ±20.0%.
Prolonged ileus/bowel obstruction	25.97	1.15	0.0012	0.92; 1.38	
Intra-abdominal abscess	9.90	0.40	0.0004	0.32; 0.48	
Anastomotic leak	23.40	1.02	0.0010	0.82; 1.22	

Abbreviations: DSA, deterministic sensitivity analysis; NICE, National Institute for Health and Care Excellence; SE, standard error; TA, technology appraisal.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

B.3.4.1.1 CDAI-based health utilities (base case)

EQ-5D-5L data were collected from the risankizumab CD induction (ADVANCE, MOTIVATE) and maintenance (FORTIFY) studies. Individual patient data were used to estimate the mean EQ-5D-3L health utility, using UK tariffs and the Hernandez-Alava et al. (2020) crosswalk (172). The crosswalk from EQ-5D-5L to EQ-5D-3L was conducted for each of the CDAI-based health states. Data for all patients in the ITT1A population were included. Observations were limited to those where both a CDAI score and EQ-5D score were recorded.

The mean EQ-5D score associated with each health state was estimated by regressing EQ-5D on CDAI-based health state using ordinary least squares (OLS) regression. The health utility estimates used as inputs in the base case of the model based on the OLS regression are presented in Table 81. Surgical health utility was assumed to be the same as in the 'Moderate-to-severe CD' health state (i.e., the utility experienced when undergoing surgery was assumed to be equivalent to having moderate-to-severe disease); this assumption was made due to a lack of utility data for patients undergoing surgery. Additionally, it was assumed that the post-surgical tunnel states have the same utility score as in remission. Essentially, in the first cycle of a surgery, the utility values for surgery were the same as for the 'Moderate-to-severe CD' state; for the next three cycles, the utility values were the same as for remission. The same utility values were used regardless of population or treatment status (i.e., there is no difference assumed in utilities between the CCF and BF populations) with the logic that the health state patients are in is the driver of their utility and not the class of treatments they are on.

Table 81: Health utilities used in base case (based on RZB clinical trial analysis)

Parameter	Mean (SE)	DSA (low; high)	Source/Note
Remission (CDAI < 150)	[redacted]	[redacted]	Base and low/high: RZB trial data. Post-hoc analysis of ADVANCE, MOTIVATE and FORTIFY ITT1A population
Mild CD (150 ≤ CDAI < 220)	[redacted]	[redacted]	
Moderate-to-severe CD (CDAI 220+)	[redacted]	[redacted]	
Surgery (first cycle)	[redacted]	[redacted]	Assumed equal to the 'Moderate-to-severe CD' health state
Surgery (subsequent three cycles)	[redacted]	[redacted]	Assumed equal to the 'remission' health state
Age-adjusted disutilities (average age of utility research: 40)			
Age	-0.000173	-0.0009050; .000560	Base and low/high: NICE TA456, ERG Report Table 63. Data from Ara and Brazier 2010 (173).
Age^2	-0.000034	-0.000042; -0.000026	

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; DSA, deterministic sensitivity analysis; ERG, Evidence Review Group; ITT, Intention-to-treat; NICE, National Institute for Health and Care Excellence; RZB, risankizumab; RCT, randomised controlled trial; SE, standard error; TA, technology appraisal.

B.3.4.2 Mapping

Mapping of utilities was performed to convert the EQ-5D-5L utilities gathered in the risankizumab CD studies (ADVANCE, MOTIVATE, FORTIFY) using the Hernandez-Alava et al. (2020) (172) mapping algorithm, as described in Section B.3.4.1. Scenario analyses using alternative utility data sources also utilised mapping, conducted by the original researchers; the methods used for these scenarios are described alongside the scenario results in Section B.3.11.3.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify studies reporting on the HRQoL of patients with moderate-to-severe CD. Full details of the methodology and results of included studies are presented in Appendix H.

B.3.4.4 Adverse reactions

Disutilities associated with treatment-related AEs were included in the model base case analyses and are presented in Table 82. These were one-time decrements experienced in the cycle when a simulated patient incurred an AE based on the treatment specific probabilities.

Table 82: Utility decrements of adverse events

Parameter	Mean	SE	DSA (low; high)	Source
Adverse event-related utility decrements				
Serious infections	-0.520	0.01	-0.510; -0.530	Brown et al. (2001) (174)
Tuberculosis	-0.550	0.01	-0.539; -0.561	Porco et al. (2006) (175)
Lymphoma	-0.195	0.00	-0.191; -0.199	Hornberger et al. (2008) (176)
Hypersensitivity	-0.110	0.00	-0.108; -0.112	Beusterien et al. (2010) (177)
Skin reactions	-0.030	0.00	-0.029; -0.031	Beusterien et al. (2009) (178)

Abbreviations: DSA, deterministic sensitivity analysis; SE, standard error.

Note that surgical complications did not incur health utility decrements in the model but only affected costs. Because surgery is modelled as a health state, the utility for surgery was presumed to include the expected utility loss from complications.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The base-case utility values that were used in the model were the risankizumab CD trial data, as per NICE reference case (179), are listed below in Table 83.

Table 83: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission	Justification
Remission (CDAI < 150)	[redacted]	[redacted]	Section B.3.4.1, page 159	Utilises risankizumab CD trial data directly; corresponds with NICE reference case (179)
Mild CD (150 ≤ CDAI < 220)	[redacted]	[redacted]		
Moderate-to-severe CD (CDAI 220+)	[redacted]	[redacted]		
Surgery (first cycle) †	[redacted]	[redacted]		
Surgery (subsequent three cycles)	[redacted]	[redacted]		

Abbreviations: CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; NICE, National Institute for Health and Care Excellence; SE, standard error.
† Assumed same as in moderate-to-severe CD.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Details of the systematic identification of studies reporting cost and resource use data are presented in Appendix I. In total, 91 studies were identified which reported cost or resource use data relating to the management of CD. Fourteen studies were considered relevant to the UK. None of the identified studies had more recent data available than the sources identified below, and therefore none of the studies identified via the literature review were used as a source for costs or healthcare resources in the model.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Drug acquisition costs were taken from the British National Formulary (BNF) (180-183). The acquisition costs for risankizumab and other biologic therapy comparators are presented in Table 85. Expected induction and maintenance drug acquisition costs on continuous treatment are presented in Table 86. Maintenance costs are for patients who are responders and remain on therapy for one year. Dosing for each cycle was taken from the approved labels for each therapy (see Section B.3.2.3, Table 58). Weight-based dosing (as used for ustekinumab induction) utilised the weight distribution of patients from the post-hoc analysis of risankizumab CD trials as shown below in Table 84.

Table 84: Weight distributions and corresponding ustekinumab induction doses

Parameter	Value	Ustekinumab induction dose	Source
Proportion ≤55kg	17.83%	260 mg	Distribution: Post-hoc analysis of MOTIVATE and ADVANCE ITT1A population; dosing: ustekinumab SmPC (92)
Proportion >55kg and ≤85kg	65.46%	390 mg	
Proportion >85kg	16.71%	520 mg	
Weighted average	N/A	389 mg	Calculation

Abbreviations: ITT, intention-to-treat; SmPC, Summary of Product Characteristics.

Table 85: Drug acquisition costs

Treatment	Per dose (£)	Source/Note
RZB IV (600 mg)	[redacted]	[redacted]
RZB SC (360 mg)	[redacted]	
UST IV (130 mg)	2,147.00	Base: BNF accessed on 7 June 2022. Low/high: not varied.
UST SC (90 mg)	2,147.00	
VDZ IV (300 mg)	2,050.00	
VDZ SC (108 mg)	512.50	
ADA (cheapest biosimilar available) (per 40 mg)	316.80	
ADA 160/80 (Humira®) (per 40 mg)	352.14	
ADA 80/40 (Humira®) (per 40 mg)	352.14	
IFX IV (Remicade®)	419.62	
IFX IV (cheapest biosimilar available)	377.00	
IFX SC (Remsima® SC)	377.66	
Conventional care (per cycle)†	13.76	Base: Daily cost: eMIT, where drugs were not available, BNF data was used (accessed 08 June 2022). The cheapest non-proprietary prices (drug tariff price) have been used in the model. Dose per day taken from TA352 (47), ACD table 27, assuming mean weight of 71.15kg. Usage weight: TA456. Low/high: not varied.

Abbreviations: ADA, adalimumab; ACD, appraisal consultation document; BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; IFX, infliximab; IV, intravenous; NICE, National Institute for Health and Care Excellence; PAS, Patient Access Scheme; RZB, risankizumab; SC, subcutaneous; TA, technology appraisal; UST, ustekinumab; VDZ, vedolizumab.
† Conventional care detailed costings are shown in Table 88.

Table 86: Expected induction and maintenance drug acquisition costs

Treatment	Dosing (reference)	Induction period		Maintenance period†	
		No. of units	Total cost (£)	No. of units	Total cost (£)
Standard dose					
RZB	Induction: 600 mg IV at weeks 0, 4 and 8; Maintenance: 360 mg SC Q8W from week 12 (3, 4)	3.00	[redacted]	5	[redacted]
UST	Induction: 6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 & <85 kg: 390 mg; >85kg: 520 mg ; Maintenance: 90 mg SC Q12W from week 8 (90)	2.99	6,417	4	8,588
VDZ IV	Induction: 300 mg IV weeks 0, 2 and 6; Maintenance: 300 mg IV Q8W from week 14 (89)	3.00	6,150	5	10,250
VDZ SC	Induction: 300 mg IV at weeks 0, 2 and 6 (89); Maintenance: 108 mg SC Q2W from week 14 (155)	3.00	6,888	19	9,738
ADA 160/80 biosimilar	Induction: 160 mg SC at week 0; 80 mg SC at week 2 ; Maintenance: 40 mg SC Q2W from week 4 (113)	6.00	1,902	24	7,603
ADA 160/80	Induction: 160 mg SC at week 0; 80 mg SC at week 2; Maintenance: 40 mg SC Q2W from week 4 (113)	6.00	2,113	24	8,451
ADA 80/40	Induction: 80 mg SC at week 0; 40mg SC at week 2; Maintenance: 40 mg SC Q2W from week 4 (113)	3.00	1,056	24	8,451
IFX IV	Induction: 5 mg/kg IV at weeks 0 and 2, dose at week 6 for responders ; Maintenance: 5 mg/kg IV Q8W from week 14 (114)	8.00	3,357	24	10,071
IFX IV biosimilar	Induction: 5 mg/kg IV at weeks 0 and 2, dose at week 6 for responders; Maintenance: 5 mg/kg IV Q8W from week 14 (97)	8.00	3,016	24	9,048
IFX SC	Induction: 5 mg/kg IV at weeks 0 and 2 (114); Maintenance: 120 mg SC Q2W from Week 6 (156)	8.00	3,016	23	8,686
High dose					
UST	Maintenance: 90 mg SC Q8W (90)	2.99	6,417	6	12,882
VDZ	Maintenance: 300 mg IV Q4W (89)	3.00	6,150	11	22,550
ADA 160/80 biosimilar	Maintenance: 40 mg SC every week (113)	6.00	1,901	48	15,206
ADA 160/80	Maintenance: 40 mg SC every week (113)	6.00	2,113	48	16,903
ADA 80/40	Maintenance: 40 mg SC every week (113)	3.00	1,056	48	16,903
IFX IV	Maintenance: 10 mg/kg IV Q8W (114)	8.00	3,357	48	20,142
IFX IV biosimilar	Maintenance: 10 mg/kg IV Q8W (97)	8.00	3,016	48	18,096

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; NICE, National Institute for Health and Care Excellence; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.
† Maintenance Year 1 includes time from Markov model start (i.e., end of induction) to the end of Week 52 and also considers discontinuation rates on a per-comparator basis.

B.3.5.1.2 Administration costs

Drug administration costs which included infusion costs and one SC training cost for self-administered injections were included in the model (Table 87). Induction doses of risankizumab, ustekinumab, vedolizumab and infliximab were administered via IV infusion. Maintenance treatment with risankizumab, ustekinumab, vedolizumab SC and infliximab SC, and all treatments with adalimumab were administered as a SC injection. Infusions (IV) were giving in a hospital setting; SC administrations assumed a cost for the first dose only (training by a nurse) and no additional cost to the NHS for subsequent doses (as these are typically self-administered).

Table 87: Drug administration costs

Admin route	Cost (£)	SE	DSA (low; high)	Source/Note
First administration				
SC	41	4.08	39; 49	Base: PSSRU 2021 (184) Cost per working hour of band 5 Nurse, accessed in June 2022. Low/high: assumption, ±20.0%
IV	245	25.00	196; 294	Base: NHS Payment by Results tariff 2020/21 (82) – Inflammatory Bowel Disease without Interventions, with CC Score 0 (item code: FD02H) accessed in June 2022, consistent with TA352 (47). Low/high: assumption, ±20.0%
Subsequent administration(s)				
SC	0	10.20	0; 41	Base: Assumption, subsequent SC are self-administered or provided free of charge to the NHS. Low: same as base. High: Same as SC first administration.
IV	245	25.00	196; 294	Base: NHS Payment by Results tariff 2020/21 (82) – Inflammatory Bowel Disease without Interventions, with CC Score 0 (item code: FD02H) accessed in June 2022, consistent with TA352 (47). Low/high: assumption, ±20.0%

Abbreviations: CC, conventional care; DSA, deterministic sensitivity analysis; IV, intravenous; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SC, subcutaneous; SE, standard error; TA, technology appraisal.

B.3.5.1.3 Concomitant medication costs

Concomitant medication costs were sourced from the Drugs and pharmaceutical electronic market information tool (eMIT) (mesalazine, sulfasalazine, prednisolone, azathioprine and methotrexate) or the BNF if the drugs were not available in the eMIT (balsalazide, olsalazine, budesonide and mercaptopurine); both accessed in June

2022. The cheapest non-proprietary prices (drug tariff price) were used in the model. Dose per day was obtained from the BNF as per the methods used in TA352 (Table 7.5.5.3) (47), assuming a mean patient weight of 71.15kg (46). The usage weight was taken from TA456, as described in Section B.3.2.3 (46). Individual concomitant drug costs and usage weights were used (i.e., the sum of the products) to calculate a daily weighted cost (£0.98) which was then used to determine the total cost of a 14-day cycle (£13.76).

Table 88: Concomitant drug costs and expected proportion of patients on each

Drug	Dose and frequency	Pack size (tablets)	Pack price (£)	Daily cost (£)	Usage weight
Balsalazide†	1500 mg BID	130	30.42	0.94	5%
Mesalazine†	1800 mg QD	30	15.50	0.58	5%
Olsalazine	500 mg BID	112	19.77	0.71	5%
Sulfasalazine	500 mg four times a day	112	10.22	0.37	5%
Budesonide†	3 mg three times a day	100	75.05	2.25	6%
Prednisolone	20 mg QD	28	3.30	0.12	19%
Azathioprine‡	143 mg QD	56	1.57	0.08	57%
Mercaptopurine†‡	178.75 mg QD	25	22.54	6.45	10%
Methotrexate‡	17.5 mg QW	100	4.23	0.04	11%

Abbreviations: BID, twice daily; QD, once daily; QW, once weekly. † Cost sourced from BNF. ‡ An average of the recommended dose range was used. Reference: drug costs: eMIT, where drugs were not available, BNF data was used (accessed 08 June 2022). The cheapest non-proprietary prices (drug tariff price) have been used in the model. Dose per day taken from TA352 (47), ACD table 27, assuming mean weight of 71.15kg. Usage weight: TA456 (46).

The proportion of patients on biologic therapies also receiving CC is presented in Table 89. Based on CC usage from FORTIFY (Table 12), it was assumed that 68.1% of patients on biologic therapies were on CC.

Table 89: Proportion of patients on biologic regimens also receiving CC

Parameter	Percent	SE	DSA (low; high values)
Treatment-related costs (£) – Percent receiving conventional care			
All biologic regimens	68.1	0.05	54; 82

Abbreviations: CC, conventional care; DSA, deterministic sensitivity analysis; SE, standard error.

B.3.5.2 Health-state unit costs and resource use

Health-state costs were taken from TA456 (46) for the base-case analysis (Table 90). This are the most recent, best available evidence available. Estimates for HCRU used in TA456 were gathered from a modified Delphi panel, in which 12 clinicians estimated resource use for each model health state. Information was collected via telephone interviews and a face-to-face meeting to determine frequency of usage for all items. Costs were inflated to 2020/21 values and adjusted to 2-week cycle values.

Table 90: Health-state costs per 2-week cycle

Parameter	Mean (£)	DSA (low; high values)	Source/Note
On biologic			
Remission (CDAI < 150)	50.39	40.31; 60.47	Base: TA456 (46). Values inflated to 2020/21. Low/high: assumption, ±20.0%
Mild CD (150 ≤ CDAI < 220)	250.64	200.51; 300.77	
Moderate-to-severe CD (CDAI 220+)	609.17	487.34; 731.01	
Off biologic			
Remission (CDAI < 150)	18.40	14.72; 22.08	Base: TA456 (46). Values inflated to 2020/21. Low/high: assumption, ±20.0%
Mild CD (150 ≤ CDAI < 220)	335.54	268.43; 402.65	
Moderate-to-severe CD (CDAI 220+)	609.17	487.34; 731.01	

Abbreviations: CD, Crohn's disease; CDAI, Crohn's disease activity index; DSA, deterministic sensitivity analysis; SE, standard error; TA, technology appraisal.

B.3.5.3 Adverse reaction unit costs and resource use

The cost of surgery as used in the model is shown below in Table 91. The cost of surgical complications and adverse reactions, with their corresponding International Classification of Diseases (ICD-10) and Health Resource Group (HRG) codes, are shown in Table 92 and Table 93.

Table 91: Surgical procedure costs

Surgical procedure costs	Value (£)	Reference
Surgery cost	9,947	NICE TA456, ERG Report Table 68 (46). Values inflated to 2020/21

Abbreviations: ERG, Evidence Review Group; NICE, National Institute for Care and Health Excellence; TA, technology appraisal.

Table 92: List of surgical complications and summary of costs in the economic model

Surgical complication costs	Value (£)	ICD-10 code (HRG code)	Reference
Wound infection	986	T81.4 (WH07G)	NHS HRG4+ Payment Grouper 2021/22 (185); NHS Schedule of Reference Costs 2019/20(186)
Prolonged ileus / bowel obstruction	839	K56.6 (FD10M)	
Intra-abdominal abscess	986	T81.4 (WH07G)	
Anastomotic leak	986	T81.4 (WH07G)	

Abbreviations: HRG, health resource group; ICD, International Classification of Diseases; NHS, National Health Service.

Table 93: List of adverse reactions and summary of costs in the economic model

Adverse reactions	Value (£)	ICD-10 code (HRG code)	Reference
Serious infections	1,531	A41.X (WJ06J)	NHS HRG4+ Payment Grouper 2021/22 (185); NHS Schedule of Reference Costs 2019/20 (186)
Tuberculosis	1,894	A15.0 (DZ14J)	
Lymphoma	842	C85.1 (SA31F)	
Hypersensitivity	412	T78.4 (WH05Z)	
Skin reactions	986	T88.1 (WH07G)	

Abbreviations: HRG, health resource group; ICD, International Classification of Diseases; NHS, National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

No additional miscellaneous costs are considered in the cost-effectiveness model.

B.3.6 Severity

CD has a significant burden on patients in terms of QoL, as discussed in B.1.3.2. No impact on survival for CD patients was considered in the model, so the probability of survival of a CD patient is assumed to be equivalent to that of the general population, as validated by clinical experts (187). The QALY shortfall calculator developed by Schneider et al. (2022) (188) was used to generate results. The key inputs for the QALY shortfall analysis are presented in Table 94.

Table 94: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	54.9% male (CCF), 52.5% male (BF)	Section B.3.3.1, Table 60
Starting age	38.83 (CCF), 38.22 (BF)	
EQ-5D dataset used	Hernandez Alava et al. (2020) (172), EQ-5D-5L to 3L mapping + HSE 2017-2018	Section B.3.4.5, Table 83

Abbreviations: BF, biologic failure; CCF, conventional care failure; ED-5D-5L, EuroQol, 5 Dimension health questionnaire; HSE, Health Survey for England; QALY, quality-adjusted life year.

The QALY shortfall identified in TA456 (ustekinumab) (46) is presented in Table 95. 'Current treatment' is defined as 'conventional care' as this is likely to be the least effective frequently used treatment and will have the largest potential QALY shortfall. TA352 (vedolizumab) did not attempt to model a lifetime time horizon, and therefore it was not possible to gain lifetime QALY estimates for conventional care in this appraisal. TA456 (46) did not meet the 12-year absolute shortfall threshold required to trigger the QALY weight modifier. The population demographics for TA456 (46), i.e., mean age of 39.2 and male proportion of 47.1% were used to estimate general population utility values.

Table 95: Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment (conventional care)	QALY shortfall (absolute)	QALY shortfall (proportional)
TA456 (CCF population)	18.07	12.65	5.42	30.00%
TA456 (TNF failure population)	18.07	12.72	5.35	29.61%

Abbreviations: CCF, conventional care failure; QALY, quality-adjusted life year; TA, technology appraisal; TNF, tumour necrosis factor.

The disaggregated utilities and life years used in the model for CC are shown in Table 96, with the summary of the results for the QALY shortfall analysis in Table 97.

Table 96: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value mean (SE)	Undiscounted life years	
		CCF	BF
Remission (CDAI < 150)	0.859	2.074	2.150
Mild CD (150 ≤ CDAI < 220)	0.756	15.432	15.618
Moderate-to-severe CD (CDAI 220+)	0.596	20.758	21.135
Surgery	0.596	0.087	0.088
Post-surgery	0.859	0.261	0.264

Abbreviations: BF, biologic failure; CCF, conventional care failure; CD, Crohn's disease; CDAI, Crohn's disease activity index; QALY, quality-adjusted life year; SE, standard error; TA, technology appraisal; TNF, tumour necrosis factor.

Table 97: Summary of QALY shortfall analysis

Treatment	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall (absolute)	QALY shortfall (proportional)
CCF population				
RZB	18.07	[redacted]	[redacted]	[redacted]
UST	18.07	[redacted]	[redacted]	[redacted]
ADA 160/80	18.07	[redacted]	[redacted]	[redacted]
ADA 80/40	18.07	[redacted]	[redacted]	[redacted]
IFX IV	18.07	[redacted]	[redacted]	[redacted]
IFX SC	18.07	[redacted]	[redacted]	[redacted]
BF population				
RZB	18.30	[redacted]	[redacted]	[redacted]
UST	18.30	[redacted]	[redacted]	[redacted]
VDZ IV	18.30	[redacted]	[redacted]	[redacted]
VDZ SC	18.30	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

B.3.7 Uncertainty

Whilst all practical measures were taken to minimise uncertainty in the analysis, there are still several key areas of uncertainty. These are described in the following section along with explanations of how they were addressed.

B.3.7.1 Uncertainty concerning subsequent treatment options and the impact they may have on patient outcomes

The model used a simplifying assumption when patients discontinue biologic therapy; all patients were assumed to transition to CC alone. This assumption was made due to a lack of treatment sequencing efficacy data available following discontinuation of biologic therapy. In addition to the lack of data, there are other challenges for modelling treatment sequencing, including that there is no set order in which all available biologics may be used, and this is heavily dependent on clinician and patient choice. Previous biologic (or class) exposure influences potential responses to subsequent biologic treatment, creating further obstacles for accurate and informative modelling.

A key assumption was therefore made (consistent with the assumption made in all previous CD submissions including TA456 (46)): patients would experience the same outcomes following discontinuation of initial biologic therapy regardless of which subsequent treatment they were on. This limited the time horizon where incremental differences in treatment effect were experienced to the duration of first biologic therapy. As all treatments would experience the same outcomes (i.e., transition probabilities) after their initial biologic therapy, no incremental difference in outcomes would be experienced; therefore, the model does not need to capture these. Hence, it was assumed that all patients would move to CC after discontinuation of initial biologic treatment.

B.3.7.2 Uncertainty concerning previous treatment options and the impact they may have on patient outcomes

Uncertainty concerning previous treatment options were due to the different previous treatments that subjects received in the comparator trials: reporting of prior treatments or patient response to prior treatments was not known. The analysis was also impacted by the availability of biologic therapies at the time the trials were conducted. For example, the vedolizumab registrational trials (GEMINI 2 (105), GEMINI 3 (116)), were conducted prior to the availability of ustekinumab and therefore only included TNF-alpha inhibitors in its BF population (116). However, in later studies (e.g., the risankizumab studies), the BF population included patients who had been on ustekinumab and/or vedolizumab previously. Overall, the risankizumab studies enrolled a more refractory population when compared with the other recently licensed biologic therapies (i.e., ustekinumab and vedolizumab). To date, the registrational trials for all approved biologics enrolled a CCF population and/or a single or multiple TNF-alpha inhibitor failure population (89, 92, 113, 114).

B.3.7.3 Uncertainty inherent to the NMAs

The clinical evidence used to inform the NMA is another key area of uncertainty. The primary driver of uncertainty in the NMA was the difference in placebo rates; this was addressed in part by the use of the RD method which sought to minimise the impact of variable placebo rates experienced across trials (previously discussed in Section B.2.9.3). Another way in which between-trial heterogeneity (namely lack of a common

comparator in the maintenance phase, placebo efficacy in maintenance trials and different criteria used for patients entering the maintenance phase) was addressed was by splitting the maintenance NMA into two separate networks (previously discussed in Section B.2.9.3.2).

B.3.7.4 Use of CDAI outcomes

The use of CDAI-based outcomes introduced uncertainty as this measure of disease activity is not widely used in UK clinical practice. However, CDAI has some relevance to the HBI, a commonly used measure of disease severity in the UK, given that both disease severity measures share several common items for disease measurement (32). CDAI was used as this is a well-reported outcome in CD clinical trials and facilitates indirect treatment comparisons with previous trials of treatments for CD (104, 105), maximising the potential to construct networks in the NMAs. Endoscopic outcomes, such as mucosal healing, are recognised as important clinical targets in UK clinical practice (35). The company acknowledges that an NMA performed using endoscopic outcomes would potentially be more relevant to UK clinical practice. However, this approach was not taken due to limited availability of endoscopic data for comparators (limited data was only available for risankizumab and ustekinumab overall populations), heterogeneity in trial design, trial populations and outcome definitions. Consequently, whilst endoscopic outcomes are also relevant to UK clinical practice, any analysis would be limited in its usefulness due to the limitations described.

B.3.8 Managed access proposal

Not applicable.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Base-case results are presented for both the CCF and BF populations. Results are shown using list prices for all treatments, except risankizumab. Several comparators have a confidential Patient Access Scheme (PAS); results are therefore presented using their list prices.

Results are reported below based on probabilistic analysis using the following settings in Table 98 and all variables reported in Table 99.

Table 98: Base-case settings

Setting	Base case setting	Reference to section in submission
Perspective	NHS in England and Wales, and PSS	Section B.3.2.2
Time horizon	60 years (to a max of 101 years of age)	Section B.3.2.2
Annual probability of surgery	7.28% ('Moderate-to-severe CD' health state only)	Section B.3.3.6
Main source of efficacy data	Risk-difference fixed-effects NMA data (pivotal trial data used)	Section B.2.9.2.1
Utility values	ADVANCE/MOTIVATE/FORTIFY trial EQ-5D-5L values mapped to EQ-5D-3L using Hernandez-Alava et al. (2020) (172)	Section B.3.4.5
Treatment duration (biologic)	1 year	Section B.3.3.4
Duration of post-discontinuation residual treatment effect	1 year	Section B.3.3.4
Proportion of patients on concurrent conventional care whilst on biologic treatment	68.1%	Section B.3.5.1.3

Abbreviations: CD, Crohn's disease; EQ-5D, EuroQol 5 Dimensions health questionnaire; NHS, National Health Service; NMA, network meta-analysis; PSS, Personal Social Services.

Table 99: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
General model parameters					
Time horizon (years)	60 (Table 59)	N/A	N/A	40; 80	B.3.3.1
Discount rates (cost and utilities) (%)	3.5 (Table 59)	N/A	N/A	N/A	B.3.3.1
Baseline patient characteristics (CCF population)					
Mean patient age (years)	38.83 (Table 60)	0.73 (NORM)	N/A	37.40; 40.26	B.3.3.1
Mean proportion male (%)	54.9 (Table 60)	0.03 (BETA)	196.5; 161.5	49.7; 60.0	B.3.3.1
Weight (kg) mean	71.15 (Table 60)	0.93 (NORM)	N/A	69.33; 72.97	B.3.3.1
Weight (kg) <55kg	17.8 (Table 60)	(DIRICHLET)	64.00	100.0; 0.0	B.3.3.1
Weight (kg) >55kg and ≤85kg	65.5 (Table 60)	(DIRICHLET)	235.00	0.0; 0.0	B.3.3.1
Weight (kg) >85kg	16.7 (Table 60)	(DIRICHLET)	60.00	0.0; 100.0	B.3.3.1
Baseline patient characteristics (BF population)					
Mean patient age (years)	38.2 (Table 60)	0.40 (NORM)	N/A	37.43; 39.01	B.3.3.1
Mean proportion male (%)	52.5 (Table 60)	0.02 (BETA)	555.47; 503.52	49.4; 55.5	B.3.3.1
Weight (kg) mean	71.2 (Table 60)	0.59 (NORM)	N/A	70.05; 72.35	B.3.3.1
Weight (kg) <55kg	19.1 (Table 60)	(DIRICHLET)	202.00	100.0; 0.0	B.3.3.1
Weight (kg) >55kg and ≤85kg	61.1 (Table 60)	(DIRICHLET)	648.00	0.0; 0.0	B.3.3.1
Weight (kg) >85kg	19.8 (Table 60)	(DIRICHLET)	210.00	0.0; 100.0	B.3.3.1
Induction: CCF population CDAI-100 response (%)					
RZB	[redacted]Table 61[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
UST	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
ADA 160/80 / ADA 160/80 biosimilar†	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
ADA 80/40	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
IFX IV / IFX IV biosimilar	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
IFX SC	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
Induction: BF population CDAI-100 response (%)					
RZB	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
UST	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
VDZ IV	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
VDZ SC	[redacted]Table 60[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.1
Induction: CCF population remission (CDAI < 150) (%)					
RZB	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
UST	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
ADA 160/80 / ADA 160/80 biosimilar†	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
ADA 80/40	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
IFX IV / IFX IV biosimilar† / IFX SC	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
Induction: BF population remission (CDAI < 150) (%)					
RZB	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
UST	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
VDZ IV	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
VDZ SC	[redacted]Table 62[redacted]	(CODA)	N/A	[redacted]	B.3.3.2.2
Induction - Percent of responders remaining moderate-severe: CCF population					
Moderate-severe (CDAI 220+)	8.4 (Table 63)	0.019 (BETA)	17.92; 196.08	4.7; 12.1	B.3.3.3.1
Induction - Percent of responders remaining moderate-severe: BF population					
Moderate-severe (CDAI 220+)	7.8 (Table 63)	0.011 (BETA)	42.92; 510.08	5.5; 10.0	B.3.3.3.1
Induction - Percent of non-responders remaining moderate-severe: CCF population					
Moderate-severe (CDAI 220+)	71.8 (Table 63)	0.042 (BETA)	83.28; 32.72	63.6; 79.9	B.3.3.3.1
Induction - Percent of non-responders remaining moderate-severe: BF population					

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
Moderate-severe (CDAI 220+)	73.5 (Table 63)	0.022 (BETA)	287.27; 103.73	69.1; 77.8	B.3.3.3.1
Maintenance treatment phase (weeks)					
Maximum treatment duration	52	N/A	N/A	52; 156	B.3.3.3
Duration of post maintenance response	52	N/A	N/A	24; 72	B.3.3.3
Maintenance - Proportion starting standard (vs. high) dose: CCF population (%)					
UST	7.5 (Table 78)	0.01 (BETA)	88.76; 1,094.69	6.0; 9.0	B.3.3.4.5
ADA 160/80 / ADA 160/80 biosimilar† / ADA 80/40	100.0 (Table 78)	0.05 (BETA)	16.70; 0.90	80.0; 100.0	B.3.3.4.5
IFX IV / IFX IV biosimilar†	100.0 (Table 78)	0.05 (BETA)	16.70; 0.90	80.0; 100.0	B.3.3.4.5
IFX SC	100.0 (Table 78)	0.00 (BETA)	N/A	100.0; 100.0	B.3.3.4.5
Maintenance - Proportion starting standard (vs. high) dose: BF population (%)					
UST	7.5 (Table 78)	0.01 (BETA)	88.76; 1,094.69	6.0; 9.0	B.3.3.4.5
VDZ IV	100.0 (Table 78)	0.05 (BETA)	16.70; 0.90	80.0; 100.0	B.3.3.4.5
VDZ SC	100.0 (Table 78)	0.00 (BETA)	N/A	100.0; 100.0	B.3.3.4.5
Maintenance - Dose escalation per 2-week cycle (%)					
UST	9.4 (Table 74)	0.0096 (BETA)	86.95; 841.16	7.5; 11.2	B.3.3.4.1
ADA 160/80 / ADA 160/80 biosimilar† / ADA 80/40	2.6 (Table 74)	0.0027 (BETA)	93.51; 3,503.16	2.1; 3.1	B.3.3.4.1
IFX IV / IFX IV biosimilar†	1.9 (Table 74)	0.0019 (BETA)	94.19; 4,863.32	1.5; 2.3	B.3.3.4.1
IFX SC	0.0 (Table 74)	0.0000 (BETA)	N/A	N/A	B.3.3.4.1
VDZ IV	1.4 (Table 74)	0.0014 (BETA)	94.71; 6,857.00	1.1; 1.6	B.3.3.4.1
VDZ SC	0.0 (Table 74)	0.0000 (BETA)	N/A	N/A	B.3.3.4.1
Maintenance - Discontinuation due to lack of efficacy per 2-week cycle (%)					
RZB	0.2 (Table 75)	0.0002 (BETA)	95.87; 57,275.88	0.1; 0.2	B.3.3.4.2
UST	0.3 (Table 75)	0.0003 (BETA)	95.73; 29,818.63	0.3; 0.4	B.3.3.4.2
ADA 160/80 / ADA 160/80 biosimilar† / ADA 80/40	0.3 (Table 75)	0.0003 (BETA)	95.72; 29,599.83	0.3; 0.4	B.3.3.4.2

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
IFX IV / IFX IV biosimilar† / IFX SC	0.3 (Table 75)	0.0003 (BETA)	95.72; 29,599.83	0.3; 0.4	B.3.3.4.2
VDZ IV	2.0 (Table 75)	0.0021 (BETA)	94.06; 4,530.84	1.6; 2.4	B.3.3.4.2
VDZ SC	2.0 (Table 75)	0.0021 (BETA)	94.06; 4,530.84	1.6; 2.4	B.3.3.4.2
Maintenance - Standard dose maintenance: CCF population remission (CDAI < 150) (%)					
RZB	[redacted]	(CODA)	N/A	[redacted]	
UST	[redacted]	(CODA)	N/A	[redacted]	
ADA 160/80 / ADA 160/80 biosimilar† / ADA 80/40	[redacted]	(CODA)	N/A	[redacted]	
IFX IV / IFX IV biosimilar† / IFX SC	[redacted]	(CODA)	N/A	[redacted]	
Maintenance - Standard dose maintenance: BF population remission (CDAI < 150) (%)					
RZB	[redacted]	(CODA)	N/A	[redacted]	
UST	[redacted]	(CODA)	N/A	[redacted]	
VDZ IV	[redacted]	(CODA)	N/A	[redacted]	
VDZ SC	[redacted]	(CODA)	N/A	[redacted]	
Maintenance CC after response: CCF population remission (CDAI < 150) (%)					
RZB	[redacted]	(CODA)	N/A	[redacted]	
UST	[redacted]	(CODA)	N/A	[redacted]	
ADA 160/80 / ADA 160/80 biosimilar† / ADA 80/40	[redacted]	(CODA)	N/A	[redacted]	
IFX IV / IFX IV biosimilar† / IFX SC	[redacted]	(CODA)	N/A	[redacted]	
Maintenance CC after response: BF population remission (CDAI < 150) (%)					
RZB	[redacted]	(CODA)	N/A	[redacted]	
UST	[redacted]	(CODA)	N/A	[redacted]	
VDZ IV	[redacted]	(CODA)	N/A	[redacted]	
VDZ SC	[redacted]	(CODA)	N/A	[redacted]	
Surgery - Surgery per 2-week cycle (%)					

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
Moderate-severe (CDAI 220+)	0.28 (Table 76)	0.0021 (BETA)	1.82; 652.68	0.00; 0.81	B.3.3.4.3
Surgery - Post-surgery distribution - CCF (%) (N=199)					
Remission (CDAI < 150)	0.021 (Table 77)	0.00 (BETA)	94.00	0.017; 0.025	B.3.3.4.4
Surgery - Surgical complications per 2-week cycle (%)					
Wound infection	1.15 (Table 80)	0.0012 (BETA)	94.92; 8,159.04	0.92; 1.38	B.3.3.6
Prolonged ileus/bowel obstruction	0.40 (Table 80)	0.0004 (BETA)	95.65; 23,816.43	0.32; 0.48	B.3.3.6
Intra-abdominal abscess	1.02 (Table 80)	0.0010 (BETA)	95.05; 9,223.26	0.82; 1.22	B.3.3.6
Anastomotic leak	0.19 (Table 80)	0.0002 (BETA)	95.85; 51,061.79	0.15; 0.22	B.3.3.6
AEs - Serious infections per 2-week cycle (%)					
RZB	0.34 (Table 79)	0.0003 (BETA)	95.71; 28,053.28	0.27; 0.41	B.3.3.5
UST	0.32 (Table 79)	0.0003 (BETA)	95.73; 29,818.63	0.26; 0.38	B.3.3.5
ADA 160/80 / ADA 160/80 biosimilar†	0.32 (Table 79)	0.0003 (BETA)	95.73; 29,818.63	0.26; 0.38	B.3.3.5
ADA 80/40	0.20 (Table 79)	0.0002 (BETA)	95.84; 47,825.36	0.16; 0.24	B.3.3.5
IFX IV / IFX IV biosimilar†	0.20 (Table 79)	0.0002 (BETA)	95.84; 47,825.36	0.16; 0.24	B.3.3.5
IFX SC	0.32 (Table 79)	0.0003 (BETA)	95.73; 29,818.63	0.26; 0.38	B.3.3.5
VDZ IV	0.32 (Table 79)	0.0003 (BETA)	95.73; 29,818.63	0.26; 0.38	B.3.3.5
VDZ SC	0.30 (Table 79)	0.0003 (BETA)	137.87; 45,820.34	0.25; 0.35	B.3.3.5
Conventional care	0.01 (Table 79)	0.0000 (BETA)	96.02; 665,541.36	0.01; 0.02	B.3.3.5
AEs - Tuberculosis per 2-week cycle (%)					
RZB	0.01 (Table 79)	0.0000 (BETA)	96.02; 665,541.36	0.01; 0.02	B.3.3.5
AEs - Hypersensitivity per 2-week cycle (%)					
RZB	0.01 (Table 79)	0.00001 (BETA)	96.02; 665,541.36	0.01; 0.02	B.3.3.5
UST	0.01 (Table 79)	0.00001 (BETA)	96.03; 960,171.64	0.01; 0.01	B.3.3.5
AEs - Skin reactions per 2-week cycle (%)					

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
RZB	0.75 (Table 79)	0.0008 (BETA)	95.31; 12,612.52	0.60; 0.90	B.3.3.5
UST	2.66 (Table 79)	0.0027 (BETA)	93.46; 3,419.90	2.13; 3.19	B.3.3.5
ADA 160/80 / ADA 160/80 biosimilar†	2.66 (Table 79)	0.0027 (BETA)	93.46; 3,419.90	2.13; 3.19	B.3.3.5
ADA 80/40	0.72 (Table 79)	0.0007 (BETA)	95.34; 13,146.02	0.58; 0.86	B.3.3.5
IFX IV / IFX IV biosimilar†	0.72(Table 79)	0.0007 (BETA)	95.34; 13,146.02	0.58; 0.86	B.3.3.5
IFX SC	0.59 (Table 79)	0.0006 (BETA)	95.46; 16,084.87	0.47; 0.71	B.3.3.5
VDZ IV	0.59 (Table 79)	0.0006 (BETA)	95.46; 16,084.87	0.47; 0.71	B.3.3.5
VDZ SC	2.00 (Table 79)	0.0020 (BETA)	94.10; 4,610.69	1.60; 2.40	B.3.3.5
Health-state utilities: RZB RCTs EQ-5D					
Remission (CDAI < 150)	0.866 (Table 81)	0.01 (BETA)	4,985.39; 4,601.89	-0.5100; -0.5300	B.3.4.5
Mild (150 ≤ CDAI < 220)	0.752 (Table 81)	N/A	N/A	N/A	B.3.4.5
Moderate-severe (CDAI 220+) / surgery	0.604 (Table 81)	N/A	N/A	N/A	B.3.4.5
AE-related utility decrements					
Serious infections	-0.550 (Table 82)	0.01 (BETA)	4,321; 3,535	-0.539; -0.561	
Tuberculosis	-0.195 (Table 82)	0.00 (BETA)	7,349; 30,338	-0.191; -0.199	
Lymphoma	-0.110 (Table 82)	0.00 (BETA)	10,342; 83,677	-0.108; -0.112	
Hypersensitivity	-0.030 (Table 82)	0.00 (BETA)	3,354; 108,432	-0.029; -0.031	
Age-related utility decrements					
Age	41.00	4.18 (GAMMA)	96.04; 0.43	32.80; 49.20	
Cost per unit (mg) available (£)					
RZB (600 mg)	[redacted] (Table 85)	N/A	N/A	N/A	B.3.5.1
RZB (360 mg)	[redacted](Table 85)	N/A	N/A	N/A	B.3.5.1
UST (130 mg)	2,147.00 (Table 85)	N/A	N/A	N/A	B.3.5.1
UST (90 mg)	2,147.00 (Table 85)	N/A	N/A	N/A	B.3.5.1

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
ADA (biosimilar) (40 mg)	316.80 (Table 85)	N/A	N/A	N/A	B.3.5.1
ADA (40 mg)	352.14 (Table 85)	N/A	N/A	N/A	B.3.5.1
IFX IV (100 mg)	419.62 (Table 85)	N/A	N/A	N/A	B.3.5.1
IFX IV (biosimilar) (100 mg)	377.00 (Table 85)	N/A	N/A	N/A	B.3.5.1
IFX SC (120 mg)	377.66 (Table 85)	N/A	N/A	N/A	B.3.5.1
VDZ IV (300 mg)	2,050.00 (Table 85)	N/A	N/A	N/A	B.3.5.1
VDZ SC (108 mg)	512.50 (Table 85)	N/A	N/A	N/A	B.3.5.1
CC (per cycle)	13.76 (Table 85)	N/A	N/A	N/A	B.3.5.1
Cost per administration - First administration (£)					
IV	245 (Table 87)	25.00 (GAMMA)	96.04; 2.55	196; 294	B.3.5.1.2
SC	0 (Table 87)	10.46 (GAMMA)	1.00; 10.46	0; 41	B.3.5.1.2
Cost per administration - Subsequent administrations (£)					
IV	245 (Table 87)	25.00 (GAMMA)	96.04; 2.55	196; 294	B.3.5.1.2
SC	0 (Table 87)	0.07 (BETA)	30.05; 14.14	0; 41	B.3.5.1.2
Percent receiving CC (%)					
RZB	68 (Table 89)	0.07 (BETA)	30.05; 14.14	54; 82	B.3.5.1.3
UST	68 (Table 89)	0.07 (BETA)	30.05; 14.14	54; 82	B.3.5.1.3
ADA 160/80 / ADA 160/80 biosimilar†	68 (Table 89)	0.07 (BETA)	30.05; 14.14	54; 82	B.3.5.1.3
ADA 80/40	68 (Table 89)	0.07 (BETA)	30.05; 14.14	54; 82	B.3.5.1.3
IFX IV / IFX IV biosimilar†	68 (Table 89)	0.07 (BETA)	30.05; 14.14	54; 82	B.3.5.1.3
IFX SC	68 (Table 89)	0.07 (BETA)	30.05; 14.14	54; 82	B.3.5.1.3
VDZ IV	68 (Table 89)	0.07 (BETA)	30.05; 14.14	54; 82	B.3.5.1.3
VDZ SC	50 (Table 89)	0.05 (BETA)	47.52; 47.52	40; 60	B.3.5.1.3
Health-state cost-per-cycle on-biologic (£)					

Variable	Value (reference to appropriate table)	Measurement of uncertainty and distribution			Reference to section
		CI	PSA (alpha; beta)	DSA (low; high)	
Remission (CDAI < 150)	251 (Table 90)	25.58 (GAMMA)	96.04; 2.61	201; 301	B.3.5.2
Mild (150 ≤ CDAI < 220)	609 (Table 90)	62.16 (GAMMA)	96.04; 6.34	487; 731	B.3.5.2
Moderate-severe (CDAI 220+)	609 (Table 90)	62.16 (GAMMA)	96.04; 6.34	487; 731	B.3.5.2
Health-state cost-per-cycle off-biologic (£)					
Remission (CDAI < 150)	9,947 (Table 90)	1,014.98 (GAMMA)	96.04; 103.57	7,957; 11,936	B.3.5.2
Mild (150 ≤ CDAI < 220)	986 (Table 90)	100.63 (GAMMA)	96.04; 10.27	789; 1,183	B.3.5.2
Moderate-severe (CDAI 220+)	986 (Table 90)	100.63 (GAMMA)	96.04; 10.27	789; 1,183	B.3.5.2
Surgical procedure cost (£)					
Surgical procedure cost	1,531 (Table 91)	156.19 (GAMMA)	96.04; 15.94	1,225; 1,837	B.3.5.3
Surgical complication cost (£)					
Wound infection	1,894 (Table 92)	193.30 (GAMMA)	96.04; 19.73	1,515; 2,273	B.3.5.3
Prolonged ileus/bowel obstruction	842 (Table 92)	85.91 (GAMMA)	96.04; 8.77	673; 1,010	B.3.5.3
Intra-abdominal abscess	412 (Table 92)	42.05 (GAMMA)	96.04; 4.29	330; 495	B.3.5.3
Anastomotic leak	986 (Table 92)	301.90 (GAMMA)	10.67; 92.42	0; 1,183	B.3.5.3

Abbreviations: AE, adverse event; ADA, adalimumab; BF, biologic failure; CC, conventional care; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CODA, Convergence Diagnostic and Output Analysis; DSA, deterministic sensitivity analysis; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; IV, intravenous; N/A, not applicable; PSA, probabilistic sensitivity analysis; RCT, randomised controlled trial; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab. † Biosimilar formulations are assumed equal to originator drug

B.3.9.2 Assumptions

The main assumptions of the economic model alongside supporting justification are presented in Table 100.

Table 100: Key assumptions of the analysis

Model input and cross reference	Source / assumption	Justification
Perspective (B.3.2.2)	The perspective is that of the NHS in England, and PSS. Societal (indirect) costs are included in a scenario analysis.	Preference specified in NICE reference case (157).
Time horizon (B.3.2.2)	Lifetime (up to 60 years from baseline) assuming a mean starting age of 38.83 (CCF) or 38.22 (BF).	Duration sufficient to capture all benefits and costs of treatments as per NICE reference case (157), and reflective of the chronic nature of CD.
Patients entering model (B.3.2.1)	All CCF and BF patients enter the model with moderate-to-severe active CD. The CCF patients are assumed to have not been previously provided a dose of any biologic (e.g., ADA, IFX, VDZ, UST, or RZB), i.e., they are biologic-naïve. BF patients are assumed have failed any prior biologic and are analysed separately.	Reflective of licensed indication for all biologics.
Discontinuation (B.3.3.4.2)	It is assumed that discontinuation due to lack of efficacy may occur from any health state.	Assumption validated by clinical/HE expert feedback (80).
Surgery (B.3.3.4.3)	Surgery cannot occur in the induction period and is only possible if patients are in the 'Moderate-to-severe CD' health state in the maintenance period.	Assumption made due to lack of data; also used in TA456 (46).
Mild and moderate-to-severe CD proportions at end of induction (B.3.3.3.1)	The mild and moderate-to-severe CD proportions at end of induction are the same across all treatments; data from the RZB trials were used to inform the proportions.	Data were not available for all comparators, so RZB-specific data were used as a conservative assumption.
Maintenance and post-maintenance Markov matrices (B.3.3.3.4.2)	RZB maintenance trial data with calibration to the other biologics' maintenance NMA output were used to approximate the other biologics' maintenance Markov matrices after calibration.	This approach made the best use of the available data and avoided many of the assumptions required in TA456 (46) and TA352 (47); addressing the issues raised in these past TAs by the EAG/NICE.
Dose escalation (B.3.3.4.1)	Dose escalation does not affect efficacy and only impacts costs of treatment.	This assumption was made given patients who underwent dose escalation were failing standard-dose therapy – they were assumed to retain average standard-dose efficacy following

Model input and cross reference	Source / assumption	Justification
		escalation. It is effectively assumed that if patients dose-escalated, they required the higher dose to achieve the same level of response as patients who did not need to dose-escalate.
Excess mortality (B.3.9.2)	CD is assumed not to cause excess mortality in the model.	Mortality outcomes were not captured in the trials included in the NMA and there are conflicting data for the impact of CD on life expectancy relative to the general population, validated by clinical experts (80).
Biologic treatment duration (B.3.2.2.2.1)	Long-term responders are eventually discontinued from treatment; patients take on the placebo outcomes from their maintenance trials, corresponding to patients who responded to induction therapy and then were discontinued; assumed to be one year.	Most trials (including RZB) provide data for approximately one year of maintenance treatment. Additionally, both UST (TA456) (46) and VDZ (TA352) (47) assumed one year in their base case. Moreover, CD patients lose response to treatment in the long-term and it is difficult to estimate this accurately. Based on NICE guidance, clinicians will evaluate whether or not the patient will continue treatment at the end of the year (53).
Post-maintenance period (B.3.2.2.2.1)	This post-treatment maintenance residual treatment effect begins when long-term responders are discontinued and lasts for a specified amount of time (one year in the base case) after which patients take on outcomes for those who never responded.	Assumption made due to lack of data, also made in TA456 (46).
Patients moving to CC after biologic treatment (B.3.2.2.1)	This was a simplifying assumption, as per the ustekinumab and vedolizumab NICE submissions (44, 45).	In clinical practice, it is unlikely that patients who did not respond to a biologic therapy would receive CC, and instead would be prescribed another biologic therapy or surgery, however, no standard biologic treatment sequence for CD exists. This assumption was also used in TA352 and TA456 (44, 45).
AEs for patients on CC (B.3.3.5)	CC does not cause AEs.	CC does cause AEs, but there are insufficient data to include into the model due to uncertainty of the CC treatments patients would be on, and a lack of AE data for the specific AEs; instead CC was assumed to experience the mean frequency of each AE for all biologic treatments included in the model.
Probability of undergoing surgery (B.3.3.4.3)	Surgery is only possible if patients are in the moderate-to-severe disease health state.	It is assumed that patients in remission or with mild disease would not undergo surgery, and therefore surgery would only take place if patients are in the moderate-to-severe disease state.

Model input and cross reference	Source / assumption	Justification
Surgical health utility (B.3.4.5)	For the two weeks patients are in the surgery state, they experience the same health utility as in the moderate-to-severe health state.	Assumption as per TA456 (46)
Surgical complications (B.3.3.4.3)	Surgical complications do not incur health utility losses.	Surgical complications are included in the model, but only affect costs, owing to a lack of data.
Post-surgery health utility (B.3.4.5)	For the six weeks patients are in the post-surgical tunnel states, they experience remission-like health utility.	Assumption as per TA456 (46).
Health-state utility values (B.3.4.5)	Health-state utility values are assumed to be independent of treatment.	The key driver of utility in the model is the health state patients are in and not the treatment they are on; there is no treatment-specific utility or disutility.
CC patient weight and treatment (B.3.5.1.3)	CC patients have a mean weight of 71.15kg. It is assumed that 68.1% of biologic patients are on CC.	FORTIFY study (Table 12).
CC treatment mix (B.3.5.1.3)	Proportions of patients receiving each type of CC taken from TA456 (144).	Weights used in TA456† (46).

Abbreviations: ADA, adalimumab; AE, adverse event; BF, biologic failure; CC, conventional care; CCF, conventional care failure; CD, Crohn's disease; EAG, External Assessment Group; IFX, infliximab; KOL, key opinion leader; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PSS, Personal Social Services; RZB, risankizumab, TA, technology appraisal; UST, ustekinumab; VDZ, vedolizumab. † Based on the report from the Inflammatory Bowel Disease Audit Steering Group by the Royal College of Physicians (154)

B.3.10 Base-case results

B.3.10.1 Base case incremental cost-effectiveness analysis results

Base-case results are presented for both the CCF and BF populations. Results are shown using list prices for all comparator treatments. Vedolizumab and ustekinumab each have a confidential PAS, while TNF-alpha inhibitor biosimilars are subject to tender agreements; however, AbbVie is not privy to confidential PAS and tender agreements, and thus results are presented using list prices for all comparators.

Incremental analyses are shown for the CCF and BF populations in Table 101 and Table 103, respectively. An incremental analysis compares multiple mutually exclusive treatments against each other to find the most cost-effective treatment option out of all the available interventions. This is done in three steps:

- Treatments are ordered from least to most expensive.
- Check for strong dominance. Treatments are dominated if they are both costlier and less effective than another treatment included in the analysis.
- Check for extended dominance. Treatments are extendedly dominated if an alternative treatment can provide more QALYs for a lower cost per QALY. This is because decision makers prefer a more effective treatment with a lower incremental cost-effectiveness ratio (ICER).

B.3.10.1.1 CCF population

The fully incremental probabilistic analysis for CCF patients is presented in Table 101. In the CCF population, risankizumab accrues [redacted] compared to adalimumab biosimilar; however, risankizumab is associated with an [redacted]. Therefore, [redacted]. The ICERs should be interpreted with caution due to the small incremental differences in QALYs and costs meaning any generated ICERs are volatile.

Table 101: Base-case results: CCF population (fully incremental CE results)

	Total		Incremental		ICER	
Technology	**Costs [SE]**	**QALYs [SE]**	**Costs**	**QALYs**	**Vs baseline (£/QALY)**	**Incremental (£/QALY)**
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; SE, standard error; UST, ustekinumab.

The expected deterministic net monetary benefit (NMB) is also presented (Table 102) as they are informative when there are several comparators. [redacted].

Table 102: Net monetary benefits for CCF population, relative to risankizumab

Technologies	NMB at £20,000/QALY	NMB at £30,000/QALY
RZB	[redacted]	[redacted]
UST	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]
ADA 160/80 biosimilar	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; IFX, infliximab; IV, intravenous; NMB, net monetary benefit; QALY, quality-adjusted life year; RZB, risankizumab SC, subcutaneous; UST, ustekinumab.

B.3.10.1.2 BF population

The fully incremental probabilistic analysis for BF patients is presented in Table 103. [redacted].

Table 103: Base case results: BF population (fully incremental CE results)

	Total		Incremental		ICER	
Technologies	Costs [SE]	QALYs [SE]	Costs	QALYs	Vs baseline (£/QALY)	Incremental (£/QALY)
RZB	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; SE, standard error; UST, ustekinumab; VDZ, vedolizumab.

The expected deterministic NMB is also presented (Table 102) as they are informative when there are several comparators.

Table 104: Net monetary benefits for BF population, relative to risankizumab

Technologies	NMB at £20,000/QALY	NMB at £30,000/QALY
RZB	[redacted]	[redacted]
UST	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]

Abbreviations: BF, biologic failure; IV, intravenous; NMB, net monetary benefit; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Clinical outcomes from the model and disaggregated results of the base case cost-effectiveness analysis are provided in Appendix J.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

The base-case results presented were probabilistic as per the updated NICE reference case (157). This section covers additional interpretations of the probabilistic results which may be useful.

For each probabilistic sensitivity analysis (PSA), 1,000 simulations were drawn for the variables' distributions. Parameters varied in the PSA were:

- Baseline patient characteristics
- Health utilities
- Efficacy rates
- Costs

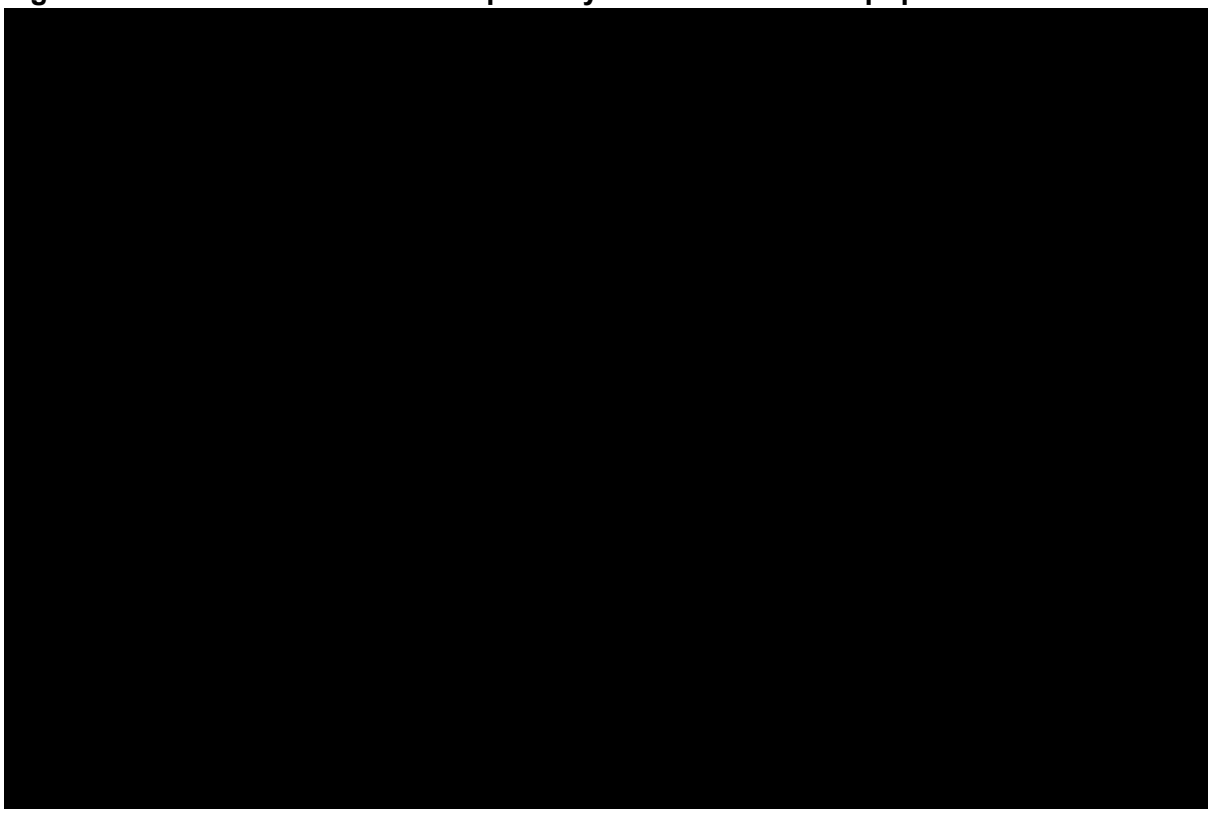
For induction and maintenance treatment efficacy, the model used Convergence Diagnostic and Output Analysis (CODA) samples to reflect uncertainty over NMA results. Therefore, this reflects the joint posterior distribution, with correlations across treatments. A total of 5,000 simulations were included and selected at random with replacement over the 1,000 PSA simulations. The number of NMA simulations (5,000) was selected by comparing the NMA point estimates and 95% CrIs to the random

CODA samples that were representative of the full CODA sample. Please refer to Section B.3.9.1 for a comprehensive list of all variables and their probability distributions used.

PSA results are included in the form of cost-effectiveness acceptability curves, presenting the probability of risankizumab being the most cost-effective treatment option at a willingness-to-pay threshold of £30,000 per QALY for both CCF and BF populations.

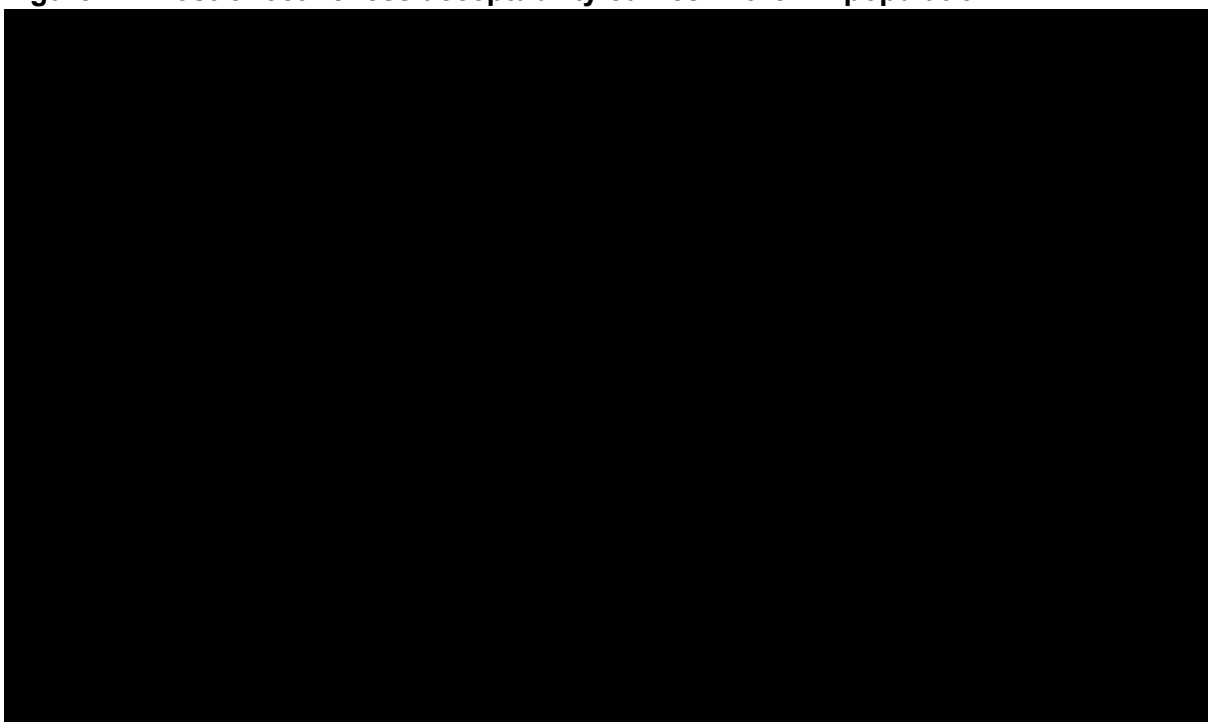
In the CCF population, risankizumab was associated with a [redacted] probability of being the most cost-effective treatment at a willingness-to-pay threshold of £30,000 per QALY (Figure 16).

Figure 16: Cost-effectiveness acceptability curves in the CCF population



In the BF population, risankizumab was associated with a [redacted] probability of being the most cost-effective treatment at a willingness-to-pay threshold of £30,000 per QALY (Figure 17).

Figure 17: Cost-effectiveness acceptability curves in the BF population



B.3.11.2 Deterministic sensitivity analysis

Parameters varied in the deterministic sensitivity analysis (DSA) include:

- Baseline patient characteristics
- Efficacy and safety parameters
- Health utilities
- Costs (direct medical costs, AE costs, indirect costs)

Additional parameters such as the time horizon of the model were not varied as these are structural assumptions and it is implicit that they would have a large impact on results. Where possible, variables were varied using the upper and lower 95% confidence / credible intervals for efficacy outputs, and all other variables were varied by ± 20% of their mean value. For parsimony, only the most impactful 20 parameters were included in tornado plots. The DSA results are presented in terms of the NMB and using the £30,000 per QALY threshold.

B.3.11.2.1 CCF population

Where there were biosimilar treatment options available, i.e., for adalimumab and infliximab IV, only the comparator with the lowest cost was considered. The tornado diagrams of risankizumab versus relevant comparators in the CCF population; ustekinumab, adalimumab (160/80 biosimilar) and infliximab (IV biosimilar; SC), are shown in Figure 18 to Figure 21. Varying the efficacy parameters for risankizumab (probability of response and remission) had the biggest impact on the NMB across all comparators. For ustekinumab, varying the body weight had also a big impact on the NMB.

B.3.11.2.2 BF population

The tornado diagrams of risankizumab versus relevant comparators in the BF population; ustekinumab and vedolizumab (IV; SC) are shown in Figure 22 to Figure 24. Varying the efficacy parameters for risankizumab (probability of response and remission) and the cost when off biologics had the biggest impacts on the NMB across all comparators. For ustekinumab, varying the body weight had also a big impact on the NMB.

Figure 18: Tornado diagram for risankizumab vs ustekinumab in the CCF population

Figure 19: Tornado diagram for risankizumab vs adalimumab 160/80 biosimilar in the CCF population

Figure 20: Tornado diagram for risankizumab vs infliximab IV biosimilar in the CCF population

Figure 21: Tornado diagram for risankizumab vs infliximab SC in the CCF population

Figure 22: Tornado diagram for risankizumab vs ustekinumab in the BF population

Figure 23: Tornado diagram for risankizumab vs vedolizumab IV in the BF population

Figure 24: Tornado diagram for risankizumab vs vedolizumab SC in the BF population

B.3.11.3 Scenario analysis

An overview of the scenario analyses conducted is shown in Table 105. Scenario analyses included variations in the model's time horizon, duration of residual treatment effect, utilitising the RE NMA model outcomes, consideration of other sources for health-state utility values, and indirect costs.

All scenarios were run using the deterministic model.

Table 105: Scenario analyses settings

#	Aspect	Base case	Scenario(s) (list number in brackets)	Justification
1	Model time horizon	60 years	1 year **(1a)**, 3 years **(1b)**, 5 years **(1c)**, and 10 years **(1d)**	Explore the impact of alternative time horizons on the model results
2	Residual treatment effect	1 year (all biologics)	6 months (all biologics) **(2)**	Explore the consideration of a shorter residual treatment effect
3	NMA	FE model results	RE model results **(3)**	Explore the impact of using RE NMA results
4	Utility values	RZB trial data	• Mapped UST IBDQ scores **(4a)** • Bodger et al. (2009) utility values **(4b)**	Considering the utility values from the latest CD NICE submission and those from a real-world study (Bodger et al. (2009)) often used in previous CD NICE submissions
5	Dose escalated regimens (start of maintenance)	Percentage of patients starting on high dose: UST: 92.5% (CCF and BF) ADA: 0% (CCF) IFX: 0% (CCF) VDZ: 0% (BF)	All comparators start on high dose (100%) at the start of maintenance • CCF population; ADA, IFX, UST **(5a)** • BF population: UST, VDZ **(5b)**	Exploring an extreme scenario of dose escalation in all comparators
6	Indirect costs	Not included	Included **(6)**	Assessing the burden of CD onto society
7	CDAI score	CDAI-100	CDAI-70 **(7)**	Evaluate the impact using a different definition of response may have

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RE, random effects; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

B.3.11.3.1 Summary of all scenario results

In the scenarios presented for the BF population, risankizumab remains cost effective (or dominant) compared with all relevant comparators across all scenarios. In the scenarios presented for the CCF population, the TNF-alpha inhibitors remain the cost-effective treatments across all scenarios.

B.3.11.3.2 Results scenario analyses 1: model time horizon

Results scenario 1a: model time horizon 1 year

Scenario 1a considered a shorter model time horizon of 1 year. Fully incremental results for the CCF and BF populations are summarised in Table 106 and Table 107, respectively.

Table 106: Scenario 1a results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 80/40	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 107: Scenario 1a results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

Results scenario 1b: model time horizon 3 years

Scenario 1b considered a shorter model time horizon of 3 years. Fully incremental results for the CCF and BF populations are summarised in Table 108 and Table 109, respectively.

Table 108: Scenario 1b results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 109: Scenario 1b results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

Results scenario 1c: model time horizon 5 years

Scenario 1c considered a shorter model time horizon of 5 years. Fully incremental results for the CCF and BF populations are summarised in Table 110 and Table 111, respectively.

Table 110: Scenario 1c results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 111: Scenario 1c results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

Results scenario 1d: model time horizon 10 years

Scenario 1d considered a shorter model time horizon of 10 years. Fully incremental results for the CCF and BF populations are summarised in Table 112 and Table 113, respectively.

Table 112: Scenario 1d results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 113: Scenario 1d results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

B.3.11.3.3 Results scenario analyses 2: residual treatment effect

Scenario 2 considered a shorter residual treatment effect of 6 months. Fully incremental results for the CCF and BF populations are summarised in Table 114 and Table 115, respectively.

Table 114: Scenario 2 results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 115: Scenario 2 results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

B.3.11.3.4 Results scenario analyses 3: NMA data from RE model

Scenario 3 considered using NMA data from the RE model. Fully incremental results for the CCF and BF populations are summarised in Table 116 and Table 117, respectively.

Table 116: Scenario 3 results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 117: Scenario 3 results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

B.3.11.3.5 Results scenario analyses 4: utility values

Results scenario 4a: use of mapped ustekinumab IBDQ utility scores

Scenario 4a considered using mapped ustekinumab IBDQ utility scores. Fully incremental results for the CCF and BF populations are summarised in Table 118 and Table 119, respectively.

Table 118: Scenario 4a results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 119: Scenario 4a results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

Results scenario 4b: use of utility values from Bodger et al. (2009)

Scenario 4b considered using utility values from Bodger et al. (2009). Fully incremental results for the CCF and BF populations are summarised in Table 120 and Table 121 respectively.

Table 120: Scenario 4b results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 121: Scenario 4b results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

B.3.11.3.6 Results scenario analyses 5: dose escalation

Results scenario 5a: Starting dose (maintenance) for CCF population comparators changed to high for 100% of patients

Scenario 5a considered setting the starting dose (maintenance) for all CCF population comparators (ustekinumab, adalimumab [160/80; 160/80 biosimilar; 80/40] and infliximab [IV; IV biosimilar; SC]) to the high dose for 100% of patients. Fully incremental results are summarised in Table 122.

Table 122: Scenario 5a results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
IFX SC	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Results scenario 5b: Starting dose (maintenance) for BF population comparators changed to high for 100% of patients

Scenario 5b considered setting the starting dose (maintenance) for all BF population comparators (ustekinumab and vedolizumab [IV; SC]) to the high dose for 100% of patients. Fully incremental results are summarised in Table 123.

Table 123: Scenario 5b results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

B.3.11.3.7 Results scenario analyses 6: Indirect costs

Scenario 6 considered including the indirect costs. Fully incremental results for the CCF and BF populations are summarised in Table 124 and Table 125, respectively.

Table 124: Scenario 6 results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
IFX SC	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 125: Scenario 6 results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous therapy; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

B.3.11.3.8 Results scenario analyses 7: CDAI score

Scenario 7 considered using the CDAI-70 response results. Fully incremental results for the CCF and BF populations are summarised in Table 126 and Table 127, respectively.

Table 126: Scenario 7 results for CCF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
ADA 80/40	[redacted]	[redacted]	N/A	N/A	Reference	Reference
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; vs, versus.

Table 127: Scenario 7 results for BF population: fully incremental CE results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	N/A	N/A	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; vs, versus.

B.3.12 Subgroup analysis

Not applicable.

B.3.13 Benefits not captured in the QALY calculation

Some people with CD may have comorbidities, including arthritic or skin conditions. These extra-intestinal manifestations have not specifically been included in QALY calculations; however, risankizumab will likely have a positive impact on these manifestations in addition to the treatment of active moderate-to-severe CD. Of note, risankizumab currently has marketing authorisation and NICE recommendations in relevant indications severe plaque psoriasis (189) and active psoriatic arthritis (2)).

Furthermore, results from the risankizumab CD studies have shown that risankizumab is associated with improved endoscopic outcomes, including mucosal healing, when compared with placebo (see Section B.2.6). Mucosal healing is associated with better long-term outcomes, such as reduced risk of relapse, decreased hospitalisation rates, steroid-free remission in follow-up examination, resection free intervals and improved HRQoL (76, 77). Despite the positive impact of risankizumab on these outcomes, endoscopic improvement has not been included in QALY calculations due to the limited availability of comparative data for other biologic therapies (further discussed in Section B.3.7.4). Additionally, there is the potential that caregiver disutility associated with caring for patients with moderate-to-severe CD has not been captured by the model, but no evidence was identified to support its inclusion nor would the inclusion of caregiver disutility adhere to the NICE reference case (157).

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The model was prepared according to the Professional Society for Health Economics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) best practices (190, 191), and aligns with NICE guidance (157).

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken to ensure that the mathematical calculations were performed correctly and were consistent with the model's specifications. This validation involved a health economist who did not develop the model, but who reviewed the model for coding errors, inconsistencies and the plausibility of inputs, which was performed as a thorough sheet-by-sheet (Excel tab-by-tab) check. This review included the following:

- Extreme value testing to ensure that the model yielded a logical output
- Logical relationship testing (e.g., if intervention drug acquisition costs increase, do total intervention costs increase accordingly? Does the ICERs increase accordingly?)
- Consistency checks (e.g., is an input parameter value cost in one cell consistently reflected elsewhere?)

- Checking of spreadsheet calculations and VBA code for implementation errors

Additionally, the TECH-VER checklist was used (192). The TECH-VER checklist consists of five domains: (1) input calculations; (2) event-state (patient flow) calculations; (3) result calculations; (4) uncertainty analysis calculations; and (5) other overall checks (e.g., validity or interface).

Validation using the different routine tests provided in the checklist yielded the expected results. Additionally, two experienced independent modellers reviewed the model structure and parameters.

B.3.15 Interpretation and conclusions of economic evidence

None of the CEAs identified in the economic SLR (Appendix G) included risankizumab as a comparator. Therefore, it was necessary to develop a *de novo* economic model for this submission, building upon learnings from prior economic evaluations in CD.

The economic evaluation conducted provides results separately for CCF and BF populations. To support decision making, scenario analysis considered a variety of factors that could impact the results.

The strengths of the analysis are that it leverages an established model framework widely used and accepted in CD. The model is populated with clinical efficacy and safety data analysed via an NMA. The base case analysis for this submission is fully probabilistic, with efficacy parameters sampled from NMA CODA to fully characterise the uncertainty in the point estimates. DSAs were conducted to assess the sensitivity of the model to individual parameters, while several scenario analyses were conducted to determine the cost-effectiveness of risankizumab across a variety of plausible scenarios.

In conclusion, the results of the cost-effectiveness analysis indicate that in the BF population, risankizumab is a cost-effective treatment option against current UK clinical practice. These outcomes remained stable in sensitivity and scenario analysis. In the CCF population, risankizumab was found to have comparable efficacy but slightly higher costs compared with current UK clinical practice. However, sensitivity

and scenario analyses proved that risankizumab can be considered a cost-effective treatment option in this population.

B.4 References

A separate .ris file has been provided within the uploaded documents/ref pack.

1. SMC. Risankizumab 150mg solution for injection in a prefilled syringe or pen (Skyrizi®) (SMC2459). 2022. Available at: https://www.scottishmedicines.org.uk/media/6795/risankizumab-skyrizi-abbreviated-final-march-2022-for-website.pdf (Accessed June 2022).
2. NICE. 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).
3. AbbVie. Skyrizi 600 mg concentrate for solution for infusion - draft SPC. Data on file. 2022.
4. AbbVie. Skyrizi 360 mg solution for injection in cartridge - draft SPC. Data on file. 2022.
5. Kashani A, Schwartz DA. The Expanding Role of Anti-IL-12 and/or Anti-IL-23 Antibodies in the Treatment of Inflammatory Bowel Disease. Gastroenterology & hepatology. 2019;15(5):255-65.
6. Ma C, Panaccione R, Khanna R, Feagan BG, Jairath V. IL12/23 or selective IL23 inhibition for the management of moderate-to-severe Crohn's disease? Best practice & research Clinical gastroenterology. 2019;38-39:101604.
7. Zhu J, Paul WE. Peripheral CD4+ T-cell differentiation regulated by networks of cytokines and transcription factors. Immunological reviews. 2010;238(1):247-62.
8. Haabeth OA, Lorvik KB, Hammarström C, Donaldson IM, Haraldsen G, Bogen B, et al. Inflammation driven by tumour-specific Th1 cells protects against B-cell cancer. Nature communications. 2011;2:240.
9. EMC. Skyrizi 150 mg solution for injection in pre-filled pen - Summary of Products Characteristics. 2021. Available at: https://www.medicines.org.uk/emc/product/12625/smpc (Accessed June 2022).
10. Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, et al. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. The Journal of allergy and clinical immunology. 2014;133(4):1032-40.
11. Patel M, Day A, Warren RB, Menter A. Emerging therapies for the treatment of psoriasis. Dermatology and therapy. 2012;2(1):16.
12. Singh S, Kroe-Barrett RR, Canada KA, Zhu X, Sepulveda E, Wu H, et al. Selective targeting of the IL23 pathway: Generation and characterization of a novel high-affinity humanized anti-IL23A antibody. mAbs. 2015;7(4):778-91.
13. Zhou L, Wang Y, Wan Q, Wu F, Barbon J, Dunstan R, et al. A non-clinical comparative study of IL-23 antibodies in psoriasis. mAbs. 2021;13(1):1964420.
14. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet (London, England). 2012;380(9853):1590-605.
15. Boyapati R, Satsangi J, Ho GT. Pathogenesis of Crohn's disease. F1000prime reports. 2015;7:44.

16. Petagna L, Antonelli A, Ganini C, Bellato V, Campanelli M, Divizia A, et al. Pathophysiology of Crohn's disease inflammation and recurrence. Biology direct. 2020;15(1):23.
17. NHS Inform. Crohn's Disease – Illness & Conditions. February 2020. Available from: https://www.nhsinform.scot/illnesses-and-conditions/stomach-liver-and-gastrointestinal-tract/crohns-disease (Accessed June 2022).
18. Perler BK, Ungaro R, Baird G, Mallette M, Bright R, Shah S, et al. Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. BMC gastroenterology. 2019;19(1):47.
19. Doherty G, Katsanos KH, Burisch J, Allez M, Papamichael K, Stallmach A, et al. European Crohn's and Colitis Organisation Topical Review on Treatment Withdrawal ['Exit Strategies'] in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2018;12(1):17-31.
20. Bots SJ, Kuin S, Ponsioen CY, Gecse KB, Duijvestein M, D'Haens GR, et al. Relapse rates and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy. Scandinavian journal of gastroenterology. 2019;54(3):281-8.
21. Crohn's and Colitis UK. Treatments. Available from: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/treatments (Accessed June 2022).
22. Gay M, Barrison I, Bean K, Bevan S, Carroll R, Clark S. Crohn's, Colitis and Employment-from career aspirations to reality. Hertfordshire: Crohn's and Colitis UK. 2011.
23. Norton BA, Thomas R, Lomax KG, Dudley-Brown S. Patient perspectives on the impact of Crohn's disease: results from group interviews. Patient preference and adherence. 2012;6:509-20.
24. Floyd DN, Langham S, Séverac HC, Levesque BG. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. Digestive diseases and sciences. 2015;60(2):299-312.
25. Lönnfors S, Vermeire S, Greco M, Hommes D, Bell C, Avedano L. IBD and health-related quality of life -- discovering the true impact. Journal of Crohn's & colitis. 2014;8(10):1281-6.
26. Irving P, Barrett K, Nijher M, de Lusignan S. Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. Evidence-based mental health. 2021;24(3):102-9.
27. Crohn's and Colitis UK. Mental health and wellbeing. 2021. Available from: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/mental-wellbeing (Accessed June 2022).
28. NHS Digital. Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 (Accessed June 2022).
29. Colombel JF, D'Haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. Journal of Crohn's & colitis. 2020;14(2):254-66.

30. Le Berre C, Danese S, Peyrin-Biroulet L. Timely Use of Biologics in Early Crohn's Disease: The Return of "Hit Hard and Early"? Digestive diseases and sciences. 2019;64(11):3035-7.
31. Frøslie KF, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412-22.
32. Freeman HJ. Use of the Crohn's disease activity index in clinical trials of biological agents. World journal of gastroenterology. 2008;14(26):4127-30.
33. Gastro training. Activity Index (CDAI). Available from: http://www.gastrotraining.com/calculators/cdai (Accessed June 2022).
34. Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Alimentary pharmacology & therapeutics. 2015;41(1):77-86.
35. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1-s106.
36. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw Index. Inflammatory bowel diseases. 2006;12(4):304-10.
37. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. The American journal of gastroenterology. 2009;104(2):465-83; quiz 4, 84.
38. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease (ADVANCE [M16-006]). Clinical Study Report. Risankizumab. 2021.
39. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment (MOTIVATE [M15-991]). Clinical Study Report. Risankizumab. 2021.
40. AbbVie. Multicenter, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Crohn's Disease (FORTIFY [M16-000]). Clinical Study Report. Risankizumab. 2021.
41. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointestinal endoscopy. 2004;60(4):505-12.
42. Koutroumpakis E, Katsanos KH. Implementation of the simple endoscopic activity score in crohn's disease. Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association. 2016;22(3):183-91.
43. ONS. Principal projection - England population in age groups. 2022. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/tablea24principalprojectionenglandpopulationinagegroups (Accessed June 2022).
44. King D, Reulen RC, Thomas T, Chandan JS, Thayakaran R, Subramanian A, et al. Changing patterns in the epidemiology and outcomes of inflammatory

bowel disease in the United Kingdom: 2000-2018. Alimentary pharmacology & therapeutics. 2020;51(10):922-34.
45. ONS. Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland. Accessed on: April 2022
46. NICE. Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy STA (TA456). 2017. Available at: https://www.nice.org.uk/guidance/ta456/documents/committee-papers (Accessed June 2022)
47. NICE. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [TA352]. 2014. Available at: https://www.nice.org.uk/guidance/ta352/documents/crohns-disease-moderate-to-severe-vedolizumab-committee-papers2 (Accessed June 2022).
48. Pasvol TJ, Horsfall L, Bloom S, Segal AW, Sabin C, Field N, et al. Incidence and prevalence of inflammatory bowel disease in UK primary care: a population-based cohort study. BMJ open. 2020;10(7):e036584.
49. Selin KA, Hedin CRH, Villablanca EJ. Immunological Networks Defining the Heterogeneity of Inflammatory Bowel Diseases. Journal of Crohn's & colitis. 2021;15(11):1959-73.
50. Wolters FL, Russel MG, Sijbrandij J, Schouten LJ, Odes S, Riis L, et al. Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. Gut. 2006;55(4):510-8.
51. Loftus EV, Jr. Crohn's disease: why the disparity in mortality? Gut. 2006;55(4):447-9.
52. Oberhuber G, Stangl PC, Vogelsang H, Schober E, Herbst F, Gasche C. Significant association of strictures and internal fistula formation in Crohn's disease. Virchows Archiv : an international journal of pathology. 2000;437(3):293-7.
53. NICE. Crohn's disease: management (NG129). 2019. Available at: https://www.nice.org.uk/guidance/ng129/resources/crohns-disease-management-pdf-66141667282885 (Accessed June 2022).
54. Vadstrup K, Alulis S, Borsi A, Jørgensen TR, Nielsen A, Munkholm P, et al. Extraintestinal Manifestations and Other Comorbidities in Ulcerative Colitis and Crohn Disease: A Danish Nationwide Registry Study 2003–2016. Crohn's & Colitis 360. 2020;2(3):otaa070.
55. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet (London, England). 2017;389(10080):1741-55.
56. Román AL, Muñoz F. Comorbidity in inflammatory bowel disease. World journal of gastroenterology. 2011;17(22):2723-33.
57. Restellini S, Chazouillères O, Frossard JL. Hepatic manifestations of inflammatory bowel diseases. Liver international : official journal of the International Association for the Study of the Liver. 2017;37(4):475-89.
58. Park YE, Park SJ, Park JJ, Cheon JH, Kim T, Kim WH. Incidence and risk factors of micronutrient deficiency in patients with IBD and intestinal Behçet's disease: folate, vitamin B12, 25-OH-vitamin D, and ferritin. BMC gastroenterology. 2021;21(1):32.

59. Habibi F, Habibi ME, Gharavinia A, Mahdavi SB, Akbarpour MJ, Baghaei A, et al. Quality of life in inflammatory bowel disease patients: A cross-sectional study. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2017;22:104.
60. Qualter P, Rouncefield-Swales A, Bray L, Blake L, Allen S, Probert C, et al. Depression, anxiety, and loneliness among adolescents and young adults with IBD in the UK: the role of disease severity, age of onset, and embarrassment of the condition. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2021;30(2):497-506.
61. Hu S, Chen Y, Chen Y, Wang C. Depression and Anxiety Disorders in Patients With Inflammatory Bowel Disease. Frontiers in psychiatry. 2021;12:714057.
62. Piercy J, Ozbay AB, Roughley A, Chao J, Skup M. Tu1256 Comparison of Ulcerative Colitis With Crohn's Disease From the Perspective of Patient Burden. Gastroenterology. 2015;148(4):S-839.
63. Chavarría C, Casanova MJ, Chaparro M, Barreiro-de Acosta M, Ezquiaga E, Bujanda L, et al. Prevalence and Factors Associated With Fatigue in Patients With Inflammatory Bowel Disease: A Multicentre Study. Journal of Crohn's & colitis. 2019;13(8):996-1002.
64. Williet N, Sarter H, Gower-Rousseau C, Adrianjafy C, Olympie A, Buisson A, et al. Patient-reported Outcomes in a French Nationwide Survey of Inflammatory Bowel Disease Patients. Journal of Crohn's & colitis. 2017;11(2):165-74.
65. Bassi A, Dodd S, Williamson P, Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut. 2004;53(10):1471-8.
66. Kahn SA, Lin CW, Ozbay B, Wang A, Chao J, Skup M. Indirect Costs and Family Burden of Pediatric Crohn's Disease in the United States. Inflammatory bowel diseases. 2017;23(12):2089-96.
67. Luces C, Bodger K. Economic burden of inflammatory bowel disease: a UK perspective. Expert review of pharmacoeconomics & outcomes research. 2006;6(4):471-82.
68. Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. Frontline gastroenterology. 2015;6(3):169-74.
69. Frolkis AD, Dykeman J, Negrón ME, Debruyn J, Jette N, Fiest KM, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology. 2013;145(5):996-1006.
70. 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. Journal of Crohn's & colitis. 2007;1(1):10-20.
71. Crohn's and Colitis UK. Surgery for Crohn’s Disease. 2017. Available at: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/surgery-for-crohns-disease (Accessed June 2022).
72. Frolkis AD, Lipton DS, Fiest KM, Negrón ME, Dykeman J, deBruyn J, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a

systematic review and meta-analysis of population-based studies. The American journal of gastroenterology. 2014;109(11):1739-48.
73. Casellas F, Herrera-de Guise C, Robles V, Navarro E, Borruel N. Patient preferences for inflammatory bowel disease treatment objectives. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2017;49(2):152-6.
74. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. The American journal of gastroenterology. 2015;110(9):1324-38.
75. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-83.
76. Casellas F, Barreiro de Acosta M, Iglesias M, Robles V, Nos P, Aguas M, et al. Mucosal healing restores normal health and quality of life in patients with inflammatory bowel disease. European journal of gastroenterology & hepatology. 2012;24(7):762-9.
77. Klenske E, Bojarski C, Waldner M, Rath T, Neurath MF, Atreya R. Targeting mucosal healing in Crohn's disease: what the clinician needs to know. Therapeutic advances in gastroenterology. 2019;12:1756284819856865.
78. Iacucci M, Ghosh S. Looking beyond symptom relief: evolution of mucosal healing in inflammatory bowel disease. Therapeutic advances in gastroenterology. 2011;4(2):129-43.
79. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. Journal of Crohn's & colitis. 2020;14(1):4-22.
80. AbbVie. Crohn’s disease HTA advisory board report. Data on file. 2021. (MAP ID: 2021-GB-MNP-00091).
81. Afzali A, Armuzzi A, Bouhnik Y, Bressler B, Hart A, Rubin D, et al. P393 Patient and physician perspectives on the management of inflammatory bowel disease: Role of steroids in the context of biologic therapy. Journal of Crohn's and Colitis. 2020;14(Supplement_1):S366-S7.
82. NHS England. Clinical Commissioning Policy: Ustekinumab for refractory Crohn’s disease in pre-pubescent children [200404P]. 2020. Available at: https://www.england.nhs.uk/wp-content/uploads/2020/07/Ustekinumab-for-refractory-Crohns-disease-in-pre-pubescent-children-1.pdf (Accessed June 2022).
83. Adegbola SO, Sahnan K, Warusavitarne J, Hart A, Tozer P. Anti-TNF Therapy in Crohn's Disease. International journal of molecular sciences. 2018;19(8).
84. Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2016;10(3):239-54.
85. Wong DJ, Roth EM, Feuerstein JD, Poylin VY. Surgery in the age of biologics. Gastroenterology report. 2019;7(2):77-90.

86. Motoya S, Watanabe M, Wallace K, Lazar A, Nishimura Y, Ozawa M, et al. Efficacy and Safety of Dose Escalation to Adalimumab 80 mg Every Other Week in Japanese Patients with Crohn's Disease Who Lost Response to Maintenance Therapy. Inflammatory intestinal diseases. 2018;2(4):228-35.
87. D'Haens GR, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? The American journal of gastroenterology. 2011;106(2):199-212; quiz 3.
88. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. Journal of Crohn's & colitis. 2017;11(1):3-25.
89. EMC. Entyvio 300 mg powder for concentrate for solution for infusion - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/5442/smpc (Accessed June 2022).
90. EMC. STELARA 90 mg solution for injection in pre-filled syringe - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/7638/smpc (Accessed June 2022).
91. Crohn's and Colitis UK. Crohn's Disease. 2016. Available at: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/crohns-disease (Accessed June 2022).
92. EMC. STELARA 130 mg concentrate for solution for infusion - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/4412/smpc#gref (Accessed June 2022).
93. Crohn's and Colitis Foundation. Managing Flares and IBD Symptoms. 2019. Available at: https://www.crohnscolitisfoundation.org/sites/default/files/2019-07/managing-flares-brochure-final-online.pdf (Accessed June 2022).
94. Shmidt E, Kochhar G, Hartke J, Chilukuri P, Meserve J, Chaudrey K, et al. Predictors and Management of Loss of Response to Vedolizumab in Inflammatory Bowel Disease. Inflammatory bowel diseases. 2018;24(11):2461-7.
95. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Alimentary pharmacology & therapeutics. 2015;41(7):613-23.
96. Crohn's and Colitis UK. Steroids. 2019. Available at: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/steroids (Accessed June 2022).
97. EMC. Inflectra 100 mg powder for concentrate for solution for infusion - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/medicine/29980#gref (Accessed June 2022).
98. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. The lancet Gastroenterology & hepatology. 2019;4(5):341-53.

99. Crohn's and Colitis UK. Azathioprine & Mercaptopurine. 2019. Available from: https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/treatments/azathioprine-and-mercaptopurine. Accessed on: April 2022
100. EMC. Azathioprine 25 mg Tablets - Summary of Products Characteristics. 2022. Avaibale at: https://www.medicines.org.uk/emc/product/2540/smpc#gref (Accessed June 2022).
101. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2018;155(2):337-46.e10.
102. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141(5):1621-28.e1-5.
103. AbbVie. Proportion of bio-naive patients in non-Bio-IR population. Data on file. 2022.
104. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. The New England journal of medicine. 2016;375(20):1946-60.
105. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. The New England journal of medicine. 2013;369(8):711-21.
106. D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel J-F, Danese S, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. The Lancet. 2022;399(10340):2015-30.
107. Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet (London, England). 2022;399(10340):2031-46.
108. EuroQol. EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument. 2021. Available at: https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-5LUserguide-08-0421.pdf (Accessed June 2022).
109. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet (London, England). 2002;359(9317):1541-9.
110. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Annals of internal medicine. 2007;146(12):829-38.
111. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52-65.
112. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in

Crohn's disease and ulcerative colitis controlled trials. Alimentary pharmacology & therapeutics. 2017;45(10):1291-302.
113. EMC. Humira 40 mg/0.4 ml solution for injection in pre-filled syringe - Summary of Product Characterisitics. 2021. Available at: https://www.medicines.org.uk/emc/product/2150/smpc#gref (Accessed June 2022).
114. EMC. Remicade 100mg powder for concentrate for solution for infusion - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/3831/smpc.%20Accessed%20July%202021 (Accessed June 2022).
115. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130(2):323-33; quiz 591.
116. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147(3):618-27.e3.
117. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. The New England journal of medicine. 1997;337(15):1029-35.
118. Rutgeerts P, Gasink C, Chan D, Lang Y, Pollack P, Colombel JF, et al. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease. Gastroenterology. 2018;155(4):1045-58.
119. Vermeire S, D'Haens GR, Baert FJ, Danese S, Kobayashi T, Loftus EV, et al. 950 The VISIBLE 2 Phase 3 Study of Efficacy and Safety of Vedolizumab SC for Moderate-to-Severe Crohn's Disease. Gastroenterology. 2020;158(6):S-194.
120. Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. Journal of Crohn's & colitis. 2012;6(2):160-73.
121. Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T, Suzuki Y, et al. Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. Journal of gastroenterology. 2020;55(3):291-306.
122. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011.
123. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-analysis for decision-making: John Wiley & Sons; 2018.
124. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.
125. NICE. Guselkumab for treating moderate to severe plaque psoriasis [TA521]. 2018. Available at: https://www.nice.org.uk/guidance/ta521 (Accessed June 2022).

126. Choy E, Freemantle N, Proudfoot C, Chen CI, Pollissard L, Kuznik A, et al. Evaluation of the efficacy and safety of sarilumab combination therapy in patients with rheumatoid arthritis with inadequate response to conventional disease-modifying antirheumatic drugs or tumour necrosis factor α inhibitors: systematic literature review and network meta-analyses. RMD open. 2019;5(1):e000798.
127. Cameron C, Hutton B, Druchok C, McElligott S, Nair S, Schubert A, et al. Importance of assessing and adjusting for cross-study heterogeneity in network meta-analysis: a case study of psoriasis. Journal of comparative effectiveness research. 2018;7(11):1037-51.
128. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(5):597-606.
129. Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. Statistics in medicine. 2002;21(11):1601-23.
130. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2002;64(4):583-639.
131. Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet (London, England). 2017;389(10080):1699-709.
132. AbbVie. Risankizumab Summary of Clinical Safety. Data on file. 2022.
133. ClinicalTrials.gov. Study Comparing Intravenous (IV)/Subcutaneous (SC) Risankizumab to IV/SC Ustekinumab to Assess Change in Crohn's Disease Activity Index (CDAI) in Adult Participants With Moderate to Severe Crohn's Disease (CD). Available at: https://clinicaltrials.gov/ct2/show/NCT04524611 (Accessed June 2022).
134. Lo B, Zhao M, Vind I, Burisch J. The Risk of Extraintestinal Cancer in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis of Population-based Cohort Studies. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2021;19(6):1117-38.e19.
135. EMA. Remicade 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf (Accessed June 2022).
136. EMC. Remsima 100 mg powder for concentrate for solution for infusion - Summary of Products Characteristics. 2020. Available at: https://www.medicines.org.uk/emc/product/3709/smpc (Accessed June 2022).
137. Abreu MT, Sandborn WJ. Defining Endpoints and Biomarkers in Inflammatory Bowel Disease: Moving the Needle Through Clinical Trial Design. Gastroenterology. 2020;159(6):2013-8.e7.
138. Kakkar A, Wasan SK, Farraye FA. Targeting mucosal healing in Crohn's disease. Gastroenterology & hepatology. 2011;7(6):374-80.

139. 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(8):915-27.
140. Rutgeerts PJ. Review article: the limitations of corticosteroid therapy in Crohn's disease. Alimentary pharmacology & therapeutics. 2001;15(10):1515-25.
141. Lauriot Dit Prevost C, Azahaf M, Nachury M, Branche J, Gerard R, Wils P, et al. Bowel damage and disability in Crohn's disease: a prospective study in a tertiary referral centre of the Lémann Index and Inflammatory Bowel Disease Disability Index. Alimentary pharmacology & therapeutics. 2020;51(9):889-98.
142. Vulliemoz M, Brand S, Juillerat P, Mottet C, Ben-Horin S, Michetti P. TNF-Alpha Blockers in Inflammatory Bowel Diseases: Practical Recommendations and a User's Guide: An Update. Digestion. 2020;101 Suppl 1:16-26.
143. Sands BE, Chen J, Feagan BG, Penney M, Rees WA, Danese S, et al. Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study. Gastroenterology. 2017;153(1):77-86.e6.
144. NICE. Methods for the development of NICE public health guidance (third edition). 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 June 2022).
145. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. 2009. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (Accessed June 2022).
146. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Alimentary pharmacology & therapeutics. 2009;30(3):265-74.
147. Catt H, Bodger K, Kirkham JJ, Hughes DA. Value Assessment and Quantitative Benefit-Risk Modelling of Biosimilar Infliximab for Crohn's Disease. Pharmacoeconomics. 2019;37(12):1509-23.
148. Lindsay J, Punekar YS, Morris J, Chung-Faye G. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease--modelling outcomes in active luminal and fistulizing disease in adults. Alimentary pharmacology & therapeutics. 2008;28(1):76-87.
149. Loftus EV, Jr., Johnson SJ, Yu AP, Wu EQ, Chao J, Mulani PM. Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease. European journal of gastroenterology & hepatology. 2009;21(11):1302-9.
150. Robson RE, Vanoli A, Tolley K. Cost-effectiveness of vedolizumab compared with conventional therapy in patients with Crohn's disease in the United Kingdom (UK). Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(Supplement 3):S455-S6.
151. Saito S, Shimizu U, Nan Z, Mandai N, Yokoyama J, Terajima K, et al. Economic impact of combination therapy with infliximab plus azathioprine for

drug-refractory Crohn's disease: a cost-effectiveness analysis. Journal of Crohn's & colitis. 2013;7(2):167-74.
152. Wilson M, Lucas A. Cost-effectiveness of vedolizumab versus ustekinumab in United Kingdom Crohn's disease patients who previously failed TNF inhibitor therapy. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(Supplement 3):S145.
153. NICE. Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]. Committee papers. 2017. Availbale at: https://www.nice.org.uk/guidance/ta480/documents/committee-papers (Accessed June 2022).
154. Royal College of Physicians. National clinical audit of biological therapies: UK inflammatory bowel disease (IBD) audit. 2013. Available at: https://www.royalwolverhampton.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=5738 (Accessed June 2022).
155. EMC. Entyvio 108mg solution for injection in pre-filled pen - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/12640/smpc (Accessed June 2022).
156. EMC. Remsima 120 mg solution for injection in pre-filled pen - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/11101/smpc (Accessed June 2022).
157. NICE. Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#measuring-and-valuing-health-effects (Accessed June 2022).
158. AbbVie. Post-hoc analysis of responders in moderate-to-severe states after induction (ADVANCE and MOTIVATE). Data on file. 2022.
159. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004;126(2):402-13.
160. McLeod RS, Wolff BG, Ross S, Parkes R, McKenzie M. Recurrence of Crohn's disease after ileocolic resection is not affected by anastomotic type: results of a multicenter, randomized, controlled trial. Diseases of the colon and rectum. 2009;52(5):919-27.
161. Milsom JW, Hammerhofer KA, Böhm B, Marcello P, Elson P, Fazio VW. Prospective, randomized trial comparing laparoscopic vs. conventional surgery for refractory ileocolic Crohn's disease. Diseases of the colon and rectum. 2001;44(1):1-8; discussion -9.
162. Zurbuchen U, Kroesen AJ, Knebel P, Betzler MH, Becker H, Bruch HP, et al. Complications after end-to-end vs. side-to-side anastomosis in ileocecal Crohn's disease--early postoperative results from a randomized controlled multi-center trial (ISRCTN-45665492). Langenbeck's archives of surgery. 2013;398(3):467-74.
163. Kusunoki M, Ikeuchi H, Yanagi H, Shoji Y, Yamamura T. A comparison of stapled and hand-sewn anastomoses in Crohn's disease. Digestive surgery. 1998;15(6):679-82.
164. Fazio VW, Marchetti F, Church M, Goldblum JR, Lavery C, Hull TL, et al. Effect of resection margins on the recurrence of Crohn's disease in the small

bowel. A randomized controlled trial. Annals of surgery. 1996;224(4):563-71; discussion 71-3.
165. Irvin TT, Goligher JC, Johnston D. A randomized prospective clinical trial of single-layer and two-layer inverting intestinal anastomoses. The British journal of surgery. 1973;60(6):457-60.
166. Eshuis EJ, Slors JF, Stokkers PC, Sprangers MA, Ubbink DT, Cuesta MA, et al. Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. The British journal of surgery. 2010;97(4):563-8.
167. Maartense S, Dunker MS, Slors JF, Cuesta MA, Pierik EG, Gouma DJ, et al. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. Annals of surgery. 2006;243(2):143-9; discussion 50-3.
168. Ikeuchi H, Kusunoki M, Yamamura T. Long-term results of stapled and hand-sewn anastomoses in patients with Crohn's disease. Digestive surgery. 2000;17(5):493-6.
169. Cameron JL, Hamilton SR, Coleman J, Sitzmann JV, Bayless TM. Patterns of ileal recurrence in Crohn's disease. A prospective randomized study. Annals of surgery. 1992;215(5):546-51; discussion 51-2.
170. Stocchi L, Milsom JW, Fazio VW. Long-term outcomes of laparoscopic versus open ileocolic resection for Crohn's disease: follow-up of a prospective randomized trial. Surgery. 2008;144(4):622-7; discussion 7-8.
171. Funayama Y, Fukushima K, Shibata C, Takahashi K-I, Ogawa H, Haneda S, et al., editors. Early postoperative results of novel procedure of side-to-side isoperistaltic ileocolonic anastomosis for Crohn's disease-randomized controlled trial. Gastroenterology; 2006.
172. Alava MH, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. 2020. Available at: https://eepru.sites.sheffield.ac.uk/projects/estimating-the-relationship-between-eq-5d-5l-and-eq-5d-3l (Accessed June 2022).
173. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(5):509-18.
174. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. Pharmacoeconomics. 2001;19(11):1091-102.
175. Porco TC, Lewis B, Marseille E, Grinsdale J, Flood JM, Royce SE. Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. BMC public health. 2006;6:157.
176. Hornberger J, Reyes C, Lubeck D, Valente N. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. Leukemia & lymphoma. 2008;49(2):227-36.
177. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health and quality of life outcomes. 2010;8:50.
178. Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. British journal of cancer. 2009;101(3):387-9.

179. NICE. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 (Accessed June 2022).
180. British National Formulary. Ustekinumab costs. Available at: https://bnf.nice.org.uk/medicinal-forms/ustekinumab.html (Accessed June 2022).
181. British National Formulary. Adalimumab costs. Available at: https://bnf.nice.org.uk/medicinal-forms/adalimumab.html (Accessed June 2022).
182. British National Formulary. Infliximab costs. Available at: https://bnf.nice.org.uk/medicinal-forms/infliximab.html (Accessed June 2022).
183. British National Formulary. Vedolizumab costs. Available at: https://bnf.nice.org.uk/medicinal-forms/vedolizumab.html (Accessed June 2022).
184. PSSRU. Unit Costs of Health and Social Care 2021. 2022. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/ (Accessed June 2022).
185. NHS Digital. HRG4+ 2021/22 Local Payment Grouper application. 2022. Available at: HRG4+ 2021/22 Local Payment Grouper application (Accessed June 2022).
186. NHS. National Schedule of NHS Costs 2019/20. 2022. Available at: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ (Accessed June 2022).
187. AbbVie. Mortality risk in CD. Data on file. 2022. .
188. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. medRxiv. 2021.
189. NICE. 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).
190. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(6):835-42.
191. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2003;6(1):9-17.
192. Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, Al M. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. Pharmacoeconomics. 2019;37(11):1391-408.

B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional supporting data from the risankizumab clinical trial programme

Appendix N: Additional supportive data – CD disease measures and adults/paediatric data

Appendix O: On-body device

Appendix P: Additional NMA results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

July 2022

File name	Version	Contains confidential information	Date
ID3986 EAG clarification letter Fv2_fully redacted	V2	Yes	23 Sept 2022

Abbreviations list

ACR	American College of Rheumatology
AE	adverse event
AIC	Akaike information criterion
APS	abdominal pain score
BF	biologic failure
Bio-IR	biologic inadequate response
BSC	best supportive care
CCF	conventional care failure
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CE	cost-effectiveness
CR-70	clinical response based on a change of 70 points or more (CDAI score)
CR-100	clinical response based on a change of 100 points or more (CDAI score)
CrI	credible interval
CS	company submission
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
FE	fixed effects
FEA	fixed-effects baseline-risk adjusted
HBI	Harvey-Bradshaw Index
HSUV	health-state utility value
HTA	health technology assessment
IBD	inflammatory bowel disease
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
IV	intravenous
KM	Kaplan–Meier
MC	Monte Carlo
MCMC	Markov Chain Monte Carlo
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
Non-Bio-IR	inadequate response/intolerance to conventional care
OBD	on-body device
OLS	ordinary least squares
OR	odds ratio
OUS	outside of United States
PIM	Promising Innovative Medicine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	patient-reported outcome
PSRF	Potential Scale Reduction Factor
QALY	quality-adjusted life year
RCT	randomised controlled trial
RD	risk difference
RE	random effects
REA	random-effects baseline-risk adjusted
RLHS	real-life handling study
RR	relative risk
SC	subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn’s disease
SF	stool frequency
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review
SUCRA	Surface Under the Cumulative Ranking
TA	technology appraisal
TNF	tumour necrosis factor
TTD	time to treatment discontinuation

Section A: Clarification on effectiveness data

Literature searches

A1. Appendix D Table 1. Please clarify which RCT filter was used for the clinical effectiveness searches.

Company response

The randomised controlled trial (RCT) filter used for clinical effectiveness searches is adopted from the National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk/guidance/ng50/documents/search-strategies). Additional terms from the Scottish Intercollegiate Guidelines Network (SIGN) RCT search filter (https://www.sign.ac.uk/what-we-do/methodology/search-filters/) were added to supplement the NICE filter. Table 1 presents the sources of the terms used to create the final RCT search filter presented in Appendix D, Section D.1.1 of the company submission (CS).

Table 1: Sources of the terms used to create the final RCT search filter

Search Terms	Source
Embase	
exp Randomized Controlled Trial/	**NICE:** randomized controlled trial/ **SIGN:** Randomized Controlled Trial/
exp Random Allocation/	**Additional term**
exp randomization/	**SIGN:** exp RANDOMIZATION/
exp placebo/	**SIGN:** PLACEBO/
exp double blind procedure/	**NICE**: double blind procedure/ **SIGN:** Double Blind Procedure/
exp single blind procedure/	**NICE**: single blind procedure/ **SIGN:** Single Blind Procedure/
exp crossover procedure/	**NICE**: crossover procedure/ **SIGN:** Crossover Procedure/
exp clinical trial/ or exp controlled clinical trial/	**SIGN:** Clinical Trial/ **SIGN:** controlled clinical trial/
exp phase 3 clinical trial/	**SIGN:** Phase 3 clinical trial/
exp phase 2 clinical trial/	**Additional term**
exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/	**Additional term**
exp multicenter Study/	**SIGN:** multicenter study/
Medline	
exp Randomized Controlled Trial/ or exp Random Allocation/	**SIGN:** randomized controlled trial/ **SIGN:** Random Allocation/
exp randomization/	**Additional term**
exp Placebos/	**SIGN:** PLACEBOS/
exp Double-Blind Method/ or exp Single-Blind Method/	**SIGN:** Double Blind Method/ **SIGN**: Single Blind Method/
exp clinical trial/	**SIGN**: clinical trial/
exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp controlled clinical trial/	**Additional term**

Search Terms	Source
exp Randomized Controlled Trials as Topic/ or exp clinical trials as topic/ or exp controlled clinical trials as topic/	**NICE:** clinical trials as topic.sh. **SIGN:** exp Clinical Trials as topic/ **SIGN:** Randomized Controlled Trials as Topic/
exp Multicenter Study/	**SIGN:** multicenter study.pt.
All databases	
randomized controlled trial.pt.	**NICE:** randomized controlled trial.pt. **SIGN:** randomized controlled trial.pt
controlled clinical trial.pt.	**NICE:** controlled clinical trial.pt. **SIGN:** controlled clinical trial.pt
random$.ti,ab,kw.	**NICE:** randomi#ed.ab. **NICE**: randomly.ab. **NICE**: random*.ti,ab. **SIGN:** randomi?ed controlled trial$.tw **SIGN:** randomly allocated.tw **SIGN:** (random$ adj2 allocat$).tw
blind$.ti,ab,kw.	**Additional term**
(placebo$ or assign* or allocat* or volunteer*).ti,ab,kw.	**NICE:** placebo.ab. **SIGN:** placebo$.tw **NICE**: (assign* or allocat* or volunteer* or placebo*).ti,ab.
parallel$.ti,ab,kw.	**Additional term**
factorial$.ti,ab,kw.	**NICE**: factorial*.ti,ab.
(crossover* or cross over*).ti,ab,kw.	**NICE:** (crossover* or cross over*).ti,ab.
trial.ti.	**NICE:** trial.ti. **SIGN:** (clinical adj trial$).tw
('phase 3' or 'phase 2' or 'phase III' or 'phase II').af.	**Additional term**
((single or double or triple) adj3 (blind* or mask* or dummy)).af.	**SIGN:** ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw **NICE:** (doubl* or singl*) adj blind*).ti,ab. **SIGN:** single blind$.tw. **SIGN:** double blind$.tw. **SIGN:** ((treble or triple) adj blind$).tw.
('double-blind' or 'double-blinded').af.	**NICE:** (doubl* or singl*) adj blind*).ti,ab. **SIGN:** double blind$.tw.
(open label or open-label).af.	**Additional term**

Abbreviations: NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SIGN, Scottish Intercollegiate Guidelines Network.

A2. Appendix F. Were any searches carried out for adverse events?

Company response

Adverse events (AEs) were included as outcomes of interest as part of the search for clinical evidence (see CS Appendix D, Section D.1.2, Table 2). No specific search to identify studies reporting AEs was conducted.

Subgroups

A3. Please provide additional rationale for the addition of two clinical subgroups (CCF and BF) to the company decision problem that did not appear in the NICE final scope for this appraisal.

Company response

The inclusion of conventional care failure (CCF) and biologic failure (BF) subgroups in the CS is consistent with the approach taken in previous appraisals for ustekinumab (TA456) (1) and vedolizumab (TA352) (2).

The CCF and BF subgroups are considered to represent two distinct patient populations in clinical practice based on expert clinical opinion (3) and are outlined as such in the proposed licensed indication for risankizumab in Crohn's disease (CD) ([redacted]).

In UK clinical practice, while most patients with moderate-to-severe CD initiating biologic therapy would receive a first-line tumour necrosis factor (TNF)-alpha inhibitor, there is a small but significant proportion who are not suitable for TNF-alpha inhibitor therapy (18% as presented in the inflammatory bowel disease [IBD] Biological Therapies Audit Annual Report 2021 (4)). These patients may therefore be suitable for other biologics, including risankizumab, after CCF.

Response rates to treatment are expected to differ between patients who are biologic-naïve and those that have failed previous biologic treatment (i.e., are treatment refractory) (5). For example, the most recently approved biologic therapies, ustekinumab and vedolizumab, are more effective in bio-naïve patients than patients with prior exposure to biologic therapies (6-9). TNF-alpha inhibitors are typically the first biological therapy recommended by NICE guidance for the treatment of moderate-to-severe CD (10), and consequently, the majority of patients with a history of BF will have had TNF-alpha exposure. The CCF and BF clinical subgroups were utilised given the differing response rates based on prior biologic exposure status.

Network Meta-Analysis

A4. PRIORITY QUESTION In the NMA analyses, the CS indicates analyses were carried out on both log-odds and risk-difference (RD) scales, but that the RD were preferred. It is stated briefly that log-odds analyses failed to converge, lacked face validity or performed poorly (section B.2.9.3.1). Please expand on the problems encountered with the log-odds approach, especially its face validity.

Company response

In Section B.2.9.3.1 of the CS, the language regarding log-odds (i.e., logit-link analyses) which failed to converge or lacked face validity specifically refers to baseline risk-adjusted logit-link network meta-analysis (NMA) models:

> "The NMAs used in this submission utilised the RD method, which was used in this instance as it is recommended where baseline risk-adjusted models are deemed inappropriate due to lack of convergence or face validity (122). […] Due to the general paucity of data in the relevant CD evidence networks leading to poor performance of baseline-risk adjusted logit-link NMAs, RD NMAs provided an attractive option to minimise impacts of placebo heterogeneity on NMA-produced treatment effect estimates."

As a worked example of model diagnostics indicating baseline risk-adjusted logit-link models failed to converge and lacked face validity, leverage plots (following those presented by Dias et al. (2018) (11)) and model fit statistics (contained in the upper right corner of the leverage plots) for fixed-effects baseline-risk adjusted (FEA) and random-effects baseline-risk adjusted (REA) models for the induction Crohn's Disease Activity Index (CDAI) clinical remission CCF population network are presented in (Figure 1) (11). For further details on leverage plots and model fit statistics, please refer to CS Appendix D, Section D.1.3.3.5.

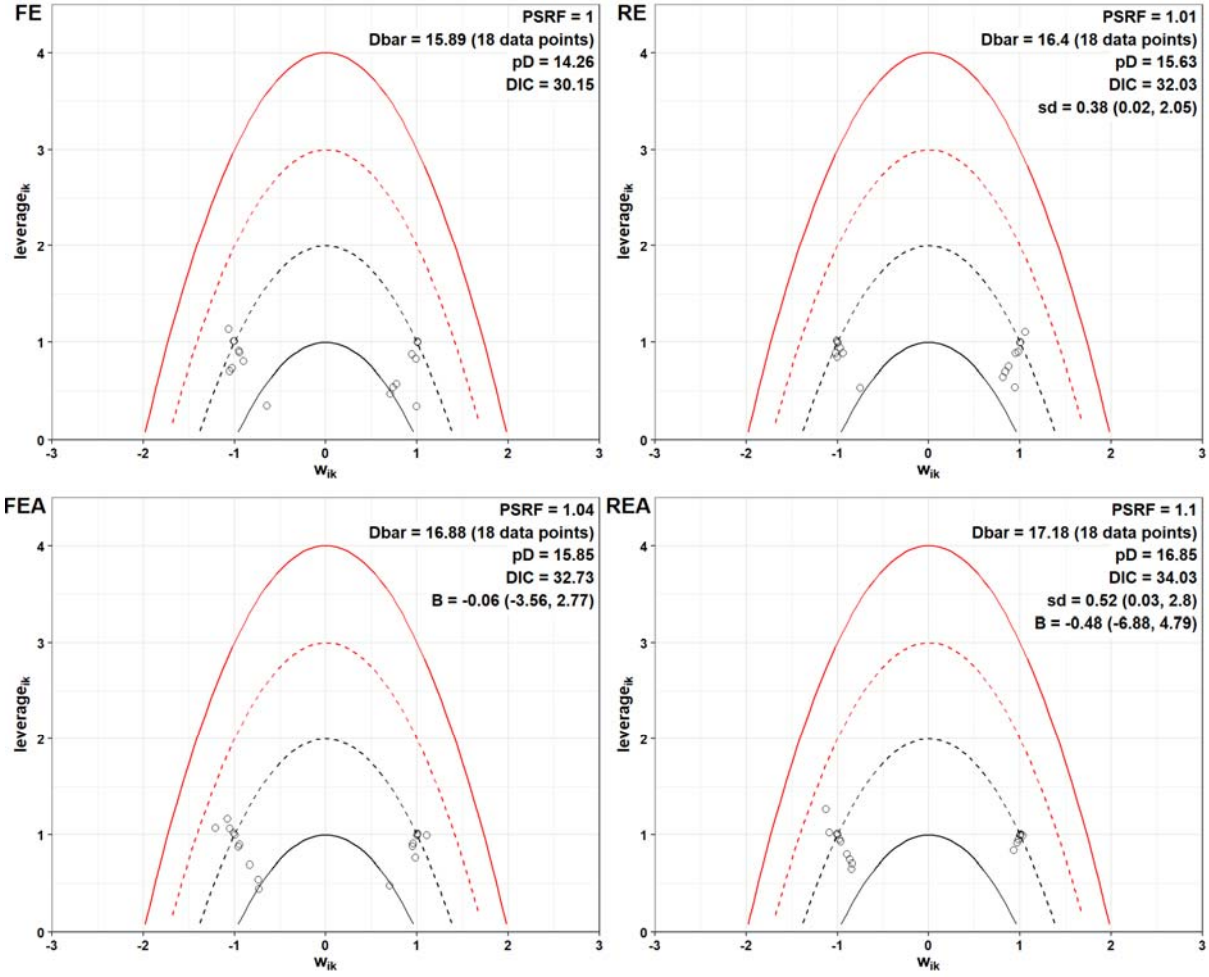
Baseline-risk adjusted models may be selected if, given model convergence, the 95% credible interval (CrI) of the associated baseline-risk regression term excludes 0 and (in instances of random effect [RE] models) the median posterior between-study

heterogeneity is reduced relative to an unadjusted model. These selection criteria are in line with the recommendations of Dias et al. (2018) and the NICE Decision Support Unit (DSU) Technical Support Document 3 (TSD 3) (11, 12).

Model convergence is assessed upon initial model diagnostic evaluation. Note that the Potential Scale Reduction Factor (PSRF) calculated for the REA model as displayed in Figure 1 is approximately 1.10. As this is greater than the threshold of 1.05 indicated in CS Appendix D, Section D.1.3.3.4, this model is considered to have failed to converge and is thus removed from model selection consideration (11, 13).

While the FEA model achieves convergence criterion (PSRF = 1.04), it is noted that the 95% CrI associated with the regression term includes 0 (B = -0.06, (-3.58, 2.77)) in Figure 1**Error! Reference source not found.**. Therefore, the regression parameter is considered non-significant and the model is removed from model selection criteria (11). Selecting a baseline risk-adjusted model with a non-significant regression parameter is considered to lack face validity.

Figure 1: Leverage plots and fit statistics of FEA and REA baseline risk-adjusted models for the induction CDAI clinical remission CCF population NMA network



Abbreviations: CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; DIC, Deviance Information Criterion; FE, fixed effects; FEA, fixed-effects baseline-risk adjusted; NMA, network meta-analysis; PSRF, Potential Scale Reduction Factor; RE, random effects; REA, random-effects baseline-risk adjusted.

A5. The CS comments that in preference to random effects, ‘a fixed effects (FE) framework was used in the base case analysis to avoid producing credible intervals that did not pass validity’ (Doc B p83 and Appendix p62). Please explain further what ‘pass validity’ means in this context, with examples of invalid intervals.

Company response

Although the RE NMA models produced median RD results comparable to the FE NMA models, the RE models produced CrIs which were excessively broad. “Validity” in this context refers to face validity. For example, in the CCF population, the FE NMA results for CDAI clinical remission in induction for placebo versus risankizumab was 0.25 (CrI 0.13, 0.37). Using the RE NMA model, the same value was calculated at 0.25 (CrI -0.05, 0.54). Differences of this magnitude were also observed for the other biologics, e.g., ustekinumab, which in the same analysis had risk differences of 0.17 (CrI 0.09, 0.25) and 0.17 (CrI -0.12, 0.45) in the FE and RE NMAs, respectively. This fundamentally changes the interpretation of the NMA result since the RE model suggests that placebo has the potential to be more effective than risankizumab and ustekinumab, which is not supported by the outcomes of the risankizumab CD induction pivotal trials (ADVANCE, MOTIVATE) nor the ustekinumab induction trial (UNITI-1) (7). In the case of a small number of trials, FE NMAs generate more consistent results than RE NMAs (please refer to NICE DSU TSD 2) (14).

A6. Please indicate whether the company analysed the baseline-risk adjusted logit-link NMAs with independent or exchangeable regression models, as alternatives to the common regression term mentioned in Appendix D.1.3.3.6. If so, please supply further explanation for their non-inclusion in the CS and a description of any problems encountered (as with A4).

Company response

Baseline-risk adjusted logit-link NMAs were conducted utilising the assumption of a common regression term in keeping with the example analyses presented in Section 4.4.1 of the NICE DSU TSD 3 (12). Furthermore, Dias et al. (2018) (11) note that the use of a common regression term is appropriate "[…] if the reference treatment is somehow different from the others, such as a placebo, an older treatment or 'standard care'" (11). As study placebo serves as the common reference treatment in all the NMAs presented in the CS, the use of a common regression term assumption would accordingly be appropriate.

Furthermore, across the networks assessed, there are multiple instances of treatments informed by only a single study (please refer to network diagrams presented within CS Section B.2.9.1.5). As stated in NICE DSU TSD3, the assumption of a common regression term "allows the interaction parameter to be estimated even for comparisons which only have one trial" (12). As such, the use of an independent or exchangeable parameter assumption was not viewed as feasible for multiple analyses given the number of treatments informed by a single study. This, along with the noted consideration of placebo as reference treatment, led to the use of a common regression term across baseline-risk adjusted logit-link NMAs.

A7. PRIORITY QUESTION Thank you for providing the NMA code.

- **Please could you also supply all data, options set and any other control parameters required to run the code. For example, the following (from the 'data setup' section) of the risk difference fixed effects model are currently not available: [redacted]. This information could be entered directly in the code files and re-supplied, or put in a separate .Rdata file. Please ensure the code can be executed with this extra information. Likewise, please also include initialisation data that were used for every NMA where these may not have been already provided.**
- **For modelling of the baseline risk as carried out in the function [redacted], please confirm the sources/studies (the EAG believes but is not certain that the model used the placebo arms of all trials in the networks). Please also provide a plot of the baseline risk posterior distribution from the Bayesian analysis.**

Company response

The clinical data have been provided in a Microsoft® Excel file, while the complete R code has been provided in a separate .Rdata file. The baseline risk posterior plots for the different endpoints examined in the NMAs can be produced using the provided R code (please see line 496 and below of the .Rdata file) and Microsoft® Excel dataset.

A8. In discussion of how study-specific baseline risks were estimated, the CS makes reference to the use of independent estimates per study. However, this discussion appears to relate primarily to NMAs using logit link. Please clarify how study-specific baseline risks were handled in the NMAs estimated using a risk difference metric.

Company response

The RD approach utilised a binomial likelihood, as shown in equations 7 and 8 in the CS (Appendix D, Section D.1.3.3.7), replicated below for ease of reference. In the equations below, μ_i is the trial-specific baseline representing the probability of the outcome of the control treatment, and δ_{ik} is the trial-specific probability of the outcome in a given treatment k compared with the control treatment.

$$p_{i,1} = \mu_i$$

$$p_{i,k} = \mu_i + \min\left(\max\left(\delta_{i,k} - p_{i,1}\right), 1 - p_{i,1}\right))$$

Please also refer to Appendix D, Section D.1.3.3.7 of the CS for further details on the discussion and explanation of the RD NMA methodology.

A9. For the baseline-risk adjustment described in Appendix D.1.3.3.6, please confirm the EAG's understanding that the indicated options for the 'network' object (under heading [redacted]) in the base case were set to:

[redacted]

Company response

The company can confirm that the [redacted] option and the [redacted] option were set for baseline risk-adjusted logit-link NMA models.

A10. Please provide a table comparing estimates from the risk difference model, converted to odds ratios, with the estimates of odds ratios from the logit-link models (unadjusted, and adjusted for baseline risk).

Company response

Please see below for the company's responses. The company advises that the baseline risk-adjusted logit-link NMA results are not presented due to the model convergence issue discussed in the response to question A4 above. The logit-link NMA results demonstrate extreme (and implausible) variance for some outcomes, particularly in the odds ratios (ORs) presented for infliximab, due to heterogeneity that the logit-link models are unable to adequately address.

Table 2: CDAI clinical response odds ratio outcomes in CCF induction NMA (FE models)

Treatment	Risk-difference model ORs			Logit-link model ORs		
	Median	LCrI	UCrI	Median	LCrI	UCrI
RZB vs PBO	2.518	1.444	4.354	2.46	1.41	4.38
UST vs PBO	3.126	2.158	4.497	3.13	2.09	4.74
ADA 160/80 Bio vs PBO	2.797	1.590	4.862	3.03	1.60	5.87
ADA 160/80 vs PBO	2.797	1.590	4.862	3.03	1.60	5.87
ADA 80/40 vs PBO	2.105	1.169	3.610	2.26	1.19	4.38
IFX IV vs PBO	7.826	2.819	42.342	14.36	3.60	79.20
IFX IV Bio vs PBO	7.826	2.819	42.342	14.36	3.60	79.20
IFX SC vs PBO	7.826	2.819	42.342	14.36	3.60	79.20
VDZ IV vs PBO	1.849	1.186	2.726	1.80	1.12	2.93
VDZ SC vs PBO	1.849	1.186	2.726	1.80	1.12	2.93

Abbreviations: ADA, adalimumab; Bio, biosimilar; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IFX, infliximab; IV, intravenous; LCrI, lower credible interval; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RZB, risankizumab; SC, subcutaneous; UCrI, upper credible interval; UST, ustekinumab; VDZ, vedolizumab.
Please note that results for ADA 160/80, IFX (all regimens) and VDZ (all regimens) utilise efficacy data for ADA 160/80, IFX IV and VDZ IV, respectively. The inductions for IFX SC and VDZ SC are performed via the IV route.

Table 3: CDAI clinical remission odds ratio outcomes in CCF induction NMA (FE models)

Treatment	Risk-difference model ORs			Logit-link model ORs		
	Median	LCrI	UCrI	Median	LCrI	UCrI
RZB vs PBO	3.834	2.125	6.312	3.233	1.761	6.176
UST vs PBO	2.686	1.780	3.894	2.523	1.605	4.013
ADA 160/80 Bio vs PBO	3.386	1.923	5.687	3.924	1.854	8.841
ADA 160/80 vs PBO	3.386	1.923	5.687	3.924	1.854	8.841
ADA 80/40 vs PBO	1.988	0.948	3.380	2.196	0.999	5.099

Treatment	Risk-difference model ORs			Logit-link model ORs		
	Median	LCrI	UCrI	Median	LCrI	UCrI
IFX IV vs PBO	7.203	3.000	17.851	31.815	4.709	917.817
IFX IV Bio vs PBO	7.203	3.000	17.851	31.815	4.709	917.817
IFX SC vs PBO	7.203	3.000	17.851	31.815	4.709	917.817
VDZ IV vs PBO	2.164	1.419	3.187	3.17	1.682	6.245
VDZ SC vs PBO	2.164	1.419	3.187	3.17	1.682	6.245

Abbreviations: ADA, adalimumab; Bio, biosimilar; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IFX, infliximab; IV, intravenous; LCrI, lower credible interval; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RZB, risankizumab; SC, subcutaneous; UcrI, upper credible interval; UST, ustekinumab; VDZ, vedolizumab.
Please note that results for ADA 160/80, IFX (all regimens) and VDZ (all regimens) utilise efficacy data for ADA 160/80, IFX IV and VDZ IV, respectively. The inductions for IFX SC and VDZ SC are performed via the IV route.

Table 4: CDAI clinical response odds ratio outcomes in BF induction NMA (FE models)

Treatment	Risk-difference model ORs			Logit-link model ORs		
	Median	Lcrl	Ucrl	Median	Lcrl	Ucrl
RZB vs PBO	3.306	2.472	4.463	3.16	2.28	4.40
UST vs PBO	1.782	1.255	2.466	1.87	1.25	2.82
ADA 160/80 Bio vs PBO	1.982	1.305	2.957	2.02	1.28	3.21
ADA 160/80 vs PBO	1.982	1.305	2.957	2.02	1.28	3.21
ADA 80/40 vs PBO	2.733	0.782	8.171	2.83	0.84	9.77
VDZ IV vs PBO	1.551	1.128	2.069	1.73	1.19	2.53
VDZ SC vs PBO	1.551	1.128	2.069	1.73	1.19	2.53

Abbreviations: ADA, adalimumab; BF, biologic failure; Bio, biosimilar; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; LCrI, lower credible interval; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RZB, risankizumab; SC, subcutaneous; UCrI, upper credible interval; UST, ustekinumab; VDZ, vedolizumab.
Please note that results for ADA 160/80, IFX (all regimens) and VDZ (all regimens) utilise efficacy data for ADA 160/80, IFX IV and VDZ IV, respectively. The inductions for IFX SC and VDZ SC are performed via the IV route.

Table 5: CDAI clinical remission odds ratio outcomes in BF induction NMA (FE models)

Treatment	Risk-difference model ORs			Logit-link model ORs		
	Median	LCrI	UCrI	Median	LCrI	UCrI
RZB vs PBO	3.325	2.370	4.552	2.577	1.823	3.666
UST vs PBO	1.977	1.340	2.789	2.341	1.373	4.101
ADA 160/80 Bio vs PBO	2.545	1.713	3.644	3.631	1.903	7.405
ADA 160/80 vs PBO	2.545	1.713	3.644	3.631	1.903	7.405
ADA 80/40 vs PBO	1.096	0.000	3.479	1.041	0.114	6.140
VDZ IV vs PBO	1.288	0.830	1.799	1.369	0.825	2.320
VDZ SC vs PBO	1.288	0.830	1.799	1.369	0.825	2.320

Abbreviations: ADA, adalimumab; BF, biologic failure; Bio, biosimilar; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; LCrI, lower credible interval; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RZB, risankizumab; SC, subcutaneous; UCrI, upper credible interval; UST, ustekinumab; VDZ, vedolizumab.
Please note that results for ADA 160/80, IFX (all regimens) and VDZ (all regimens) utilise efficacy data for ADA 160/80, IFX IV and VDZ IV, respectively. The inductions for IFX SC and VDZ SC are performed via the IV route.

Table 6: CDAI clinical remission odds ratio outcomes in CCF maintenance NMA (FE model, risk difference)

Treatment	Risk-difference model ORs			Logit-link model ORs		
	Median	LCrI	UCrI	Median	LCrI	UCrI
RZB vs PBO	1.249	0.433	3.565	1.268	0.513	3.216
UST vs PBO	1.643	0.716	4.380	1.671	0.861	3.266
ADA 160/80 Bio vs PBO	3.387	1.937	6.130	4.668	2.258	10.222
ADA 160/80 vs PBO	3.387	1.937	6.130	4.668	2.258	10.222
ADA 80/40 vs PBO	3.387	1.937	6.130	4.668	2.258	10.222
IFX IV vs PBO	2.001	1.139	3.381	2.535	1.292	5.162
IFX IV Bio vs PBO	2.001	1.139	3.381	2.535	1.292	5.162
IFX SC vs PBO	2.001	1.139	3.381	2.535	1.292	5.162
VDZ IV vs PBO	2.300	1.082	4.505	2.193	1.134	4.309
VDZ SC vs PBO	1.736	0.786	3.348	1.595	0.889	2.892

Abbreviations: ADA, adalimumab; Bio, biosimilar; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IFX, infliximab; IV, intravenous; LCrI, lower credible interval; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RZB, risankizumab; SC, subcutaneous; UCrI, upper credible interval; UST, ustekinumab; VDZ, vedolizumab.

Table 7: CDAI clinical remission odds ratio outcomes in BF maintenance NMA (FE model, risk difference)

Treatment	Risk-difference model ORs			Logit-link model ORs		
	Median	LCrI	UCrI	Median	LCrI	UCrI
RZB vs PBO	1.741	0.873	3.337	1.730	1.011	2.980
UST vs PBO	1.668	0.727	3.682	1.781	0.813	3.968
ADA 160/80 Bio vs PBO	3.036	1.514	5.817	4.173	1.807	10.73
ADA 160/80 vs PBO	3.036	1.514	5.817	4.173	1.807	10.73
ADA 80/40 vs PBO	3.036	1.514	5.817	4.173	1.807	10.73
VDZ IV vs PBO	2.562	1.232	4.939	3.144	1.431	7.376
VDZ SC vs PBO	2.633	1.088	5.369	2.166	1.145	4.241

Abbreviations: ADA, adalimumab; BF, biologic failure; Bio, biosimilar; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; LCrI, lower credible interval; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RZB, risankizumab; SC, subcutaneous; UCrI, upper credible interval; UST, ustekinumab; VDZ, vedolizumab.

A11. For each of the trials included in the maintenance NMAs, please indicate the point(s) of randomisation: whether it is prior to the induction phase or prior to the maintenance phase (or any other point). For example, FORTIFY (sub study 1) includes participants who respond to induction and these are randomised at the end of induction.

Company response

Table 8 indicates the point of randomisation in the different study phases (i.e., induction or maintenance) for the comparator biologic therapies in the risankizumab NICE submission.

Table 8: Points of randomisation for comparator biologic therapies

Author (study), therapy	Randomisation points during studies	Randomisation details
Hanauer 2002 (15) (ACCENT 1), IFX	The design of this study does not reflect the licensed induction and maintenance schedule for IFX (16); see randomisation details column	At Wk 0, all eligible patients received a 5 mg/kg IV infusion of IFX. At Wk 2, patients with response to treatment were randomly assigned to subsequent infusions, at Wk 2 and 6 and Q8W thereafter until Wk 46, of PBO (group I), 5 mg/kg IFX (group II), or 5 mg/kg IFX at Wk 2 and 6 followed by 10 mg/kg thereafter (group III)
Colombel 2007 (17) (CHARM), ADA	Induction: No Maintenance: Yes	At Wk 0, all eligible patients received open-label ADA 80 mg SC followed by a 40-mg dose at Wk 2. At Wk 4, patients were randomised to one of 3 treatment groups (ADA 40 mg Q2W, ADA 40 mg QW, or PBO) and continued treatment through Wk 56
Hanauer 2006 (5) (CLASSIC 1), ADA	Induction: Yes Maintenance: NA	At Wk 0, all eligible patients were randomly assigned to receive one of the following subcutaneous induction regimens: PBO at Wk 0 and 2, ADA 40 mg at Wk 0 and 20 mg at Wk 2, ADA 80 mg at Wk 0 and 40 mg at Wk 2, or ADA 160 mg at Wk 0 and 80 mg at Wk 2
Sandborn 2007 (18) (GAIN), ADA	Induction: Yes Maintenance: NA	Eligible patients were randomly assigned to receive SC injections of ADA, 160 mg at Wk 0 and 80 mg at Wk 2, or PBO at Wks 0 and 2 and followed patients through Wk 4
Sandborn 2013 (19) (GEMINI 2), VDZ	Induction: Yes Maintenance: Yes	Patients were randomly assigned to receive induction VDZ 300 mg IV, or PBO at Wk 0 and 2 and were followed through Wk 6 Patients who had a clinical response to VDZ at Wk 6 were randomly assigned to maintenance VDZ Q8W, Q4W, or PBO, for up to 52 weeks[†]
Sands 2014 (8) (GEMINI 3), VDZ	Induction: Yes Maintenance: NA	Patients were assigned randomly to groups given VDZ 300 mg IV or PBO at Wk 0, 2, and 6
Feagan 2016 (7) (IM-UNITI), UST	Induction: Yes	At Wk 0, patients were randomly assigned to receive a single induction infusion of UST 130 mg IV

Author (study), therapy	Randomisation points during studies	Randomisation details
	Maintenance: Yes	At Wk 8, patients with clinical response to UST were randomly assigned to receive UST 90 mg SC Q8W, Q12W, or PBO through Wk 40
Targan et al 1997 (20) (N/A), IFX	The design of this study does not reflect the licensed induction and maintenance schedule for IFX (16); see randomisation details column	Patients were randomly assigned to receive an IV infusion of PBO or IFX 5 mg per kg, 10 mg per kg, or 20 mg per kg for 12 weeks
Rutgeerts 2018 (21) (UNITI 1), UST	Induction: Yes Maintenance: Yes	At Wk 0, patients were randomly assigned to groups given a single induction dose of UST IV (130 mg or 6 mg/kg) or PBO At Wk 8, patients with a clinical response to UST were randomly assigned to groups given UST SC (90 mg Q12W or Q8W) or PBO
Rutgeerts 2018 (21) (UNITI 2), UST	Induction: Yes Maintenance: Yes	At Wk 0, patients were randomly assigned to groups given a single induction dose of UST IV (130 mg or 6 mg/kg) or PBO At Wk 8, patients with a clinical response to UST were randomly assigned to receive maintenance UST SC (90 mg Q12W or Q8W) or PBO
Vermeire 2022 (22) (VISIBILE 2), VDZ	Induction: No Maintenance: Yes	Patients were assigned open-label VDZ 300 mg IV induction therapy at Wk 0 and 2, At Wk 6, clinical responders to VDZ were randomised to maintenance VDZ 108 mg SC or PBO Q2W until Wk 50
Watanabe 2012 (23) (N/A), ADA	Induction: Yes Maintenance: Yes	Patients were randomised to receive induction ADA 160/80 mg, ADA 80/40 mg or PBO at Wk 0 and 2 At Wk 4, patients who responded to ADA entered the maintenance trial and were randomised to ADA 40 mg Q2W or PBO for 52 weeks.
Watanabe 2020 (24) (N/A), VDZ	Induction: Yes Maintenance: Yes	Patients were randomised to receive induction VDZ 300 mg IV or placebo at Wk 0, 2, and 6 At Wk 10, clinical responders to VDZ were randomised to receive maintenance VDZ 300 mg IV or PBO at Wk 14, then Q8W until Week 54

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; N/A, not applicable; PBO, placebo; QxW, every X weeks; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab; Wk, week.

† To fulfil the sample-size requirements for the maintenance trial, additional patients were enrolled in an open-label group (cohort 2), which received the same vedolizumab induction regimen that was used for the patients assigned to vedolizumab in cohort 1.

A12. Please supply a table of summary statistics for each of the potential effect modifiers listed in Doc B Appendix D (pp56-7), for each of the arms of the trials included in the NMA.

Company response

Summary statistics for each of the potential effect modifiers listed in Appendix D, Section D.1.3.3.3 of the CS are presented in Table 9, Table 10 and Table 11 for the studies used in the induction NMA, and Table 12, Table 13 and Table 14 for the studies used in the maintenance NMA.

Table 9: Baseline patient characteristics of induction by population data (overall if not available), continuous variables CCF and BF populations

Study	Treatment arm	N	Age , years – Mean (SE)	Weight, kg– Mean (SE)	Duration of disease, years – Mean (SE)	CDAI, score – Mean (SE)	IBDQ, score – Mean (SE)	CRP, mg/L – Mean (SE)	F-CAL, mg/kg – Mean (SE)
ADVANCE (M16-006) (CCF)	PBO	78	38.64 (1.56)	68.86 (1.72)	7.08 (0.9)	322.88 (7.01)	125.09 (3.89)	13.36 (2.11)	2043.58 (435.57)
ADVANCE (M16-006) (CCF)	RZB	141	40.03 (1.17)	71.41 (1.54)	7.63 (0.81)	307.38 (5.14)	118.32 (2.72)	13.85 (1.91)	1327.23 (146.19)
CLASSIC-I (CCF)	PBO	74	37 (1.51)	74 (2.21)	NR	296 (6.97)	131 (5.8)	18 (3.02)	NR
CLASSIC-I (CCF)	ADA 160/80	76	39 (1.26)	78 (2.06)	NR	295 (5.96)	127 (5.8)	14 (2.18)	NR
CLASSIC-I (CCF)	ADA 80/40	75	38 (1.39)	74 (2.31)	NR	301 (7.04)	128 (5.8)	20 (3.23)	NR
GEMINI 2 (Overall)	PBO	148	38.6 (1.09)	68.7 (1.55)	8.2 (0.64)	325 (6.41)	NR	13.7 (7.22)	653 (472.91)
GEMINI 2 (Overall)	VDZ IV	220	36.3 (0.78)	67.1 (1.29)	9.2 (0.55)	327 (4.79)	NR	15.3 (7.22)	852 (472.91)
GEMINI 3 (CCF)	PBO	50	30.6 (4.85)	71.7 (3.41)	4.4 (2.1)	286.1 (7.23)	NR	17.7 (2.28)	1321 (276.34)
GEMINI 3 (CCF)	VDZ IV	51	35.7 (4.85)	67.1 (3.41)	4.7 (2.1)	307.3 (7.67)	NR	13.9 (2.35)	836.9 (146.16)
Targan 1997 (CCF)	PBO	25	38.5 (2.2)	71.4 (2.88)	10.4 (1.54)	288 (10.8)	128 (5.8)	12.8 (2.78)	NR
Targan 1997 (CCF)	IFX IV	27	37 (2.27)	68.1 (3.41)	12.5 (1.98)	312 (10.78)	122 (5.58)	22.1 (4.54)	NR
UNITI-2 (Pure CCF)	PBO	210	40.2 (0.9)	74 (1.37)	10.4 (0.68)	302.2 (4.26)	NR	8.5 (7.22)	415.5 (472.91)

Study	Treatment arm	N	Age , years – Mean (SE)	Weight, kg– Mean (SE)	Duration of disease, years – Mean (SE)	CDAI, score – Mean (SE)	IBDQ, score – Mean (SE)	CRP, mg/L – Mean (SE)	F-CAL, mg/kg – Mean (SE)
UNITI-2 (Pure CCF)	UST	209	38.4 (0.91)	71.9 (1.3)	8.7 (0.58)	302.3 (4.07)	NR	7.8 (7.22)	523.2 (472.91)
Watanabe 2012 (Overall)	PBO	23	30.4 (1.44)	56.5 (1.75)	7.9 (0.98)	308.1 (13.3)	139.4 (5.59)	25 (4.17)	NR
Watanabe 2012 (Overall)	ADA 160/80	33	32 (1.67)	54.1 (1.83)	11 (1.24)	300.5 (11.58)	145.9 (4.39)	22 (3.48)	NR
Watanabe 2012 (Overall)	ADA 80/40	34	30.6 (1.59)	55.3 (1.78)	9.2 (1.13)	302.7 (11.42)	148.6 (4.78)	30 (4.8)	NR
Watanabe 2020 (Overall)	PBO	78	32.6 (1.23)	NR	9.1 (0.74)	295 (7.34)	NR	29 (3.62)	NR
Watanabe 2020 (Overall)	VDZ IV	79	33.9 (1.38)	NR	9 (0.7)	303.9 (7.11)	NR	22 (2.48)	NR
ADVANCE (M16-006) (BF)	PBO	97	35.95 (1.31)	71.59 (2.05)	9.14 (2.1)	316.27 (5.83)	121.3 (3.15)	18.71 (2.34)	2889.09 (472.91)
ADVANCE (M16-006) (BF)	RZB	195	37.1 (0.92)	68.85 (1.23)	10.05 (2.1)	314.03 (4.54)	120.47 (2.19)	21.28 (2.1)	2058.13 (181.15)
GAIN (BF)	PBO	166	37 (0.93)	72 (1.47)	NR	313 (5.12)	124 (2.17)	20 (2.87)	NR
GAIN (BF)	ADA 160/80	159	39 (0.95)	72 (1.51)	NR	313 (4.6)	120 (2.14)	19 (1.98)	NR
GEMINI 3 (BF)	PBO	157	36.6 (4.85)	71.2 (3.41)	9.6 (2.1)	306.1 (4.42)	NR	18.8 (1.88)	1459.5 (197.53)
GEMINI 3 (BF)	VDZ IV	158	37.5 (4.85)	70.3 (3.41)	9.4 (2.1)	316.1 (4.18)	NR	20.7 (1.97)	1249.2 (164.81)
MOTIVATE (M15-991) (BF)	PBO	187	39.3 (0.99)	72.82 (1.39)	12.52 (0.71)	319.62 (5.1)	115 (2.33)	20.4 (1.88)	2648.9 (353.29)
MOTIVATE (M15-991) (BF)	RZB	191	40.2 (0.98)	72.74 (1.47)	10.89 (0.56)	310.7 (4.6)	119.4 (2.08)	19.33 (1.9)	2379.2 (280.72)
UNITI-1 (BF)	PBO	247	37.3 (0.75)	71.5 (1.13)	12.1 (0.53)	319 (3.8)	NR	8.5 (7.22)	515.8 (472.91)
UNITI-1 (BF)	UST	249	37.3 (0.79)	69.5 (1.24)	12.7 (0.58)	327.6 (3.93)	NR	9.9 (7.22)	530.2 (472.91)

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; F-CAL, faecal calprotectin; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; IV, intravenous; PBO, placebo; RZB, risankizumab; SE, standard error; UST, ustekinumab; VDZ, vedolizumab.

Table 10: Baseline patient characteristics of induction by population data (overall if not available), discrete variables table 1

Study	Treatment arm	N	Male patients - n	GI areas involved – ileum only - n	GI areas involved – colon only - n	GI areas involved – ileum and colon - n	Draining fistulae - n
ADVANCE (M16-006) (CCF)	PBO	78	41	7	31	40	1
ADVANCE (M16-006) (CCF)	RZB	141	82	27	49	65	6
CLASSIC-I (CCF)	PBO	74	37	50	14	7	6
CLASSIC-I (CCF)	ADA 160/80	76	36	40	22	8	12
CLASSIC-I (CCF)	ADA 80/40	75	25	47	17	7	10
GEMINI 2 (Overall)	PBO	148	69	21	43	84	23
GEMINI 2 (Overall)	VDZ IV	220	105	37	62	121	38
GEMINI 3 (CCF)	PBO	50	27	9	12	29	NR
GEMINI 3 (CCF)	VDZ IV	51	23	12	8	31	NR
Targan 1997 (CCF)	PBO	25	15	8	7	10	NR
Targan 1997 (CCF)	IFX IV	27	14	3	9	15	NR
UNITI-2 (CCF)	PBO	210	99	44	37	129	NR
UNITI-2 (CCF)	UST	209	90	49	43	117	NR
Watanabe 2012 (Overall)	PBO	23	16	NR	NR	NR	NR
Watanabe 2012 (Overall)	ADA 160/80	33	20	NR	NR	NR	NR
Watanabe 2012 (Overall)	ADA 80/40	34	16	NR	NR	NR	NR
Watanabe 2020 (Overall)	PBO	78	52	9	19	50	NR
Watanabe 2020 (Overall)	VDZ IV	79	51	13	11	55	NR
ADVANCE (M16-006) (BF)	PBO	97	47	12	39	46	8
ADVANCE (M16-006) (BF)	RZB	195	107	25	66	104	12
GAIN (BF)	PBO	166	65	124	113	NR	25
GAIN (BF)	ADA 160/80	159	50	112	105	NR	20
GEMINI 3 (BF)	PBO	157	62	20	40	97	NR
GEMINI 3 (BF)	VDZ IV	158	68	21	40	97	NR
MOTIVATE (M15-991) (BF)	PBO	187	99	26	73	88	14
MOTIVATE (M15-991) (BF)	RZB	191	92	33	75	83	14
UNITI-1 (BF)	PBO	247	118	28	48	166	NR
UNITI-1 (BF)	UST	249	101	37	40	171	NR

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; GI, gastrointestinal; IFX, infliximab; IV, intravenous; NR, not reported; PBO, placebo; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

Table 11: Baseline patient characteristics of induction by population data (overall if not available), discrete variables table 2

Study	Tx arm	N	GC/CS, n	IMM, n	AZA, n	MP, n	MTX, n	5-ASA, n	Failed 1 TNFi, n	Failed ≥2 TNFi, n	Failed ≥3 TNFi, n
ADVANCE (M16-006) (CCF)	PBO	78	21	23	16	1	3	41	NR	NR	NR
ADVANCE (M16-006) (CCF)	RZB	141		45	42	2	3	70	NR	NR	NR
CLASSIC-I (CCF)	PBO	74	25	22	13	8	1	37	NR	NR	NR
CLASSIC-I (CCF)	ADA 160/80	76	24	22	11	10	1	39	NR	NR	NR
CLASSIC-I (CCF)	ADA 80/40	75	32	21	9	10	3	40	NR	NR	NR
GEMINI 2 (Overall)	PBO	148	71	51	NR	NR	NR	NR	70	42	NR
GEMINI 2 (Overall)	VDZ IV	220	105	75	NR	NR	NR	NR	105	56	NR
GEMINI 3 (CCF)	PBO	50	23	27	NR	NR	NR	32	NR	NR	NR
GEMINI 3 (CCF)	VDZ IV	51	24	28	NR	NR	NR	31	NR	NR	NR
Targan 1997 (CCF)	PBO	25	16	11	7	4	0	17	NR	NR	NR
Targan 1997 (CCF)	IFX	27	15	9	5	4	0	16	NR	NR	NR
UNITI-2 (CCF)	PBO	210	75	73	NR	NR	NR	89	NR	NR	NR
UNITI-2 (CCF)	UST	209	92	72	NR	NR	NR	93	NR	NR	NR
Watanabe 2012 (Overall)	PBO	23	5	8	NR	NR	NR	23	NR	NR	NR
Watanabe 2012 (Overall)	ADA 160/80	33	8	10	NR	NR	NR	32	NR	NR	NR
Watanabe 2012 (Overall)	ADA 80/40	34	6	11	NR	NR	NR	27	NR	NR	NR
Watanabe 2020 (Overall)	PBO	78	NR	NR	NR	NR	NR	59	29	32	NR
Watanabe 2020 (Overall)	VDZ IV	79	NR	NR	NR	NR	NR	64	29	31	NR
ADVANCE (M16-006) (BF)	PBO	97	30	19	14	1	5	22	57	40	4
ADVANCE (M16-006) (BF)	RZB	195	69	43	32	5	7	37	110	73	5
GAIN (BF)	PBO	166	73	85	NR	NR	NR	60	166	0	0
GAIN (BF)	ADA 160/80	159	55	73	NR	NR	NR	45	159	0	0
GEMINI 3 (BF)	PBO	157	85	42	NR	NR	NR	29	43	111	21
GEMINI 3 (BF)	VDZ IV	158	86	43	NR	NR	NR	37	59	96	14
MOTIVATE (M15-991) (BF)	PBO	187	69	40	29	5	6	36	103	78	8
MOTIVATE (M15-991) (BF)	RZB	191	68	36	26	3	7	31	101	76	13
UNITI-1 (BF)	PBO	247	111	81	NR	NR	NR	54	112	134	NR
UNITI-1 (BF)	UST	249	108	78	NR	NR	NR	50	120	126	NR

Abbreviations: 5-ASA, 5-aminosalicylates; ADA, adalimumab; AZA, azathioprine; BF, biologic failure; CCF, conventional care failure; CS, corticosteroids; GC, glucocorticoids; IFX, infliximab; IMM, immunomodulator; MP, mercaptopurine; MTX, methotrexate; NR, not reported; PBO, placebo; RZB, risankizumab; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VDZ, vedolizumab.

Table 12: Baseline patient characteristics of maintenance overall populations, continuous variables

Study	Treatment arm	N	Age, years – Mean (SE)	Weight, kg– Mean (SE)	Duration of disease, years – Mean (SE)	CDAI, score – Mean (SE)	IBDQ, score – Mean (SE)	CRP, mg/L – Mean (SE)	F-CAL, mg/kg – Mean (SE)
ACCENT I (CCF)	Randomised responders (IFX)	335	36 (4.85)	NR	7.5 (2.1)	299 (23.58)	129 (5.8)	11 (7.22)	NR
CHARM (Overall)	Randomised responders (ADA)	499	36.7 (0.52)	70.2 (0.8)	NR	316.6 (2.8)	125 (5.8)	24 (1.66)	NR
FORTIFY (M16-000) (Overall)	PBO	164	38 (1.01)	71.76 (1.5)	9.61 (0.68)	307.38 (5.06)	118.8 (2.56)	17.15 (1.99)	1640.7 (160.52)
FORTIFY (M16-000) (Overall)	RZB Q8W	141	37 (1.08)	70.41 (1.48)	9.3 (0.68)	308.92 (5.15)	125.5 (2.65)	22.78 (2.41)	2182.5 (208.15)
GEMINI 2 (Overall)	PBO	153	37.3 (0.97)	69 (1.47)	9.6 (0.72)	325 (5.34)	NR	9.8 (7.22)	684 (472.91)
GEMINI 2 (Overall)	VDZ IV Q4W	154	34.9 (0.98)	71.5 (1.48)	7.7 (0.55)	317 (5.32)	NR	9.8 (7.22)	776 (472.91)
GEMINI 2 (Overall)	VDZ IV Q8W	154	35.1 (0.98)	68.5 (1.5)	8.4 (0.59)	326 (5.56)	NR	8.6 (7.22)	584 (472.91)
IM-UNITI (Overall)	PBO	133	39.5 (1.1)	72.3 (1.5)	10.6 (0.82)	319.1 (5.27)	NR	9.6 (7.22)	587.4 (472.91)
IM-UNITI (Overall)	UST Q12W	132	37.9 (1.15)	70.6 (1.47)	10.3 (0.76)	320.4 (5.81)	NR	8.8 (7.22)	536.5 (472.91)
IM-UNITI (Overall)	UST Q8W	132	38.6 (1.19)	70 (1.71)	9.5 (0.76)	313.1 (5.05)	NR	9.1 (7.22)	567.5 (472.91)
VISIBLE 2 (Overall)	PBO	135	36.1 (1.11)	69.79 (1.56)	8.2 (0.72)	NR	109 (5.8)	NR	871 (472.91)
VISIBLE 2 (Overall)	VDZ SC Q2W	275	38.2 (0.84)	74.08 (1.15)	9.5 (0.5)	NR	107.7 (5.8)	NR	736 (472.91)
Watanabe 2020 (Overall)	PBO	12	35.2 (3.75)	NR	7.5 (1.91)	303.3 (23.58)	NR	24 (7.22)	NR
Watanabe 2020 (Overall)	VDZ IV Q8W	12	36.7 (4.85)	NR	9 (1.41)	319.8 (22.89)	NR	20 (4.62)	NR

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; F-CAL, fecal calprotectin; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; IV, intravenous; PBO, placebo; QXW, every x weeks; RZB, risankizumab; SC, subcutaneous; SE, standard error; UST, ustekinumab; VDZ, vedolizumab.

Table 13: Baseline patient characteristics of maintenance overall populations, discrete variables table 1

Study	Treatment arm	N	Male patients - n	GI areas involved – ileum only - n	GI areas involved – colon only - n	GI areas involved – ileum and colon - n	Draining fistulae - n
ACCENT I (CCF)	Randomised responders (IFX)	335	130	NR	NR	NR	NR
CHARM (Overall)	Randomised responders (ADA)	499	188	357	375	NR	NR
FORTIFY (M16-000) (Overall)	PBO	164	89	23	62	79	11
FORTIFY (M16-000) (Overall)	RZB Q8W	141	81	15	59	67	11
GEMINI 2 (Overall)	PBO	153	72	19	43	91	18
GEMINI 2 (Overall)	VDZ IV Q4W	154	82	34	47	73	22
GEMINI 2 (Overall)	VDZ IV Q8W	154	68	29	27	98	17
IM-UNITI (Overall)	PBO	133	59	19	28	86	NR
IM-UNITI (Overall)	UST Q12W	132	56	26	23	83	NR
IM-UNITI (Overall)	UST Q8W	132	58	19	29	84	NR
VISIBLE 2 (Overall)	PBO	135	66	21	26	74	12
VISIBLE 2 (Overall)	VDZ SC Q2W	275	157	66	55	122	14
Watanabe 2020 (Overall)	PBO	12	9	2	1	9	NR
Watanabe 2020 (Overall)	VDZ IV Q8W	12	6	2	5	5	NR

Abbreviations: ADA, adalimumab; CCF, conventional care failure; GI, gastrointestinal; IFX, infliximab; IV, intravenous; NR, not reported; PBO, placebo; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Table 14: Baseline patient characteristics of maintenance overall populations, discrete variables table 2

Study	Treatment arm	N	GC/CS, n	IMM, n	AZA, n	MP, n	MTX, n	5-ASA, n	TNFi Tx history
ACCENT I (CCF)	Randomised responders (IFX)	335	175	91	81	81	10	159	0
CHARM (Overall)	Randomised responders (ADA)	499	210	240	165	38	49	206	238
FORTIFY (M16-000) (Overall)	PBO	164	51	40	33	2	5	48	119
FORTIFY (M16-000) (Overall)	RZB360/Q8W	141	42	40	32	3	5	45	91
GEMINI 2 (Overall)	PBO	153	82	49	NR	NR	NR	NR	82
GEMINI 2 (Overall)	VDZ300/Q4W	154	80	53	NR	NR	NR	NR	83
GEMINI 2 (Overall)	VDZ300/Q8W	154	82	50	NR	NR	NR	NR	88
IM-UNITI (Overall)	PBO	133	59	47	NR	NR	NR	46	81
IM-UNITI (Overall)	UST90/Q12W	132	58	52	NR	NR	NR	47	79
IM-UNITI (Overall)	UST90/Q8W	132	64	44	NR	NR	NR	49	80
VISIBLE 2 (Overall)	PBO	135	22	34	NR	NR	NR	NR	0
VISIBLE 2 (Overall)	VDZ108/Q2W	275	39	51	NR	NR	NR	NR	0
Watanabe 2020 (Overall)	PBO	12	NR	NR	NR	NR	NR	11	7
Watanabe 2020 (Overall)	VDZ300/Q8W	12	NR	NR	NR	NR	NR	8	8

Abbreviations: 5-ASA, 5-aminosalicylates; ADA, adalimumab; AZA, azathioprine; CCF, conventional care failure; CS, corticosteroids; GC, glucocorticoids; IFX, infliximab; IMM, immunomodulators; MP, mercaptopurine; MTX, methotrexate; PBO, placebo; RZB, risankizumab; TNFi, tumour necrosis factor inhibitor; Tx, treatment; UST, ustekinumab; VDZ, vedolizumab.

A13. Please provide justification for choice of priors, in particular the use of half-normal (0, 0.322) or gamma (0.001, 0.001) in cases where convergence failed. Both choices are moderately informative; please discuss their consequences.

Company response

To clarify, the EAG's noted priors of interest (half-normal (0, 0.32^2), gamma (0.001, 0.001)) are not used in the risk-difference link NMAs presented in the CS (please find further details on when these priors were used in Appendix D, Section D.1.3.3.4 and Section D.1.3.3.8). RD link NMAs presented utilise only vague/noninformative priors such as those discussed in NICE DSU TSD 2 (14). Specifically, as Appendix D, Section D.1.3.3.8 of the CS states, "For risk-difference-link models, a uniform (0,1) prior distribution was used for study baselines and a uniform (-1,1) [uniform (-0.999, 0.999) in RE models to assist computation] prior distribution was used for treatment effects. For the between-study standard deviation (for RE models), a uniform (0, 5) prior distribution was used."

A14. How was autocorrelation of NMA estimates assessed, and was any thinning applied?

Company response

Per NICE DSU TSD 2, a commonly used methodology to indirectly assess the degree of autocorrelation (and also reflect the number of samples used) in an analysis is to compare the Monte Carlo standard error (MC error) to the posterior standard deviation (SD) of the parameter of interest (posterior SD) (14). In the CS NMAs, given the RD link, this would constitute comparing the risk difference MC error (RD MC error) to the posterior standard deviation of the risk difference (RD posterior SD). It is suggested in NICE DSU TSD 2 that the MC error should be less than 5% of the posterior SD (14). In the tables below (Table 15 to Table 22), this recommended comparison is conducted. The RD posterior SD, RD MC error and NICE DSU TSD 2 suggested threshold value (5% of RD posterior SD) are presented for each treatment across NMAs contained in CS Section B.2.9.2. If the RD MC error is less than 5% of the RD posterior SD, the last column (RD MC error <5% of RD posterior SD) of the tables presented below displays “TRUE”. Please note that all cells of this column across tables display “TRUE”. This suggests that a sufficient number of Markov Chain Monte Carlo (MCMC) samples are utilised in the analyses and autocorrelation is likely not problematic in the CS NMAs.

Thinning was not applied. Given the robust number of MCMC samples utilised in the NMA (100,000 samples following a 50,000-sample burn-in for risk-difference link NMAs, see Appendix D Section D.1.3.3.4 of the CS), the company would not anticipate thinning to have a tangible impact on the NMA results.

Table 15: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical response in CCF induction NMA (FE model)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CDAI, Crohn’s Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; IFX, infliximab; IV, intravenous; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RD, risk difference; RZB, risankizumab; SD, standard deviation; TSD, Technical Support Document; UST, ustekinumab; VDZ, vedolizumab.

Table 16: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical response in BF induction NMA (FE model)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CDAI, Crohn's Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; IV, intravenous; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RD, risk difference; RZB, risankizumab; SD, standard deviation; TSD, Technical Support Document; UST, ustekinumab; VDZ, vedolizumab.

Table 17: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical remission in CCF induction NMA (FE model)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; IFX, infliximab; IV, intravenous; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RD, risk difference; RZB, risankizumab; SD, standard deviation; TSD, Technical Support Document; UST, ustekinumab; VDZ, vedolizumab.

Table 18: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical remission in BF induction NMA (FE model)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CDAI, Crohn's Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; IV, intravenous; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RD, risk difference; RZB, risankizumab; SD, standard deviation; TSD, Technical Support Document; UST, ustekinumab; VDZ, vedolizumab.

Table 19: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical remission in CCF maintenance NMA (FE model) (risankizumab and ustekinumab network)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
RZB Q8W	[redacted]	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; QxW, every x weeks; RD, risk difference; RZB, risankizumab; SD, standard deviation; TSD, Technical Support Document; UST, ustekinumab.

Table 20: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical remission in CCF maintenance NMA (FE model) (infliximab, adalimumab and vedolizumab network)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
ADA Q2W	[redacted]	[redacted]	[redacted]	[redacted]
ADA QW	[redacted]	[redacted]	[redacted]	[redacted]
IFX5/10 IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]
IFX5 IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; IFX, infliximab; IV, intravenous; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; QxW, every x weeks; RD, risk difference; SC, subcutaneous; SD, standard deviation; TSD, Technical Support Document; VDZ, vedolizumab.

Table 21: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical remission in BF maintenance NMA (FE model) (risankizumab and ustekinumab network)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
RZB Q8W	[redacted]	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; QxW, every x weeks; RD, risk difference; RZB, risankizumab; SD, standard deviation; TSD, Technical Support Document; UST, ustekinumab.

Table 22: Error terms and NICE DSU TSD 2 recommended check for CDAI clinical remission in BF maintenance NMA (FE model) (adalimumab and vedolizumab network)

Treatment	RD posterior SD	RD MC error	5% of RD posterior SD	RD MC error <5% of RD posterior SD?
ADA Q2W	[redacted]	[redacted]	[redacted]	[redacted]
ADA QW	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CDAI, Crohn's Disease Activity Index; DSU, Decision Support Unit; FE, fixed effects; IV, intravenous; MC, Markov Chain; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; QxW, every x weeks; RD, risk difference; SC, subcutaneous; SD, standard deviation; TSD, Technical Support Document; VDZ, vedolizumab.

A15. PRIORITY QUESTION The EAG notes that differences in half-life, duration of induction and study heterogeneity are cited as reasons for why vedolizumab was included in the network with TNFis. However, the CS states (Document B, p.20) that 'For individuals who have biologic failure…ustekinumab or vedolizumab (an integrin α4β7 inhibitor) are the therapy options. Ustekinumab and vedolizumab are also the therapy options when TNF-alpha inhibitors are contraindicated'; suggesting these treatments may belong in the same network. Furthermore, Appendix M.8.1 (Appendices, p.389) states that risankizumab has a half-life of 21 days; various literature sources indicate that this is similar for other treatments: 15-32 days for ustekinumab [1], 25.5 days for vedolizumab [2], 3 weeks for infliximab [3], and 21 days for adalimumab [4]. Moreover, the induction phase of vedolizumab 300 mg IV (follow-up at 6 and 10 weeks) does not appear to be very dissimilar to the durations included for ustekinumab and risankizumab (follow-up at 8 and 12 weeks, respectively). Consequently, the EAG is not convinced that vedolizumab belongs in the network with TNFis, and would like to see results including this treatment in the ustekinumab-risankizumab network. Please could you provide the following revised maintenance NMAs for the CCF and BF subgroups, either as base case or scenario analyses: (1) grouping vedolizumab in the network with risankizumab and ustekinumab instead of the TNFis, and (2) grouping all treatments (TNFis, vedolizumab, ustekinumab and risankizumab) together in a single network.

Company response

The NMA submitted within the CS is considered to be the most appropriate method to present the relative efficacy of each biologic treatment as elaborated upon below.

The split network that groups ustekinumab and risankizumab with vedolizumab is not considered appropriate due to several differences between vedolizumab and the other two biologics. More precisely, the withdrawal placebo rates of clinical remission within the maintenance studies are vastly different between risankizumab and vedolizumab, and less so with ustekinumab, likely due to the effect of previous exposure to the drug within the induction phase (see CS Section B.2.9.3.2, Figure

11). This, along with the differing mechanisms of action for each therapy (risankizumab and ustekinumab inhibit the IL-23 pathway (25-27); vedolizumab is gut-selective, α4β7 integrin inhibitor (28)) and the study heterogeneity make the split maintenance NMA network that only includes risankizumab and ustekinumab the more appropriate comparison.

Furthermore, the single maintenance NMA network does not stand up to basic face validity as the outputs suggest that in some cases placebo is more effective than ustekinumab, vedolizumab and risankizumab; this observation goes against the results presented in the Phase 3 clinical trials of the respective biologic therapies (7, 19, 29-31). In addition, the use of a single maintenance NMA network introduces the issue of placebo heterogeneity. As discussed in the CS, substantial placebo efficacy heterogeneity exists in the single-network approach. The creation of two NMA networks mitigates the maintenance placebo heterogeneity issue, as placebo heterogeneity is greatly reduced in the risankizumab and ustekinumab network, and the direct comparability of risankizumab and ustekinumab is greatly improved when compared with that of a single-network approach. Nonetheless, to fulfil the request, the company has provided both the split maintenance NMA network (including vedolizumab) and single maintenance NMA network (including all biologics), which can be found in Table 23, Table 24 and Table 25. Please note that the split network (including vedolizumab) NMA outcomes are only provided for the BF population since vedolizumab is only recommended for use after CCF based on the NICE guidelines for the treatment of moderate-to-severe CD (32).

Table 23: Split maintenance NMA network results for CDAI remission (vedolizumab added to network with risankizumab and ustekinumab): BF population

Treatment	Median	Lower CrI	Upper CrI
RZB Q8W	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; CrI, credible interval; IV, intravenous; PBO, placebo; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Table 24: Single maintenance NMA network results for CDAI remission: CCF population

Treatment	Median	Lower CrI	Upper CrI
ADA 40 QW	[redacted]	[redacted]	[redacted]
ADA 40 Q2W	[redacted]	[redacted]	[redacted]
IFX 5/10 Q8W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]
IFX5 Q8W	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]
RZB Q8W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CrI, credible interval; IFX, infliximab; IV, intravenous; PBO, placebo; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Table 25: Single maintenance NMA network results for CDAI remission: BF population

Treatment	Median	Lower CrI	Upper CrI
ADA 40 QW	[redacted]	[redacted]	[redacted]
ADA 40 Q2W	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
RZB Q8W	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CrI, credible interval; IV, intravenous; PBO, placebo; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Trial protocol

A16. In section B.2.3.2 of the CS, it is stated that for all three trials there were two protocols – one for US sites (US protocol) and one for other sites (OUS protocol) and that this was for regulatory reasons. Could the company expand on why the different protocols were required and provide additional clarification as to the extent of differences between how the studies were conducted at US and non-US sites.

Company response

In the original protocol for the risankizumab CD studies (ADVANCE, MOTIVATE and FORTIFY), the definition of the co-primary endpoint was patient-reported outcomes 2-item (stool frequency/abdominal pain score) (PRO2 [SF/APS]) clinical remission and endoscopic response. However, subsequent discussions with the FDA led to the creation of a US-specific protocol, which defined the co-primary endpoint as CDAI clinical remission and endoscopic response. An outside-US (OUS) protocol was created which retained the original definition of the co-primary endpoint, i.e., using PRO2 (SF/APS) to assess clinical remission. Consequently, the co-primary endpoint for the OUS protocol was clinical remission (PRO2 [SF/APS]) and endoscopic response, while the co-primary endpoint for the US protocol was clinical remission (CDAI) and endoscopic response. Both co-primary endpoints were measured at all trial sites, regardless of region. The only differences between the protocols are the outcomes used to determine clinical remission for the co-primary endpoints, the ranking of secondary endpoints and the sample size power calculation based on the revised co-primary endpoint.

A17. For each trial, could the company clarify the number of UK sites, the number of UK patients and whether – based on available data – UK patients differed significantly from non-UK patients in terms of baseline characteristics and study results?

Company response

The risankizumab CD study programme enrolled a total of [redacted] subjects at [redacted] UK centres. In the UK, [redacted] patients were enrolled across [redacted] sites in ADVANCE, [redacted] patients were enrolled across [redacted] sites in MOTIVATE, and [redacted] patients were enrolled across [redacted] sites in FORTIFY.

Subgroup analyses for baseline characteristics and clinical outcomes by region were not conducted as part of the clinical study protocol; post hoc analyses for these subgroups have not been completed. Based on expert clinical opinion (3), the subjects enrolled in the risankizumab CD studies are reflective of people with moderate-to-severe CD observed in current clinical practice in the UK.

A18. Could the company please justify the use of the CDAI outcome measure as the company says it is not widely used in the target market for this submission (the UK) and (CS, p.116) that other measures such as the Harvey Bradshaw Index (HBI) are "more suited to clinical practice". In addition, it would be useful to know how similar the HBI and CDAI measures are.

Company response

As stated in the CS, the CDAI outcome measure was used as it is a frequently used endpoint in CD clinical trials and therefore facilitates indirect treatment comparisons other treatments for CD (7, 19). Furthermore, the cost-effectiveness model presented in the CS utilises CDAI outcomes to define CD health states in alignment with previous CD NICE submissions (1, 2).

The Harvey-Bradshaw Index (HBI) and CDAI measures are distinct in terms of administration and the duration over which symptoms are captured. The HBI is physician administered and captures symptoms over the preceding 24 hours, while CDAI is a 7-day patient recorded dairy (33). The HBI is based on a simplified version of the CDAI, and shares several common items for disease measurement, which include number of liquid or very soft stools, abdominal pain score, complications (e.g., arthralgia, fissures, fistulas) mucocutaneous lesions (e.g., erythema nodosum, aphthous ulcers) and general well-being (33). In addition, studies have shown that results from HBI correlate with CDAI results (34, 35).

Whilst the HBI is more commonly used in UK clinical practice due to its ease of use (35), use of the HBI rather than CDAI in the clinical trial setting would have rendered indirect comparisons with relevant other CD treatments infeasible.

A19. Section B.2.4.1 states that the ITT population was used for the analysis of secondary endpoints. Please provide a definition for the ITT population.

Company response

This was an error and Section B.2.4.1 of the CS should read that the ITT1A population was used for the analysis of secondary efficacy endpoints. In ADVANCE and MOTIVATE, the ITT1A population was defined subjects who were randomised and received ≥1 dose of risankizumab during Induction Period 1 and who had a baseline eligible Simple Endoscopic Score for Crohn's disease (SES-CD) of ≥6 (≥4 for isolated ileal disease). In FORTIFY, the ITT1A population was defined as randomised subjects in the ITT1 set who had eligibility SES-CD of ≥6 (≥4 for isolated ileal disease) at Baseline of the induction study (ADVANCE or MOTIVATE) and received IV risankizumab for only 1 period of 12 weeks in the induction study (ADVANCE or MOTIVATE). This population included subjects who had PRO2 (SF/APS) clinical response to IV risankizumab at Week 12 and subjects with placebo IR at Week 12, who proceeded to receive IV risankizumab in Induction Period 2 and had PRO2 (SF/APS) clinical response at Week 24.

A20. The EAG notes the similar mode of action of ustekinumab when compared to risankizumab, i.e. inhibition of IL-23 sub-unit p19; as well as the additional non-specific inhibition of sub-unit p40 common to IL-12 and IL-23. However, the EAG would like some justification as to why the proportion of participants with exposure to ustekinumab, including intolerance or inadequate response, was restricted to 20% in the ADVANCE and MOTIVATE trials.

Company response

The trials were designed to reflect the anticipated label, and which was broad and not designed to demonstrate efficacy in IL-12/23-IR patients specifically. The limit on ustekinumab participants was based on previous experience of the adalimumab clinical trial programme (5, 18); subjects that lost response or were intolerant to infliximab subsequently received adalimumab, and the remission rate was lower in this population when compared with a bio-naïve population.

As both risankizumab and ustekinumab inhibit the IL-23 pathway (albeit via binding to different subunits on the IL-23 cytokine, p19 and p40, respectively (25-27)), there was potential for reduced efficacy based on observations from the adalimumab clinical trial programme. Consequently, the proportion of participants with exposure to ustekinumab (including intolerance or inadequate response) in the risankizumab CD studies was restricted to 20% because in the study protocol as this permitted sufficient statistical power and probability of success for the co-primary endpoints.

Moreover, the proportion of patients with prior ustekinumab treatment in the clinical trial is not markedly different from what is expected in a sample representing UK clinical practice[1] (36).

[redacted]

Epidemiology

A21. In Section B1.3.2, the company refers to England throughout the first paragraph, except for two references to the UK. Please confirm that these values are applied to the correct populations (i.e., England and the UK as stated). Also please clarify why the target population has been calculated as England, rather than England and Wales, which is the geographical scope for NICE.

Company response

The company can confirm that the values quoted are correctly applied to the populations as detailed in the CS. The target population for the budget impact analysis has been calculated for England only based on guidance from NICE health technology evaluations: the manual (2022) (37). Section 4.11.2 of this document states “When possible, the information on NHS impact should include details on key epidemiological and clinical assumptions, resource units and costs with reference to a general England population”. As such, target population estimates reported in Document B, Section B1.3.2 of the CS have been reported to align with those presented in the budget impact analysis for consistency.

Safety

A22. The CS states on p.11 that ‘By targeting the p19 subunit of IL-23 with high specificity, risankizumab inhibits IL-23-dependent inflammation, whilst sparing IL-12 derived signals (9-12) and thus preserves TH1 pathway for the protection against infections and tumour immune surveillance’. Please could you comment on the mortality event related to invasive squamous cell carcinoma of the left lung in the risankizumab 1200 mg arm (CS Document B, p.104)? The EAG notes that this was considered unrelated to the study drug, but is there any biological plausibility to risankizumab having some non-specific inhibition of IL-12 via sub-unit p40, given this interleukin’s involvement in cancer surveillance?

Company response

Risankizumab is specific to the p19 subunit of IL-23 (38, 39), and a previous study has reported no binding to the IL-12 cytokine at concentrations up 1.2 µM (40). Consequently, risankizumab is expected to have no impact on the p40 subunit or the Th1 pathway for tumour surveillance.

Section B: Clarification on cost-effectiveness data

Literature searching and use of expert advice

B1. Table 5 The PRISMA diagram does not appear to add up correctly (e.g. records excluded in the first box on the right adds up to 349 not 780 as stated), please supply a correct version.

Company response

In Figure 5: PRISMA flow diagram – economic SLR (CS Appendix G, Section G.1.2), the first PRISMA box for excluded records was compressed during the conversion of PRISMA diagram leading to non-visibility of all exclusion reasons. Similar formatting issue is also observed in the Figure 7: PRISMA flow diagram – cost and healthcare resource use SLR (CS Appendix I, Section I.1), where the box is compressed and all exclusion reasons are not visible. The updated PRISMA for both Figure 5 and Figure 7 of the CS Appendices with the complete details of exclusion reasons have now been appended. As seen in Figure 2 and Figure 3 below, the excluded records do now add up to 780 in both cases.

Figure 2: PRISMA flow diagram – economic SLR (CS Appendix G, Section G.1.2)

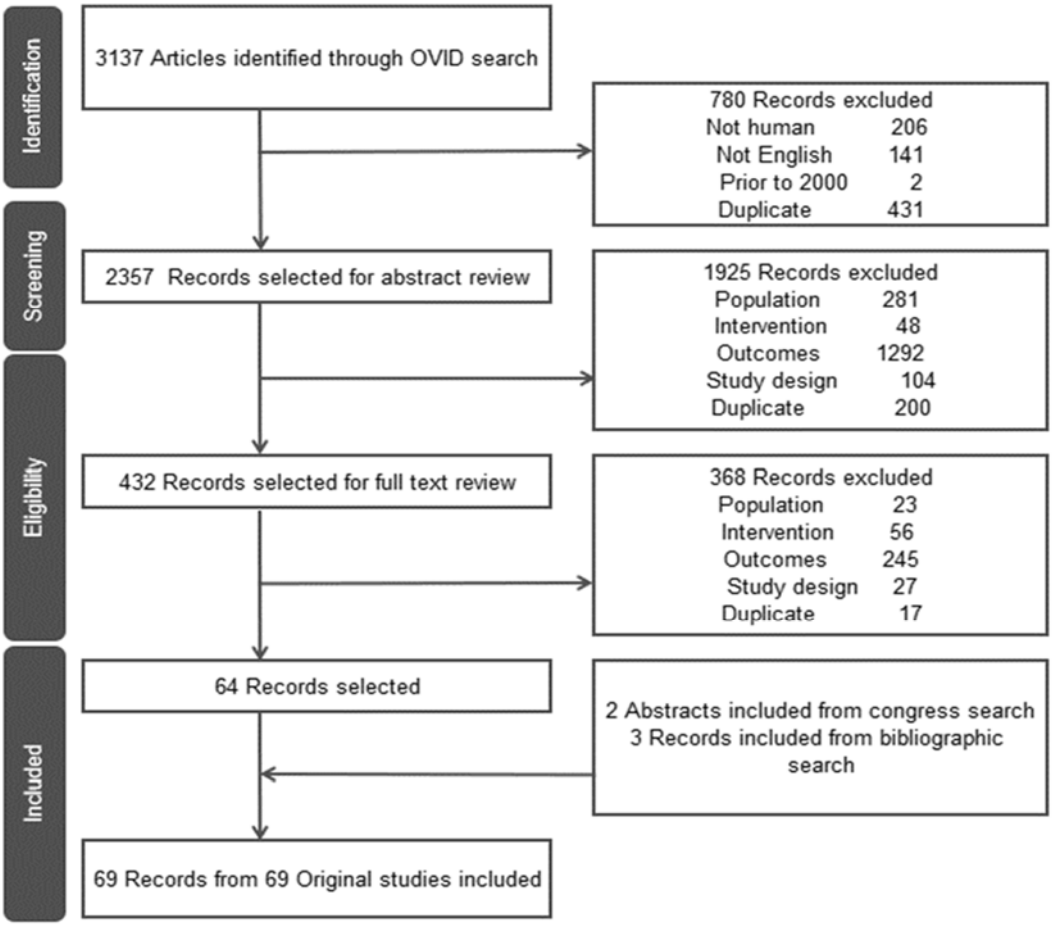
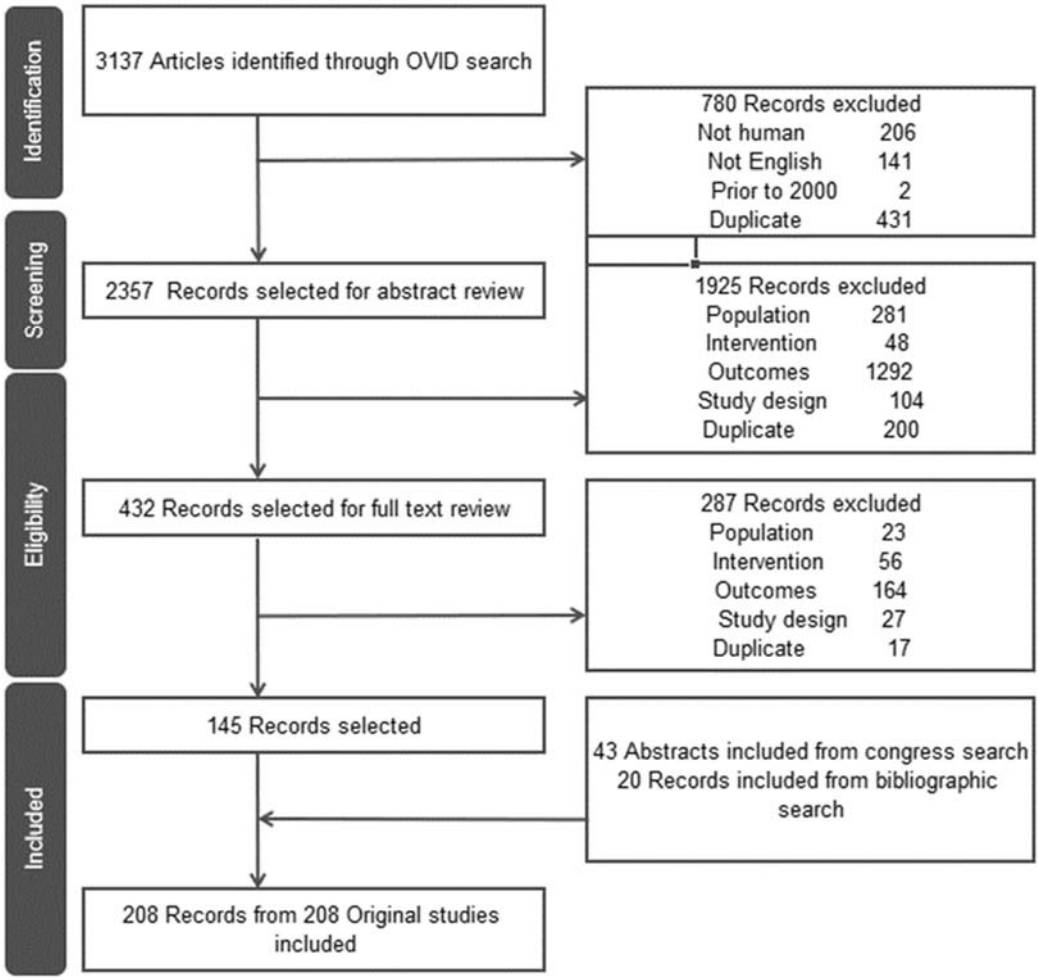


Figure 3: PRISMA flow diagram – cost and healthcare resource use SLR (CS Appendix I, Section I.1)



B2. To justify approaches and assumptions throughout the submission dossier, advice from a clinical expert advisory board meeting is cited. The report for this meeting is citation 80 in Document B, but the report itself is not provided. Please provide this meeting report, as commercial-in-confidence material. As requested in the NICE user guide for the company evidence submission template, please ensure the meeting report includes the following details:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert whose opinion was sought
- the background information provided and its consistency with all the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Company response

The Advisory Board was conducted by AbbVie with external third-party support and brought together expert stakeholders within the limits of a pre-defined scope of work. The key aims of the Advisory Board were to understand the stakeholders' expert views on (i) the generalisability and suitability of the risankizumab CD trial programme to the UK National Health Service; and (ii) the proposed economic model framework, assumptions made and input parameters used. Parts of the discussions conducted in the Advisory Board will have encompassed elements that are not pertinent to the ongoing NICE appraisal. These elements constitute proprietary and confidential AbbVie information that is not relevant for the purposes of the appraisal. Therefore, the Report cannot be disclosed in full. Where information from the Advisory Board has been referenced in our submission, the company have disclosed the relevant excerpts of the Report within the Document B reference pack.

Decision problem and model structure

B3. PRIORITY QUESTION. B.1.2 states Risankizumab SC was delivered using SC injections in the risankizumab CD studies. In clinical practice, risankizumab SC will be delivered using an on-body device (OBD). See Appendix O for further information." Appendix O contains three sentences only, also marked commercial-in-confidence. Please provide details of the OBD; how it will be dispensed and administered, and any evidence available for its use in other indications, in terms of adherence, adverse events and any other factors that may affect cost and health consequences of treatment, relative to health-professional administered subcutaneous injections.

Company response

Risankizumab 600mg intravenous (IV) induction will be administered in a hospital setting whilst risankizumab 360mg subcutaneous (SC) maintenance will be administered through the on-body-device (OBD) either at home or in clinic.

[redacted]

[redacted]

B4. The anticipated license for risankizumab includes “patients who were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable”. In light of this, and the final scope, please provide further rationale for the lack of a comparison to BSC for patients who are intolerant or contraindicated to available therapies, or for whom such therapies are inadvisable.

Company response

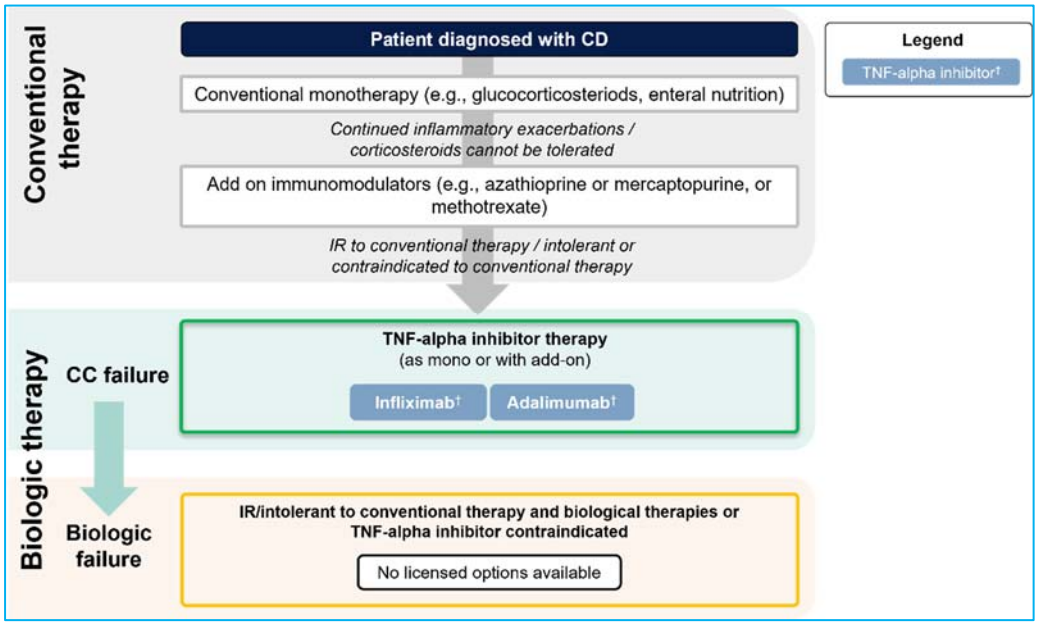
Based on clinician feedback on the CS, best supportive care (BSC) was not deemed an appropriate comparator as biologic therapies are the established standard of therapy for people with moderate-to-severe CD. If a patient was intolerant to or unsuitable for a biologic therapy, they would be considered for a different class of biologic rather than BSC (42).

B5. The anticipated license [redacted]. Please comment on how the treatment pathway is expected to differ for these patients (e.g., with respect to license restrictions to other therapies in the pathway) and provide interpretation for relative clinical and cost-effectiveness estimates for this group implied by any differences.

Company response

The initial treatment for [redacted] with moderate-to-severe CD consists of the same treatment options that are used for adults. Conventional care is usually the first treatment step, enteral nutrition or steroids are generally induction treatments for all disease severity, with subsequent use of stronger immunosuppressive medications, such as azathioprine and methotrexate, to maintain remission (43). Surgery is also a treatment option available for both [redacted]. However, biologic therapy options are limited for [redacted] individuals with moderate-to-severe CD when compared with adults. TNF-alpha inhibitors (infliximab, adalimumab) are the only biologic therapies licensed for those [redacted] (31). For [redacted], there is no alternative licensed biologic therapy to TNF-alpha inhibitors for individuals [redacted], and there is no licensed biologic therapy for those [redacted] (Figure 4).

Figure 4: Treatment pathway based on CD management guidance by NICE for [redacted]



Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor. Figure adapted from NICE guidance. Source: Crohn's disease: management (NG129). 2019. NHS England, Clinical Commissioning Policy. 2020 (10). † Biosimilars are also available.

Risankizumab was granted a Promising Innovative Medicine (PIM) designation by the MHRA in November 2021. Risankizumab subsequently received an Early Access to Medicines Scheme (EAMS) positive final scientific opinion from the Medicines and Healthcare products Regulatory Agency (MHRA) in April 2022 for the treatment of moderately to severely active CD in both adult patients and adolescent patients ([redacted]) who have had an inadequate response, lost response or are not suitable for currently licensed treatments. Consequently, risankizumab may provide an important treatment option for individuals [redacted] with moderate-to-severe CD.

With regard to comparing clinical and cost-effectiveness estimates between the populations, these are difficult to estimate given the small number of individuals [redacted] enrolled in the risankizumab studies (approximately 1% of individuals enrolled across the studies, broadly reflective of the proportion seen in UK clinical practice, according to expert clinical opinion (3)). However, despite not having comparisons of clinical or cost effectiveness estimates between the populations available, the evidence from the risankizumab CD studies has exhibited signs of efficacy and safety in subjects [redacted]. Based on expert clinical opinion (3),

the [redacted] population was expected to have similar treatment response to an adult population if both populations have the same treatment history (i.e., bio-naïve or treatment refractory).

B6. Please provide rationale as to why the 7 studies identified in the Economic SLR (in addition to the prior NICE appraisals) were not used to inform the model structure, functionality, assumptions and data sources.

Company response

The seven studies identified in the economic SLR (CS Appendix G, Section G.1.3) were not deemed appropriate to be used to inform the economic model for the following reasons:

- The Catt et al. (2019) study (44) was reviewed but was not used to inform the model structure; the model structure outlined in this study was a decision tree which relied on several strong assumptions underpinning it. For example, patients were assigned to health states which they remained in for 12 months with no possibility of improvement or deterioration (due to the linear nature of decision trees). Furthermore, the decision tree structure limited its validity in modelling long-term outcomes. No treatment discontinuation was assumed. Considering these factors, the company concluded that this study would have limited usefulness in informing the model.

- The Robson et al. (2018) study (45) was an abstract and contained limited information on the model structure, data used and assumptions underpinning the model. This was also the case for the Wilson et al. (2018) study (46).

- The Saito et al. (2013) study (47) incorporated outcomes and health states beyond the scope of this economic evaluation and utilised a decision tree structure. The time horizon of the analysis was 1 year, which did not meet the requirements of the NICE reference case (37) (which requires the time horizon to be long enough to reflect all important differences in costs or outcomes between the technologies that are compared) or the final scope. Furthermore, it would have been challenging to populate this model with the data available for the different comparators given the complexity of its structure, while the model was not considered to accurately represent how risankizumab CD is expected to be used in future clinical practice.

- The Bodger et al. (2009) study (48) was indirectly used to inform the model, as this was used to inform the model structures in both TA352 (2) and TA456 (1).

- The Loftus et al. (2009) study (49) utilised a regression approach to estimate CDAI outcomes and to calculate model outcomes based on these scores. The authors acknowledged difficulty in estimating long-term outcomes with this approach. As the NICE reference case (37) emphasises a time horizon long enough to capture all costs and benefits (lifetime, in the case of CD), the use of a regression approach, as per this study, was deemed inappropriate.

- The Lindsay et al. (2008) study (50) focused specifically on luminal CD and used health states which were not aligned to the licence for risankizumab CD; specifically, “active CD” and health states relating to fistulising CD (i.e., specific health states such as active CD and fistula), which would be difficult to populate using CDAI-based outcomes from the trials of the different biologics.

B7. The model includes a “Free state” health state that does not appear to be used. If this understanding is incorrect, please explain the purpose of the “Free state” health state.

Company response

In the model, the “free state” health state is provided as a placeholder to allow for the addition of another health state if this was required by the user.

B8. PRIORITY QUESTION. A maximum maintenance treatment duration of 12 months is assumed in the company base case. This is explained in B.3.2.2.2 as reflecting "clinical practice and NICE guidance, which states that patients should be re-assessed at 12 months to determine whether continuing with biologic treatment is appropriate".

a) **Please justify the use of an exponential distribution for time to treatment discontinuation, in the context of the available trial data**

Company response

To fit alternative distributions to time to treatment discontinuation (TTD), Kaplan–Meier (KM) plots of TTD would be required so that parametric models could be fitted to the curves, either using patient-level data, or using the KM plots and the number of patients at risk, as per the methods described by Guyot et al. (2012) (51). In the biologic comparator trials, patient-level data were not available and no KM data were identified for TTD for inclusion in the economic model.

The exponential distribution only requires the calculation of a rate, which was obtained from the pivotal trial data for each comparator. Whilst it was possible to calculate the TTD for risankizumab from the FORTIFY TTD KM data, this was not done as NICE DSU TSD 14 advises that using different types of parametric models for different treatment arms requires substantial justification as the distribution shapes could differ greatly (52). As only exponential distributions could be fitted to the comparators, the company deemed it appropriate to fit an exponential distribution to the risankizumab TTD data as well.

b) **Please describe how patients are re-assessed after 12 months' maintenance treatment to determine whether continuing with biologic treatment is appropriate (e.g., through laboratory testing, scans etc.), and provide appropriate cost estimates for such assessment**

Company response

Methods of patient assessment after 12 months of maintenance treatment can vary considerably across hospital trusts based on cost, capacity and available

resources. Tests to determine whether continuation of biologic therapy is appropriate may comprise any of the following: colonoscopy, C-reactive protein levels in blood, measurement of faecal calprotectin, HBI, and potentially even magnetic resonance imaging. However, within a centre, testing would be expected to be the same regardless of biologic treatment. Due to the high variability in methods across different centres, it is challenging to estimate an approximate cost for an assessment. In addition, as the method of assessment is not expected to differ between different biologics, inclusion of assessment costs would not be expected to impact on the cost-effectiveness results.

c) Please explain and attempt to justify the assumption that all patients discontinue at assessment for continuation, when a treatment continuation assessment suggests at least some patients will be deemed appropriate for ongoing treatment

Company response

The approach adopted in the CS was chosen for two main reasons. Firstly, discontinuing at 1 year (i.e., the timepoint of assessment) reflects the trial data available for risankizumab and the other comparator biologic therapies in CD (i.e., all maintenance trials assessed clinical outcomes for up to 52 weeks). Modelling outcomes for risankizumab beyond 1 year would require assumptions regarding clinical effectiveness as there are no trial data or real-world evidence available beyond this timepoint. Similarly, there are no trial data available for the biologic comparators. Although there may be real-world clinical data available for the biologic comparators, these evidence sources are of lower quality when compared with RCTs. Secondly, the same approach was also used in the recent NICE CD submissions for ustekinumab (TA456) (1) and vedolizumab (TA352) (2) for their preferred base case.

d) Please provide the latest available treatment discontinuation / duration data from the FORTIFY study, as Kaplan-Meier data.

Company response

The CS presents the latest available treatment discontinuation / duration data from the FORTIFY maintenance study. Figure 5 demonstrates the KM curve produced from these data.

Figure 5: Kaplan–Meier curve for time to discontinuation due to lack of efficacy (FORTIFY ITT1A population)

Abbreviations: ITT, intent-to-treat; IV, intravenous; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's disease.+ censored observations.
ITT1A population includes randomised subjects in the ITT population who received risankizumab IV for only one period of 12 weeks in ADVANCE or MOTIVATE, and ≥1 dose of the study drug in FORTIFY substudy 1 and had eligible SES-CD of ≥6 (≥4 for isolated ileal disease) at baseline of the induction study.
Note: Subjects who discontinued the study due to lack of efficacy are considered as events.

B9. On page 129 of Document B (B.3.2.2.2.1), the definition for the high-dose biologic after response matrix is “Patients entered this matrix if they had a CR-100 response at the end of induction and started high-dose biologic therapy at the beginning of the maintenance phase”. The text later states “The base case assumed that patients who have their dose escalated have lost response to standard-dose biologic treatment”. Please explain how patients can be in an “after response” matrix while also needing to start high-dose therapy at the beginning of the maintenance phase due to having lost response?

Company response

Patients who dose escalated were assumed to have been assessed to be at risk of inadequate response by a clinician and therefore were dose-escalated to maintain the same level of response they had previously. The term “loss of response” here is slightly unclear; a more accurate term would be “at risk of loss of response”. Please see further details on this topic in Section B.3.3.4.1 of the CS.

B10. Conventional care usage is taken from TA456 (guidance published 2017) based on estimates from TA352 (guidance published 2015). Please confirm if and how the conventional care therapies and proportions listed in Table 57 of the CS have been validated as reflective of current NHS practice.

Company response

Seeking clinician input on conventional care therapy would likely have given many different options and it would have been difficult to accurately estimate the split of these treatments. Conventional care is applied in the same way across all treatment arms, so the overall cost of conventional care does not have a large impact on the incremental cost-effectiveness ratios (ICERs) (see CS Section B.3.2.2.1).

Patient characteristics

B11. Please present the baseline disease severity distribution across mild, moderate and severe disease of the ADVANCE and MOTIVATE ITT1A sample.

Company response

Table 26 presents the baseline disease severity distribution based on CDAI score for the combined ADVANCE and MOTIVATE ITT1A populations for the biologic inadequate response (Bio-IR) and non-Bio-IR (inadequate response/intolerance to conventional care) populations. Please note that as well as including patients who were randomised to receive risankizumab 600 mg IV and placebo IV, this pooled summary also includes patients who were randomised to receive risankizumab 1,200 mg IV (a non-licensed dose; not reported in the CS).

Table 26: Baseline disease severity distribution – ADVANCE and MOTIVATE (ITT1A population)

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval, ITT, intent-to-treat; Non-Bio-IR, inadequate response/intolerance to conventional care.

Efficacy inputs

B12. PRIORITY QUESTION Using the results provided in response to priority question A15, please provide cost-effectiveness scenarios using revised maintenance NMAs for the CCF and BF subgroups: (1) grouping vedolizumab in the network with risankizumab and ustekinumab instead of the TNFis, and (2) grouping all treatments (TNFis, vedolizumab, ustekinumab and risankizumab) together in a single network.

Company response

The company considers the NMA submitted in the CS to be the most appropriate method to present the relative efficacy of each biologic treatment for the reasons outlined in CS Section B.2.9.3.2 and the response to question A15 in this document.

However, to fulfil the request, the company provides the ICERs that have been estimated using both (1) the split maintenance NMA network that groups vedolizumab with ustekinumab and risankizumab, and (2) the single maintenance NMA network that groups all biologics. Please note that for the split maintenance NMA network that groups vedolizumab with ustekinumab and risankizumab, results are presented for the BF population only since vedolizumab is only used in BF patients in UK clinical practice.

Please see Table 27 for the cost-effectiveness results produced when the outcomes of the split maintenance NMA network that groups vedolizumab with ustekinumab and risankizumab are used as efficacy inputs in the economic model. The cost-effectiveness results for the single maintenance NMA network (all biologics) are shown in Table 28 and Table 28 for the CCF and BF population, respectively.

These two scenario analyses show that the ICERs remain relatively stable despite being produced from the outcomes of (1) a split maintenance NMA that favours vedolizumab, but not ustekinumab and risankizumab; and (2) a single maintenance NMA that lacks face validity (please see the company's response in question A15). The company interprets these results as demonstrative that the results presented in base case (CS Section B.3.10) are robust even when tested in extreme conditions.

Table 27: Split maintenance NMA network (with vedolizumab) CE results: BF population

Regimen	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER vs Baseline	ICER Incremental
RZB	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; SE, standard error; UST, ustekinumab; VDZ, vedolizumab.

Table 28: Single maintenance NMA network (all biologics) CE results: CCF population

Regimen	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER vs Baseline	ICER Incremental
ADA 160/80 Bio	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£9,918	£9,918
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	Not calculable	Not calculable
IFX IV Bio	[redacted]	[redacted]	[redacted]	[redacted]	£28,453	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	£45,606	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£1,224,627	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; SE, standard error; UST, ustekinumab.

Table 29: Single maintenance NMA network (all biologics) CE results: BF population

Regimen	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER vs Baseline	ICER Incremental
RZB	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

B13. Model NMA inputs sheet, cell F66 shows 42.3% of adalimumab (80/40mg + 40mg EOW) patients with a biologic failure CDAI-70 response, with cell F33 showing 47.0% of adalimumab (80/40mg + 40mg EOW) patients had a biologic failure CDAI-100 response. Please check all NMA outputs and provide corrected versions if applicable.

Company response

The outputs noted by the EAG in the F66 and F33 cells of the model NMA inputs sheet are correct. These initially unintuitive outputs are driven by data reported in the Watanabe et al. (2012) study (23) and NMA modelling assumptions.

The CS follows the same approach as that taken in TA456 (1) regarding the inclusion of Watanabe et al. (2012) (23) in the induction NMAs for the BF population. Therefore, the induction efficacy of adalimumab 80/40 in the BF population is informed only by the Watanabe et al. (2012) study (23).

NMA results are ultimately driven by the relative efficacy of a treatment versus a common comparator (e.g., placebo) (14, 53). Thus, induction NMA estimates of adalimumab 80/40 in the BF population are driven by the relative efficacy of adalimumab 80/40 versus placebo as reported by Watanabe et al. (2012) (23). The study reported that the relative efficacy (both on the RD and OR scales) of adalimumab 80/40 in the BF population is greater for CDAI-100 clinical response (CR-100) than CDAI-70 clinical response (CR-70). This is illustrated below in Table 30. Although the absolute rate of adalimumab 80/40 is higher for CR-70 than CR-100 (see column “n/N” in Table 30), it is the efficacy relative to placebo which drives the CS NMA results. The greater relative efficacy in CR-100 than CR-70 as reported in the study results is thus mirrored in the CS NMA results. The NMA produced RD point estimate of adalimumab 80/40 for BF induction CR-100 is [redacted]; the NMA produced RD point estimate of adalimumab 80/40 for BF induction CR-70 is [redacted]. As NMA produced relative effects are the ultimate basis for the NMA estimated absolute rates (see CS Appendix D, Section D.1.3.3.10), the greater relative efficacy of adalimumab 80/40 in BF induction CR-100 than induction CR-70 is a key driver of the outputs noted by the EAG.

Table 30: Data reported in the Watanabe et al. (2012) (23) study (BF population) for induction CR-70 and CR-100 with associated relative effect values

Study	Outcome	Treatment	n	N	n/N	RD	OR
Watanabe et al. (2012) (23) (BF population)	CR-70	PBO	5	13	38.46%	N/A	N/A
		ADA 80/40	10	20	50.00%	0.12	1.6
	CR-100	PBO	2	13	15.38%	N/A	N/A
		ADA 80/40	9	20	45.00%	0.30	4.5

Abbreviations: ADA, adalimumab; BF, biologic failure; CR, clinical response; PBO, placebo; n, responders; N, patients eligible; N/A, not applicable; OR, odds ratio; PBO, placebo; RD, risk difference.

It is also noted that the sample sizes associated with Watanabe et al. (2012) (23) in the BF population are relatively small (see column “N” in Table 30). Small sample sizes will naturally lead to uncertainty in NMA estimates. Indeed, the NMA produced estimates of BF induction adalimumab 80/40 (as noted above, informed only by Watanabe et al. (2012) (23) in the BF population) are subject to high uncertainty with wide 95% CrI resulting in non-significant RDs between adalimumab 80/40 and placebo. The NMA produced RD of adalimumab 80/40 for BF induction CR-100 is [redacted]) with an associated absolute rate estimate of [redacted]); the NMA produced RD of adalimumab 80/40 for BF induction CR-70 is [redacted] with an associated absolute rate estimate of [redacted]. This relatively high level of uncertainty in estimates is also a driver of the outputs noted by the EAG.

For completeness, please see Table 31.

Table 31: Results for CDAI-70 in BF induction NMA (FE model)

Treatment	RD (vs PBO) Median (95% CrI)	SUCRA score	NMA est. absolute outcome rate Median (95% CrI)
RZB	[redacted]	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CDAI, Crohn’s Disease Activity Index; CrI, credible interval; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RD, risk difference; RZB, risankizumab; SUCRA, Surface Under the Cumulative Ranking; UST, ustekinumab; VDZ, vedolizumab. Treatments listed in descending RD order.
**Indicates a statistically significant result.

B14. PRIORITY QUESTION Are patients who underwent a second induction phase included in the efficacy analyses?

Company response

No second induction data are included in the CS.

B15. Ordered probit models rely on a number of strong assumptions. Please expand on the justification for choosing this approach over alternatives (e.g. model CDAI directly and then infer severity) and provide evidence that assumptions are not infringed. It is also not clear that the repeated-measures nature of the data is adequately reflected, nor how the explanatory variables were selected. Lagged dependent variable is reported as an explanatory variable; has any consideration been given to the dynamic implications of this - in particular, the implications for bias in the error term?

Company response

The ordered probit model is an appropriate framework for statistical analysis when the dependent variable is categorical and ordinal (i.e., ordered). CDAI-based remission, mild and moderate-to-severe CD health states are mutually exclusive, ordered outcomes that have been used in prior publications and NICE submissions in CD (TA352 (2) and TA456 (1)) as health states. A categorical, or multinomial, ordered model should be used given that there are three ordered outcomes (based on disease severity). The probit distribution was chosen given that it is one of the most commonly used distributions in multinomial, ordered models – the logit and probit form the majority of these models. The company chose the ordered probit model as it is based on the (cumulative) normal or Gaussian distribution.

Using an ordered probit is an approach mentioned as a valid method when simultaneously estimating transitions to multiple outcomes in NICE TSD 5, Section 3.2, page 18 (53):

> "3.2. Joint Synthesis Of Multiple Outcomes To Inform Natural History: The natural history model usually consists of a succession of "states" or sub-processes and involves a series of parameters which may impact on life-times costs, quality and length of life. It is preferable for these parameters to be estimated simultaneously from all the available data, as this is likely to allow more information to be incorporated and more validation to be carried out on the agreement between the model predictions and the evidence. The simplest examples of a coherent modelling of multiple outcomes are provided by the

competing risk and the ordered probit analyses described in TSD 2 (Sections 3.3 and 3.6, respectively). For example, use of the ordered probit model for the baseline and treatment effects guarantees coherent prediction of the probability that patients will achieve the different levels of response on categorical scales such as the Psoriasis Area Severity Index or the American College of Rheumatology (ACR) score. By contrast, if ACR 20, ACR 50, and ACR 70 response are analysed separately, it is possible to end up with a model that makes impossible predictions, for example that more patients experience a 50% improvement on ACR than experience a 20% improvement."

Of note, the company did consider other approaches. The company required a model that could handle competing risks – which would be the ordered categorical model (which was used) or a multistate survival model. The company ruled out the multistate survival method since it would have made the model overly complex and computationally intensive.

Multiple NICE submission models, including in autoimmune conditions, have used the ordered probit regression. For example, an ordered probit was used in TA547 (tofacitinib for ulcerative colitis) (54), TA350 (secukinumab for treating moderate to severe plaque psoriasis) (55), HST6 (asfotase alfa for paediatric-onset hypophosphatasia) (56), among others. Published models of CD have also used the ordered probit, e.g., Panaccione et al. (2020) (57). Importantly, given that the logit and probit functions are nearly identical, the company is confident that an ordered logit would not produce different model results.

Modelling CDAI as a continuous, bounded variable and then mapping to ordered health states may be possible but would introduce unneeded complexity. The company believes that it is more awkward to estimate an econometric model and then transform the scale of the output rather than transform the scale of the data – to what is required to answer the research questions – and then estimate a model. Note that the primary clinical outcome is the percent of patients in remission (CDAI <150); it is not raw CDAI score. There are many econometric models that are tailor-

made for dependent variables with different distributions but less econometric direction on post-estimation modifications of model output to a new scale.

Explanatory variables were selected to make the most parsimonious model; the research question involves estimating a static Markov matrix. If additional variables were selected (such as individual patient characteristics), model fit may have been improved, but the CE model itself would have become more complex (e.g., a hypothetical machine learning specification might have identified smoking status as a predictor, but then such a covariate would need to be tracked, despite lack of data and endogeneity with health status). An already complex model would have been made even more complex, with no or low improvement in accuracy.

The company estimated regressions without accommodating for repeated measures within patients. While this specification may affect standard errors, the company is less interested in statistical inference and more interested in fitting a simple model that provides reasonable baseline estimates for patient trajectories. Given that subsequent calibration steps in the CE model tailor maintenance-phase Markov matrices using comparator-specific NMA results (potentially significantly altering the baseline matrix estimate), it was deemed preferable to employ a relatively simple regression framework.

The coefficients of the base model are not estimated in a biased way, so existing deterministic results are not affected. Fixes for accommodating for repeated measures within patients include using a patient-level random effects model – this was impractical to include in the company's existing Microsoft® Excel submission. Clustered standard errors may have improved the standard error estimates but can introduce other problems.

Regarding the inclusion of the lagged dependent variable in regression model specification, the company suspect there may be some confusion. It is well known that a panel data model specification with both individual fixed effects and lagged dependent variables is inconsistent because of induced correlation between the residual error term and the lagged dependent variable (e.g., Angrist and Pischke, Mostly Harmless Econometrics, 2009, pp. 244-245 (58)), which in turn would lead to biased coefficient estimates. However, the company's model specification does not

include person fixed effects. Absent those fixed effects, there is no implication of bias from including lagged dependent variables. For example, data from clinical trials are often estimated with an ANCOVA specification that models outcomes in the follow-up period as a function of exposure status and outcome values measured in the baseline period (i.e., lagged dependent variables).

In conclusion, the company believes that the approach for estimating maintenance phase transitions in the CS is superior to the approach presented in TA456 (1), where ad-hoc imputation was used to estimate long-term patient outcomes. Specifically, the company followed the advice of the EAG to incorporate trial data in estimation of maintenance phase outcomes. As described in more detail below, the company believes that the approach used provides reasonable a-priori estimates for post-induction phase transition probabilities. The company also notes that all comparators are evaluated using the same estimated matrices (prior to the calibration process) and that calibration to maintenance-phase NMA estimates drives comparative results.

B16. PRIORITY QUESTION. Please provide the equations and all regression output for the ordered probit model. Please also specify the statistical software used to fit the ordered probit model and provide the code used.

Company response

Data management and ordered probit analyses were conducted with R version 4.1.0 (R Foundation for Statistical Computing; Vienna, Austria).

The ordered probit model is estimated using the R code shown in Figure 6 below, where the dependent variable "state" is a categorical variable representing the CDAI-based health state, "mild_lag" is a binary variable indicating whether a patient's most recent CDAI-based health state was mild, "moderate_severe_lag" is a binary variable indicating whether a patient's most recent CDAI-based health state was moderate-severe, and "days" which is a continuous variable indicating the number of days since a patient's last observation.

Figure 6: R code used for the ordered probit model

```
risa360_probit <- polr(state ~ mild_lag + moderate_severe_lag + days,
method="probit", data=risa360_trans, Hess=TRUE )
```

Regression outputs for the ordered probit model are shown in

Figure 7 below. Outputs include beta coefficients, cutpoints, residual deviance and the Akaike information criterion (AIC).

Figure 7: Ordered probit regression outputs

B17. There appears to be no model selection for the ordered probit models, although a goodness-of-fit statistic (AIC) is provided. Were alternative models assessed? Was AIC used to assess the choice of link function (logit vs probit)?

Company response

As indicated in the response to B15, given that the logit and probit functions are nearly identical, an ordered logit would not produce different model results. The company is aware of NICE DSU guidelines on survival model fit (i.e., NICE DSU TSD 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data (52)), which focus on AIC but not on ordered categorical dependent variable models. The company considered multistate survival models, but the data were not in a survival format and such an approach would have made the model overly complex.

B18. Please present the estimated 52-week results from the ordered probit model alongside a comparison to the 52-week results observed in FORTIFY.

Company response

The company compares observed vs predicted patient trajectories in the risankizumab CD maintenance arm of the FORTIFY trial. Predicted patient trajectories are derived by:

1. Estimating a 182-week transition matrix from the ordered probit model fit using all observed CDAI observation pairs in the FORTIFY trial (for patients on risankizumab)
2. Converting the 182-week matrix to a 2-week matrix using the exponential approximation (see response to question B19 below for further details)
3. Predicting maintenance-phase trajectories using the empirical baseline distribution at the beginning of the FORTIFY trial.

In Figure 8 below, the predicted trajectories (*blue*) are for all ITT1A patients with an available CDAI measurement at trial baseline (n=138), whereas the observed trajectory (*red*) plots the observed CDAI distribution for patients with an available CDAI measurement at the applicable measurement point. That is, each point on the observed trajectory represents a different subset of patients. Hence, the model predictions and observed distributions are not perfectly comparable. Considering this limitation, it is unsurprising that the subset of patients with an observed CDAI measurement at Week 52 (n=96, patients who neither discontinued nor required rescue therapy) have better health outcomes compared to the predictions made for the full patient cohort. Conversely, the model's predictions for the fraction of patients in remission at Week 52 is more optimistic relative to the top line trial proportion (52.2%, see Table 27 in CS Section B.2.6.3.1). This discrepancy might be explained by the fact that the model predicts that some patients without Week 52 CDAI measurements will be in remission.

Figure 8: Predicted trajectories (blue) for all ITT1A patients with an available CDAI measurement at trial baseline (n=138) and observed trajectory (red) for patients with a CDAI measurement at the applicable measurement point (as observed population)

To further validate the ordered probit approach, the company fit the model within a subsample of patients (on risankizumab) with available Week 52 predictions. In this way, one can compare Week 52 model projections to the week 52 empirical health state distribution for the same patient population (in contrast to the comparisons in Figure 8. Predicted versus actual Week 52 CDAI distributions for this subset of patients are presented in Table 32.

Table 32: Predicted vs actual Week 52 health state distribution (model fit and projections using a risankizumab patient subset with Week 52 CDAI observations available)

	Remission	Mild CD	Moderate-to-Severe CD
Prediction	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]

Abbreviations: CD, Crohn's disease; CDAI, Crohn's disease activity index.

The company notes that the dynamic analysis of FORTIFY trial data is complicated by patient discontinuation (particularly between Week 24 and 52) and the possibility of time-varying transitions. Ordered probit models estimated using simple imputation methods (last observation carried forward, return to baseline CDAI) were also considered, but to avoid undue complexity, the ordered probit model including only observed CDAI measurement pairs was selected for use in the CE model. In addition, time-varying dynamics are not considered as the goal was to estimate a static Markov matrix.

The company believes that the ordered probit approach for maintenance-phase Markov matrix estimation provides reasonable baseline predictions. The company notes that within the CE model itself, both the beginning-of-maintenance patient distribution and the 52-week remission target are provided by NMA results for each comparator. Furthermore, the initial matrix estimate (derived from risankizumab CD data but used for every comparator) is subsequently calibrated using comparator specific NMA induction and maintenance estimates. In particular, the calibration process ensures that the Markov matrix for each comparator yields a prediction for Week 52 remission that exactly matches the corresponding NMA estimate. Hence, considering the subsequent transformation of matrices during the calibration process, a simple data model that produces reasonable baseline matrix estimates is sufficient.

B19. PRIORITY QUESTION Please provide a worked example of the calibration process for a comparator.

Company response

The company describes the calibration for maintenance ustekinumab in the BF population. A first step is to determine the end-of-induction/start of maintenance health state distribution for responding patients (i.e., those who continue therapy post-induction). The percentage of responding patients in remission is computed using the NMA estimates for induction response and remission (for ustekinumab in BF, 0.2198/0.367 = 0.599 enter maintenance in remission). It is assumed that the proportion of patients in moderate/severe matches that for responders in the risankizumab CD trials: 0.078. Remaining patients are assigned to the mild state.

Afterwards, a 26-week uncalibrated transition matrix is estimated from the ordered probit model fit using data from patients treated with risankizumab CD (Prior to calibration, all treated patients across comparators have identical disease progression dynamics). The uncalibrated 26-week matrix using the model-estimated remission|mild cutpoint is presented in Table 33.

Table 33: Uncalibrated 26-week Markov matrix for patients on treatment

	Remission	Mild CD	Moderate-to-Severe CD
Remission	0.81162	0.14343	0.04495
Mild CD	0.42580	0.30820	0.26601
Moderate-to-Severe CD	0.21082	0.29255	0.49663

An uncalibrated 2-week Markov matrix is subsequently approximated by conversion of 26-week exit probabilities (from each health state) to 2-week probabilities using an exponential assumption. Alternative methods for identifying a 2-week matrix, including eigen-value decomposition, were considered. However, to keep the model self-contained in Microsoft® Excel (and to minimise computational burden), the simpler approximation method was chosen.

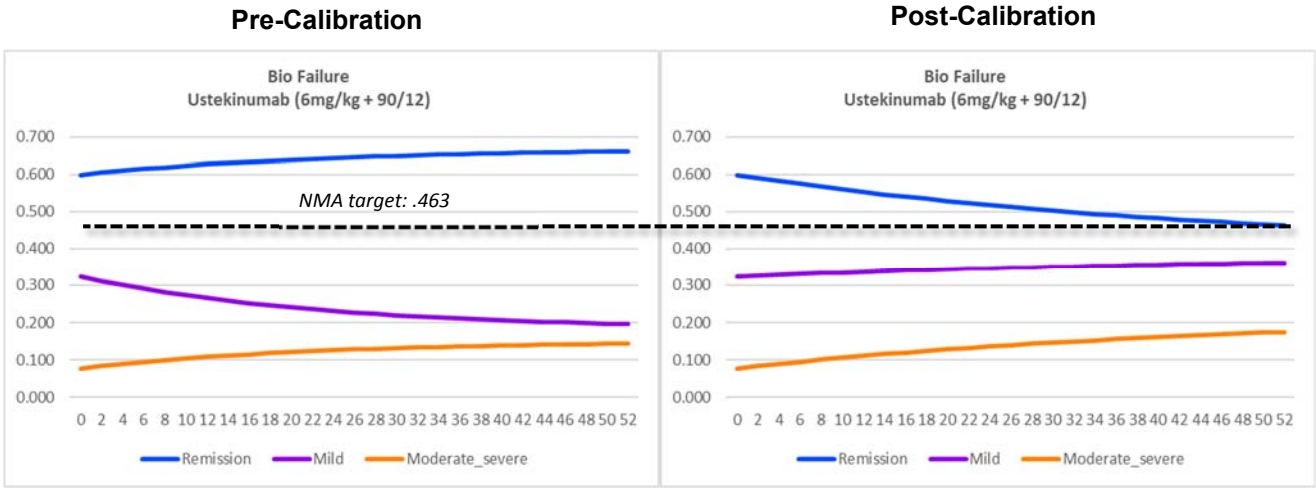
Using the uncalibrated 2-week matrix, the probability of 52-week remission is calculated with respect to the initial distribution described above. This probability is then compared to the target remission proportion for ustekinumab produced by the

NMA – in the BF setting, the weighted average of low dose and high dose remission (0.44 and 0.465, respectively), where weights depend on the fraction of patients assigned to low dose (0.075 for ustekinumab). Hence, the final maintenance remission target is 0.463.

The uncalibrated estimate for 52-week remission is a function of the remission|mild cutpoint in the ordered probit model. Shifting the cutpoint to the right decreases the probability of moving to the "mild" health state, relative to moving to or remaining in remission, in each row of the estimated Markov matrix. Shifting the cutpoint to the left has the opposite effect. To calibrate, the cutpoint is varied until the estimated 52-week remission matches the remission target (0.463). After solving this calibration problem, the resulting 2-week matrix (that, when applied to the baseline distribution computed above, results in a Week 52 remission probability equal to the target value) is used as the comparator-specific Markov-matrix on the model engine sheet.

Markov traces before and after calibration are presented in Figure 9 below.

Figure 9: Markov traces before and after calibration for maintenance ustekinumab in the BF patient population



B20. Please justify the adjustment of the remission|mild cutpoint only in the calibration, and not the mild|moderate-to-severe cutpoint, or other parameters, which could have achieved a similar calibration. This adjustment would appear to rebalance the remission/mild transitions, but not directly the transitions to moderate-to-severe. (Although the latter is impacted directly in later cycles.) Please provide cost-effectiveness scenarios using other calibrations.

Company response

As noted above, multiple calibration methods could be used to alter transition probabilities such that the estimated proportion of patients in remission at the end of maintenance matches the NMA outcomes target. Adjusting the mild|moderate cutpoint to achieve the desired calibration constrains the problem to the adjustment of a single parameter, adding clarity and reducing computational overhead in the fitting procedure.

Testing alternative scenarios

As requested, net monetary benefit (NMB) results for alternative calibration scenarios are presented below (compare to the base case results presented in Tables 102 [CCF] and 104 [BF] of the CS; Section B.3.10.1.1 and Section B.3.10.1.2, respectively). Specifically, the company tests the following methods:

1. Calibration by shifting both the remission|mild and mild|moderate cutpoint in the estimated ordered probit by a fixed value.
2. Calibration by changing the relative probabilities of remaining in remission vs entering mild leaving the moderate/severe transition probability fixed (the pure conventional care arm is calibrated as in the base case, as changing only probabilities from remission does not have a feasible solution).
3. Calibration by adjusting remission probabilities in each row after estimation of the 182-day matrix. Remission probabilities are converted to rates, scaled by a positive factor (tailored in the calibration process) and re-converted to probabilities. Transition probabilities to the “mild” and “moderate-to-severe” CD health states are then assigned to be proportional to the ordered probit estimates.

The scenarios above have been selected to represent a variety of possible calibration options. Methods 1 and 3 involve changing moderate-to-severe transition probabilities (not the case in the base-case calibration method). Method 2 involves only changing probabilities for patients starting the cycle in remission. Whereas the base-case calibration option and Method 1 change cutpoints in the ordered probit and subsequently re-estimate a transition matrix, Methods 2 and 3 calibrate the maintenance-phase Markov matrix after estimation.

While the choice of calibration method can impact cost and quality-adjusted life year (QALY) estimates, treatment rankings are (in general) preserved, as illustrated in Table 34 and Table 35Table 34.

CCF results

Risankizumab is dominated by other therapies aside from ustekinumab in the CCF population. Below, the company presents the NMB of risankizumab vs ustekinumab in the CCF population under the calibration scenarios described above.

Table 34: CCF results (NMB values for risankizumab vs ustekinumab calculated at £30,000/QALY)

Regimen	Base case	Calibration Method 1	Calibration Method 2	Calibration Method 3
RZB	See CS Section B.3.10	[redacted]	[redacted]	[redacted]
UST		[redacted]	[redacted]	[redacted]

Abbreviations: CCF, conventional care failure; NMB, net monetary benefit; QALY, quality-adjusted life year; RZB, risankizumab; UST, ustekinumab.

BF results

Below, the company presents the NMB of risankizumab vs ustekinumab and vedolizumab in the BF population (risankizumab dominates both).

Table 35: BF results (NMB values for risankizumab vs ustekinumab and vedolizumab calculated at £30,000/QALY)

Regimen	Base case	Calibration Method 1	Calibration Method 2	Calibration Method 3
RZB	See CS Section B.3.10	[redacted]	[redacted]	[redacted]
UST		[redacted]	[redacted]	[redacted]
VDZ IV		[redacted]	[redacted]	[redacted]
VDZ SC		[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; IV, intravenous; NMB, net monetary benefit; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

B21. Figure 15 presents an example of the calibration process. The values in Step 1 of Figure 15 differ to those presented in Table 65. Please confirm which values are correct.

Company response

The calibration diagram contains example values and is intended to be illustrative. The correct values used in the ordered probit model are presented in Section B.3.3.3.3.2 (Table 65) of the CS.

B22. Please provide further justification for the assumption of no excess mortality consequences for Crohn's disease. Provide evidence of a literature search for elevated mortality risk attributed to Crohn's disease, including a summary of assumptions and data used in previous NICE appraisals in Crohn's disease. Justifying your choice of estimates, provide cost-effectiveness scenarios using plausible elevated mortality assumptions.

Company response

Desk-based research was conducted to determine the mortality risk associated with CD. Whilst some studies were identified which reported a slightly reduced life expectancy among people with CD compared with unaffected individuals (59-62), UK clinical experts consulted during the preparation of the submission have stated that there is a lack of consistent data on the impact of CD on mortality, with slight to no impact expected in most cases.

Previous submissions have varied on the incorporation of an elevated mortality risk due to CD. The vedolizumab CD submission (TA352) reported that the mortality rate for CD patients is slightly increased compared with the general population; however the company acknowledged that the mortality risk estimates quoted were conducted prior to the availability of immunomodulatory agents (2). The vedolizumab submission included an increased mortality risk for patients with moderate to severe CD (relative risk [RR] 1.9), surgery, post-surgery remission and post-surgery complications (all RR 1.3), in their economic model.

In contrast, the ustekinumab CD submission (TA456) reported that a leading clinician in CD confirmed that patients with CD should not expect any differential mortality compared to the general population, and as such the submitting company only considered all-cause mortality in their economic model (1).

Clinical experts consulted during the preparation of the CS concluded that it was not necessary to include excess mortality in the economic model (63). This was for the reason that any implementation of long-term excess mortality due to CD would apply equally to all comparators (the model does not consider overall survival to vary based on treatment), and thus the impact of applying a standardised mortality ratio on the incremental results would be minimal.

B23. Please provide further justification for the one-year duration of post-discontinuation residual treatment effect used in the base case analysis. Please present and interpret results from a scenario assuming there is no residual treatment effect post-discontinuation of biologics.

Company response

Interviews with clinicians indicated that there is evidence of a residual treatment effect following cessation of biologic treatment, but there is considerable uncertainty around the duration of these effects. Due to a lack of data, the company assumed that all biologics would have a 1-year duration of residual treatment effect, although in practice, risankizumab and ustekinumab are expected to have a longer duration of residual treatment effect due to their mechanism of action. Accordingly, a residual treatment effect duration of zero is considered to not be reflective of what would happen in clinical practice. The company provided a scenario analysis with a different duration of residual treatment effect (6 months) due to the uncertainty around this parameter in the original submission. Deterministic results for the zero duration of residual treatment effect scenario are presented in Table 36 and Table 37 for the CCF and BF population, respectively.

Table 36: Cost-effectiveness results for CCF population assuming no residual treatment effect

Regimen	Total		Incremental		ICER	
	Costs	QALYs	Costs	QALYs	vs baseline (£/QALY)	Incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	£1,233	£1,233
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	£48,736	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£34,535	£45,456
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£55,658	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	£75,067	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£426,090	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£411,258	Dominated

Abbreviations: CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 37: Cost-effectiveness results for BF population assuming no residual treatment effect

Regimen	Total		Incremental		ICER	
	Costs	QALYs	Costs	QALYs	vs baseline (£/QALY)	Incremental (£/QALY)
RZB	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£20,585	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-£47,080	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£30,843	Dominated

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Health-related quality-of-life

B24. PRIORITY QUESTION. Please provide further justification for the chosen approach to capture patient utility estimates through analysis of EQ-5D-5L data in ADVANCE, MOTIVATE and FORTIFY studies, including the following:

a) Please provide rationale for the use of the ordinary least squares model to estimate health state utilities over alternatives including a linear mixed model, in the context of within-patient repeated measures.

Company response

Ordinary least squares (OLS) is a simple, straightforward and commonly used (for estimating health state utilities) regression technique and, in the CE model, is only used to estimate health-state specific intercepts (that is, no patient, treatment or other covariates are included).

Allowing for correlated errors at the patient level may be applicable in this context; however, it is believed that such a model would yield similar coefficient estimates and utility predictions. Hence, alternative statistical techniques are unlikely to significantly alter model conclusions. Nevertheless, to fulfil the request, the details of the linear mixed model can be found in response to question B24 (c) below. As seen, these values differ only slightly from those presented in the CS.

The company also note the model includes multiple EQ-5D scenarios, including those from prior technology assessments as well as from academic publications. The estimates produced via analysis of risankizumab trial data are comparable with those used in prior submissions and publications (1, 2, 48).

b) Please provide the number and percentage of patients who completed the EQ-5D-5L questionnaire at each scheduled data collection point, and please summarise the number of EQ-5D-5L observations informing the estimated utility value for each health state.

Company response

The number of observations for each health state are shown below in Table 38.

Table 38: Number of EQ-5D-5L observations by CDAI health status in each study

Health State	M15-991	M16-006	M16-000 SS1	Pooled Data
Remission (CDAI < 150)	[redacted]	[redacted]	[redacted]	[redacted]
Mild CD (150 ≤ CDAI < 220)	[redacted]	[redacted]	[redacted]	[redacted]
Moderate-to-Severe CD (CDAI ≥ 220)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; EQ-5D, EuroQoL 5 Dimensions health questionnaire OBS, observations; SS1, Sub-study 1.

c) Please provide utility values estimated using a linear mixed model, including a random effect to account for repeated measures. Please provide the regression equation and all output.

Company response

The equation for the linear mixed model is shown below:

$$EQ5D3L = 0.83 - 0.088 * IF(CDAI\ mild) - 0.224 * IF(CDAI\ moderate\ to\ severe) + USUBJID$$

The outputs of the linear mixed model are shown in Table 39.

Table 39: Linear mixed model EQ-5D-3L regression outputs

Term	Estimate	Standard error	Mean	Lower 95% CI	Upper 95% CI
Remission (CDAI < 150)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild CD (150 ≤ CDAI < 220)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate-to-Severe CD (CDAI ≥ 220)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; EQ-5D, EuroQol 5 Dimensions health questionnaire.

B25. In B.3.4.3, the HRQL SLR that the company conducted is referred to for reference, without any interpretation of the findings and their relevance for this appraisal.

a) Please provide a table presenting the health-state utility values used in the company base case alongside the utility values reported in (i) Bodger et al. and (ii) those used for decision making in the NICE appraisals for ustekinumab (TA456) and vedolizumab (TA352) in moderately to severely active Crohn's disease. Provide interpretation of any differences observed across estimates.

Company response

Health-state utility values (HSUV) used in the model base case, Bodger et al. (2009) (48), TA456 (1) and TA352 (2) are presented in Table 40.

HSUVs used in the CS base case, Bodger et al. (2009) and TA352 were broadly similar. HSUVs from TA456 were marginally lower; in the TA456 CS EQ-5D scores mapped from IBDQ were used in contrast to the CS for the current appraisal which used EQ5D based on CDAI scores. Of note, alternative utilities from TA456 using EQ-5D mapped from CDAI were more similar to the utility estimates in our analysis, Bodger et al. (2009) and TA352 (Table 46, ustekinumab CS reports the following: remission 0.820, mild CD 0.700, moderate to severe CD 0.540).

Table 40: Comparison of HSUVs in the CS base case, Bodger et al. (2009) and previous TAs in CD

	Health state utility values (HSUVs)			
Health states	**Model base case, mean (SE)**	**Bodger et al. (2009) (48), mean (SD)**	**TA456 (1), mean (SD)**	**TA352 (2), mean (SD)**
Remission	[redacted]	0.832 (0.017)	0.680 (0.130)	0.82 (0.163)
Mild CD	[redacted]	0.700 (0.017)	0.680 (0.130)	0.73 (0.183)
Moderate-to-severe CD	[redacted]	0.550 (0.017)	0.550 (0.130)	0.57 (0.284)
Surgery	First cycle: [redacted]	0.550 (0.017)	First 2 weeks in moderate-to-severe CD health state followed by 6 weeks in remission health state	0.57 (0.284)
	Subsequent 3 cycles: [redacted]			

Abbreviations: CD, Crohn's disease; HSUV, health-state utility values; SD, standard deviation; SE, standard error; TA, technology appraisal.

b) Please present and interpret findings from the HRQL SLR inclusions, commenting on the suitability of different estimates to inform assumptions in this appraisal.

Company response

The HRQoL SLR identified 142 studies which met the prespecified inclusion criteria, of which 56 reported utility values. The CS used data from the risankizumab clinical trial programme in the base-case analysis, in line with the NICE reference case (37). The most relevant additional studies that were identified in the SLR for use in scenario analyses (see response to B26 below) were the previous CD appraisals and the Bodger (2009) study (48). These were considered to be the most relevant sources as they presented HSUVs that aligned with the CS model health states, were used in previous NICE appraisals (1, 2), and were relevant to a UK population.

B26. Please explain the process for selecting the 2 alternative scenarios for health state utility values presented in B.3.11.3, from the range of non-base case options currently in the company's cost-effectiveness model.

Company response

The alternative scenarios were used in previous health technology assessment (HTA) submissions in CD (1) and the company felt that these were the most relevant to present in lieu of the risankizumab CD clinical trial EQ-5D data, which is the company's preferred data source.

B27. The EAG interprets that the impact of experiencing any adverse event on a patient's HRQL is assumed to last one model cycle (2 weeks). Please confirm whether this understanding is correct, and if so, justify this assumption.

Company response

The EAG is correct in their assessment. The resolution of AEs within a 2-week cycle was justified by assuming that AEs would be resolved quickly; there is no additional clinical justification for this assumption. AEs are not a key driver of the model outputs; the probability of experiencing most AEs is low.

B28. The EAG are unable to identify the utility age-adjustment parameters used in the company submission (age: -0.000173 and age^2: -0.000034) in the referenced publication (Ara and Brazier 2010). Please check and clarify the original source of the utility age-adjustment parameters, and update the cost-effectiveness model if appropriate.

Company response

The company uses the age decrements presented in TA456 (1) (which cites Ara and Brazier (64)); the company assumes they fit a regression line with age and age-squared on the data points in Figure 2 of Ara and Brazier (64). Upon further investigation, the coefficients cited in TA456 appear to be slightly incorrect. The correct coefficients (age: -0.0002587, age^2: 0.0000332) as cited in the Ara and Brazier publication (64) have been incorporated into the model. The impact on the results is negligible as shown in Table 41 and Table 42 below.

Table 41: Updated base case CE results: CCF population

Regimen	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER vs Baseline	ICER Incremental
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£4,387	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£31,259	£31,259
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£55,406	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	£77,599	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£313,414	Dominated
UST6	[redacted]	[redacted]	[redacted]	[redacted]	£195,929	Dominated

Abbreviations: CCF, conventional care failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 42: Updated base case CE results: BF population

Regimen	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER vs Baseline	ICER Incremental
RZB	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£51,214	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-£36,048	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£42,643	Dominated

Abbreviations: BF, biologic failure; CE, cost effectiveness; ICER, incremental cost-effectiveness ratio; IV, intravenous; N/A, not applicable; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Costs

B29. PRIORITY QUESTION. Which risankizumab pack sizes will be available in practice is currently unclear to the EAG.

a) **Please specify all risankizumab pack sizes and doses that will be available.**
b) **Currently on the BNF website, risankizumab is available as a 150mg/ml pre-filled pen/syringe. Will patients be expected to administer 360mg per dose using three pre-filled pens/syringes (with the remaining 90mg wasted) or will alternative pack sizes be available?**

Company response

Risankizumab will be available in 600 mg vials for induction, to be administered via IV infusion at Weeks 0, 4 and 8. For maintenance treatment, a 360 mg solution will be available in 2.4 mL vials to be delivered SC using the OBD at Week 12 and then every 8 weeks thereafter.

B30. Very little information is provided in B.3.5.2 on the resource use assumptions taken from TA456 and their applicability for this appraisal.

a) What resources are included in the estimates from TA456? Please provide an itemised list of resources and frequencies assumed for each health state.
b) Please confirm if any clinical input was sought to validate the resources and frequencies sourced from TA456 for current practice in 2022.

Company response

It is only possible to report the health state costs as shown in TA456 (1) at the health-state level; the committee papers for TA456 on the NICE website do not contain the Appendices (specifically Appendix 13) where the individual cost components are detailed. UK clinicians were invited to review model inputs used in the CS, but no clinicians provided comments on them.

Cost-effectiveness results

B31. Probabilistic cost-effectiveness results are presented only in graphical form on the ‘Probabilistic Results (Multiple Comparisons)’ sheet. In an updated version of the cost-effectiveness model, ensure a full incremental analysis is presented and the CEM settings are such that the submitted base case is reflected in the model when open, including the base case probabilistic results presented in B.3.10.

Company response

The probabilistic cost-effectiveness results (CS Section B.3.10) can be sourced from the “Calc – Prob (Multi) CCF” and “Calc – Prob (Multi) BF” worksheets of the Microsoft® Excel economic model that has been provided by the company.

Section C: Textual clarification and additional points

C1. The text and equations in B.3.3.3.1, above Table 63, do not currently make logical sense to the EAG. Please review and revise this section, to improve clarity of the intended description. In this, please make clear that the appropriate samples have been used to inform the estimates in Table 63. The EAG cannot verify this in the company model, as the percent estimates in Table 63 are hardcoded.

Company response

Patients who did not achieve remission following induction had to be allocated into the "mild" or "moderate-to-severe" disease health states for the maintenance phase of treatment. The risankizumab CD induction trials (ADVANCE, MOTIVATE) were used to determine the proportion of patients who were in the "mild" health state by utilising the CDAI response outcome. Hypothetically, a patient could respond to treatment and potentially be in any health state depending on their baseline CDAI score. The proportion of patients achieving remission is captured as part of the CDAI remission outcome, so these patients can be removed. The remaining patients have either mild or moderate-to-severe CD. If these patients responded to treatment, it was assumed that they had a higher probability of being in the "mild" disease health state as opposed to the "moderate-to-severe" disease health state.

The resulting patient numbers are shown in Table 43 and Table 44 below.

Table 43: Responders in "moderate-to-severe CD" health state following induction

Population	N	Proportion	Lower 95% CI	Upper 95% CI	Std. error
CCF (n=215)	16	0.084	0.039	0.110	0.018
BF (n=554)	43	0.078	0.055	0.100	0.011

Abbreviations: BF, biologic failure; CCF, conventional care failure; CI, confidence interval.

Table 44: Non-responders in "moderate-to-severe CD" health state following induction

Population	N	Proportion	Lower 95% CI	Upper 95% CI	Std. error
CCF (n=117)	84	0.718	0.636	0.799	0.042
BF (n=392)	288	0.735	0.691	0.778	0.022

Abbreviations: BF, biologic failure; CCF, conventional care failure; CI, confidence interval.

Clarification Question References

[1]. STELARA 45 mg solution for injection (vials). https://www.medicines.org.uk/emc/product/4413/smpc#gref

[2]. Rosario M, Dirks NL, Milch C, Parikh A, Bargfrede M, Wyant T, Fedyk E, Fox I. A Review of the Clinical Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Vedolizumab. Clin Pharmacokinet. 2017 Nov;56(11):1287-1301. doi: 10.1007/s40262-017-0546-0.

[3]. Ternant D, Aubourg A, Magdelaine-Beuzelin C, Degenne D, Watier H, Picon L, Paintaud G. Infliximab pharmacokinetics in inflammatory bowel disease patients. Ther Drug Monit. 2008 Aug;30(4):523-9. doi: 10.1097/FTD.0b013e318180e300.

[4].Ternant D, Ducourau E, Fuzibet P, Vignault C, Watier H, Lequerré T, Le Loët X, Vittecoq O, Goupille P, Mulleman D, Paintaud G. Pharmacokinetics and concentration-effect relationship of adalimumab in rheumatoid arthritis. Br J Clin Pharmacol. 2015 Feb;79(2):286-97. doi: 10.1111/bcp.12509

Response references

1. NICE. Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy STA (TA456). 2017. Available at: https://www.nice.org.uk/guidance/ta456/documents/committee-papers (Accessed June 2022)
2. NICE. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [TA352]. 2014. Available at: https://www.nice.org.uk/guidance/ta352/documents/crohns-disease-moderate-to-severe-vedolizumab-committee-papers2 (Accessed June 2022).
3. AbbVie. Crohn's disease HTA advisory board report. Data on file. 2021. (MAP ID: 2021-GB-MNP-00091).
4. IBD Registry. IBD Biological Therapies Audit. 2021.
5. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130(2):323-33; quiz 591.
6. Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. Journal of Crohn's & colitis. 2018;12(6):635-43.
7. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. The New England journal of medicine. 2016;375(20):1946-60.
8. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in

whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147(3):618-27.e3.
9. Sands BE, Sandborn WJ, Van Assche G, Lukas M, Xu J, James A, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naïve to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy. Inflammatory bowel diseases. 2017;23(1):97-106.
10. NICE. Crohn's disease: management (NG129). 2019. Available at: https://www.nice.org.uk/guidance/ng129/resources/crohns-disease-management-pdf-66141667282885 (Accessed June 2022).
11. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-analysis for decision-making: John Wiley & Sons; 2018.
12. Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, meta-regression, bias and bias-adjustment. 2012.
13. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. Journal of computational and graphical statistics. 1998;7(4):434-55.
14. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011.
15. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet (London, England). 2002;359(9317):1541-9.
16. EMC. Remicade 100mg powder for concentrate for solution for infusion - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/3831/smpc.%20Accessed%20July%202021 (Accessed June 2022).
17. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132(1):52-65.
18. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Annals of internal medicine. 2007;146(12):829-38.
19. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. The New England journal of medicine. 2013;369(8):711-21.
20. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. The New England journal of medicine. 1997;337(15):1029-35.
21. Rutgeerts P, Gasink C, Chan D, Lang Y, Pollack P, Colombel JF, et al. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease. Gastroenterology. 2018;155(4):1045-58.
22. Vermeire S, D'Haens G, Baert F, Danese S, Kobayashi T, Loftus Jr EV, et al. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's disease: results from the VISIBLE 2 randomised trial. Journal of Crohn's and Colitis. 2022;16(1):27-38.

23. Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. Journal of Crohn's & colitis. 2012;6(2):160-73.
24. Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T, Suzuki Y, et al. Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. Journal of gastroenterology. 2020;55(3):291-306.
25. Kashani A, Schwartz DA. The Expanding Role of Anti-IL-12 and/or Anti-IL-23 Antibodies in the Treatment of Inflammatory Bowel Disease. Gastroenterology & hepatology. 2019;15(5):255-65.
26. Ma C, Panaccione R, Khanna R, Feagan BG, Jairath V. IL12/23 or selective IL23 inhibition for the management of moderate-to-severe Crohn's disease? Best practice & research Clinical gastroenterology. 2019;38-39:101604.
27. Zhou L, Wang Y, Wan Q, Wu F, Barbon J, Dunstan R, et al. A non-clinical comparative study of IL-23 antibodies in psoriasis. mAbs. 2021;13(1):1964420.
28. EMC. Entyvio 300 mg powder for concentrate for solution for infusion - Summary of Products Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/5442/smpc (Accessed June 2022).
29. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment (MOTIVATE [M15-991]). Clinical Study Report. Risankizumab. 2021.
30. AbbVie. Multicenter, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Crohn's Disease (FORTIFY [M16-000]). Clinical Study Report. Risankizumab. 2021.
31. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease (ADVANCE [M16-006]). Clinical Study Report. Risankizumab. 2021.
32. NICE. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. Guidance. 2015. Available at: https://www.nice.org.uk/guidance/ta352/chapter/1-Guidance (Accessed August 2022).
33. Freeman HJ. Use of the Crohn's disease activity index in clinical trials of biological agents. World journal of gastroenterology. 2008;14(26):4127-30.
34. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2010;8(4):357-63.
35. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw Index. Inflammatory bowel diseases. 2006;12(4):304-10.
36. AbbVie. Market share data for ustekinumab in the UK (IPSOS). Data on file. 2021.

37. NICE. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 (Accessed June 2022).
38. AbbVie. Skyrizi 600 mg concentrate for solution for infusion - draft SPC. Data on file. 2022.
39. AbbVie. Skyrizi 360 mg solution for injection in cartridge - draft SPC. Data on file. 2022.
40. Singh S, Kroe-Barrett RR, Canada KA, Zhu X, Sepulveda E, Wu H, et al. Selective targeting of the IL23 pathway: Generation and characterization of a novel high-affinity humanized anti-IL23A antibody. mAbs. 2015;7(4):778-91.
41. EMC. Repatha SureClick. 2022. Available from: https://www.medicines.org.uk/emc/medicine/30628#gref. Accessed on: August 2022
42. Dalal SR, Cohen RD. What to Do When Biologic Agents Are Not Working in Inflammatory Bowel Disease Patients. Gastroenterology & hepatology. 2015;11(10):657-65.
43. NHS England. Clinical Commissioning Policy: Ustekinumab for refractory Crohn's disease in pre-pubescent children [200404P]. 2020. Available at: https://www.england.nhs.uk/wp-content/uploads/2020/07/Ustekinumab-for-refractory-Crohns-disease-in-pre-pubescent-children-1.pdf (Accessed June 2022).
44. Catt H, Bodger K, Kirkham JJ, Hughes DA. Value Assessment and Quantitative Benefit-Risk Modelling of Biosimilar Infliximab for Crohn's Disease. Pharmacoeconomics. 2019;37(12):1509-23.
45. Robson RE, Vanoli A, Tolley K. Cost-effectiveness of vedolizumab compared with conventional therapy in patients with Crohn's disease in the United Kingdom (UK). Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(Supplement 3):S455-S6.
46. Wilson M, Lucas A. Cost-effectiveness of vedolizumab versus ustekinumab in United Kingdom Crohn's disease patients who previously failed TNF inhibitor therapy. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(Supplement 3):S145.
47. Saito S, Shimizu U, Nan Z, Mandai N, Yokoyama J, Terajima K, et al. Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis. Journal of Crohn's & colitis. 2013;7(2):167-74.
48. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Alimentary pharmacology & therapeutics. 2009;30(3):265-74.
49. Loftus EV, Jr., Johnson SJ, Yu AP, Wu EQ, Chao J, Mulani PM. Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease. European journal of gastroenterology & hepatology. 2009;21(11):1302-9.
50. Lindsay J, Punekar YS, Morris J, Chung-Faye G. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease--modelling outcomes in active luminal and fistulizing disease in adults. Alimentary pharmacology & therapeutics. 2008;28(1):76-87.

51. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology. 2012;12:9.
52. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Report by the Decision Support Unit. 2011.
53. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model. 2011.
54. NICE. Tofacitinib for moderately to severely active ulcerative colitis [TA457]. 2018. Available at: https://www.nice.org.uk/guidance/ta547 (Accessed July 2022).
55. NICE. Secukinumab for treating moderate to severe plaque psoriasis [TA350]. 2015. Available at: https://www.nice.org.uk/guidance/ta350 (Accessed July 2022).
56. NICE. Asfotase alfa for treating paediatric-onset hypophosphatasia [HST6]. 2017. Available at: https://www.nice.org.uk/guidance/hst6 (Accessed July 2022).
57. Panaccione R, Colombel JF, Travis SPL, Bossuyt P, Baert F, Vaňásek T, et al. Tight control for Crohn's disease with adalimumab-based treatment is cost-effective: an economic assessment of the CALM trial. Gut. 2020;69(4):658-64.
58. Angrist JD, Pischke J-S. Mostly harmless econometrics: An empiricist's companion: Princeton university press; 2009.
59. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet (London, England). 2012;380(9853):1590-605.
60. Wolters FL, Russel MG, Sijbrandij J, Schouten LJ, Odes S, Riis L, et al. Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. Gut. 2006;55(4):510-8.
61. Loftus EV, Jr. Crohn's disease: why the disparity in mortality? Gut. 2006;55(4):447-9.
62. King D, Reulen RC, Thomas T, Chandan JS, Thayakaran R, Subramanian A, et al. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. Alimentary pharmacology & therapeutics. 2020;51(10):922-34.
63. AbbVie. Mortality risk in CD. Data on file. 2022.
64. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(5):509-18.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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.

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 nearly 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	No

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 Crohn's Disease, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, blood or mucus in stools, abdominal pain and fatigue, 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] The inflammation in Crohn's Disease may lead to strictures (narrowing) of the bowel resulting in abdominal pain caused by partial blockage. Severe cases may lead to life-threatening complications such as complete blockage or perforation of the bowel. At least 50% of people with Crohn's Disease may require surgery within ten years of diagnosis and 70-80% during their lifetime. Due to the nature of Crohn's Disease and the fact that it can occur anywhere in the gastrointestinal tract, having surgery once does not preclude the potential need to have surgery again. For patients with moderate to severe Crohn's Disease, the condition is more challenging, frequently overwhelming and detrimentally life-altering. This cohort is likely to experience more severe flares, weight loss, fever and constitutional symptoms. **Comorbidities** Patients with Crohn's Disease are at a higher risk of mortality and more likely to experience several comorbidities including diabetes, hypertension, atrial fibrillation, angina, stroke, rheumatoid arthritis, asthma, chronic obstructive pulmonary disorder and chronic liver disease.[3] **Mortality** Research suggests that people with Crohn's Disease are at a higher risk of mortality particularly from intestinal cancer, intestinal failure, perioperative complication and amyloidosis.[4] **Quality of Life** Education, employment, personal relationships, social and family life may all be disrupted by the unpredictable occurrence of Crohn's Disease flare-ups. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect self-esteem and social functioning, particularly among the young and newly-diagnosed. Emotional wellbeing can be significantly affected by difficulty in coping with personal lives and feelings of embarrassment, frustration, sadness and fears of needing surgery or developing cancer.[5] Stigma and lack of

	wider understanding of the condition exacerbates the impact. Anxiety, depressive episodes and depressive disorders are higher in people with Crohn's Disease, at least in part as a consequence of the condition itself and its medical treatment (e.g. corticosteroid therapy).[6] Additionally, much research has shown that stress can be involved in triggering flares.[7] Social functioning can be impaired leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. In fact, 45% of respondents in our Quality of Life survey reported that IBD had stopped them reaching their full potential in life in general.[8] Research shows that young people aged 16-25 with Crohn's Disease who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. Over half (56%) of young people responding to our survey said they ruled out career options due to the impact of their condition.[9] The experience of caring for someone with Crohn's Disease can be especially difficult given that it is an invisible condition, 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 their child's condition. Here are a selection of quotes that highlight what living with Crohn's disease is like:

[1] Crohn's & Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards.
[2] IBD UK (2019) IBD Standards.
[3] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *Evidence-based mental health*, **24**(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.
[4] Yasukawa, S., Matsui, T., Yano, Y. *et al.,* (2019). Crohn's disease-specific mortality: a 30-year cohort study at a tertiary referral center in Japan. *Journal of gastroenterology*, **54**(1), 42–52. https://doi.org/10.1007/s00535-018-1482-y.
[5] Cosnes J, et al., (2011). Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*, **140** (6), 1785-94.
[6] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *Evidence-based mental health*, **24**(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.
[7] Sun, Y., Li, L., Xie, R., et al., (2019). Stress Triggers Flare of Inflammatory Bowel Disease in Children and Adults. *Frontiers in pediatrics*, **7**, 432. https://doi.org/10.3389/fped.2019.00432
[8] Crohn's & Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards.
[9] Crohn's & Colitis UK (2013). IBD in young people, the impact on education and employment.

	"Crohn's Disease blights my life. I am an experienced teacher and a trustee of a local charity but my ability to work and contribute to my community, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12-18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge." **Quote from a person living with with Crohn's Disease** *"I'm an active divorced 60 year old woman now who feels the impact of my symptoms have precluded me from having a regular social life and finding a partner. On the surface I'm a confident outgoing woman but emotionally I'm crying inside and feel completely isolatedThis terrible disease has robbed me of my life in many ways and at times I have felt living on into my even older age is pointless. Nobody truly understands what it's like to have Crohn's unless they themselves are patients. My friends can't comprehend why a 'woman like me never remarried'. It's easy, I'm too embarrassed to even contemplate sharing a house with a man. The psychological effects keep me in like a hermit crab at the weekends."* **Quote from a person living with with Crohn's Disease** *"I am 23 years old and I have had to leave my university place studying Mental Health Nursing three times due to my Crohn's Disease. My life has been on hold for years due to this illness and I have lost 3 years of income, which has been a great burden."* **Quote from a person living with with Crohn's Disease** *"My wife states that I have changed since being diagnosed, I never thought I had, but looking back, she is right. We are battling this illness together ... it's not just me it affects, It's everyone, my wife, work and family".* **Quote from a person living with with Crohn's Disease**

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The IBD UK national repot revealed that 28& of patients with IBD rated the quality of their care as fair or poor.[10] Patients express dissatisfaction with many of the current treatment options. The effects of steroids are extremely unpleasant and long-term safety profile of other treatments, including biologics, are of some concern. **Steroids** Corticosteroids are commonly used a first line treatment. However, there are significant short and long-term side effects with these, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis.[11] Therefore they do not represent a therapeutic option as a maintenance treatment. The BSG guidelines set out clear stipulations on the best practice of prescribing steroid therapies given their diminishing returns, harsh side effects and risk of dependency.[12] *"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 IBD** **Surgery** For many patients with Crohn's Disease, the prospect of surgery is one they face with considerable anxiety, and it can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. Clinical outcomes after pouch surgery remain variable and fertility in women can be significantly affected by any pelvic surgery. *"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 IBD** *"Personally I'm not prepared for the drastic surgery of having my colon removed*." **Quote from a person living with IBD** *"I'd had enough of being ill and hospital admissions and blood transfusions and requested surgery to remove my colon. 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 IBD**

[10] IBD UK (2021). *Crohn's and Colitis Care in the UK: The Hidden Cost and a Vision for Change*. CROJ8096-IBD-National-Report-WEB-210427-2.pdf
[11] Blackwell J, Selinger C, Raine T, *et al* (2021). Steroid use and misuse: a key performance indicator in the management of IBD. *Frontline Gastroenterology* , **12**, p.207-213.
[12] BSG (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

8. Is there an unmet need for patients with this condition?	There is currently no medical or surgical cure for Crohn's Disease. Current available treatments are aimed at inducing and maintaining remission and improving quality of life. The range of options available for treating Crohn's Disease remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies. **Immunosuppressants** Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them.[13] [14] 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. [15] [16] **Anti-TNFs** These 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.[17] In the approximately one-third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time.[18] Overall, there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with Crohn's Disease to resume their lives and restore their quality of life. *"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."* **Quote from a person living with IBD, in which drug treatments have not been effective.**

[13] Fraser, A.G, Orchard, T.R, Jewell, D.P. (2002). The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut*, **50**: 485–9.
[14] Candy, S, Wright, J, Gerber, M, *et al.,* (1995) A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut*, **37**: 674–8.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	One of the key advantages is that Risankizumab is a treatment option that can be taken at home. Furthermore, the value of an additional treatment option, which has a different mode of action, reduced likelihood of loss of response, and a convenient delivery method would result in an associated reduction in NHS costs due to reduced infusions. 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 wish that these treatments [Risankibamab] were available earlier in my [Crohn's] disease. I am sure that these would have saved me having to have 4 resection ops.* **Person with Crohn's Disease who has been treated with Risankibamab** Patients also stated that Risankibamab has reduced their symptoms and improved their quality of life: *"I suppose in-terms of every day life it's allowed me to get back to eating more normally with confidence. If I was to conclude risankibamab treatment seems to have had a generally positive effect on my disease over this short period."* **Person with Crohn's Disease who has been treated with Risankibamab**

[15] Siegel, C.A, Marden, S.M, Persing, S.M, *et al.,* (2009). Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*, **7**:874–881

[16] Jorquera, A, Solari, S, Vollrath, V. et al., (2012). Phenotype and genotype of thiopurine methyltransferase in Chilean individuals. *Rev Med Chil*, **140**:889–895

[17] Rutgeerts, P, Van Assche, G, Vermeire S. (2004). Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology*, **126**(6):1593-610.

[18] Roda, G. (2016). Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*, **7** (1), e135.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We know not all medicines work for everyone. One patient who shared their experience of Risankizumab described mixed success from the use of the medication: *"I was treated with Risankizumab for Crohn's disease between February 2020-May 2021. I had been in a severe flare beforehand with extensive disease in my colon and end of the small bowel. The medication worked initially at resolving disease in the small bowel completely, but unfortunately had little impact on my large bowel disease and therefore it was discontinued after roughly 15 months."* **Person with Crohn's Disease who has been treated with Risankibamab** Prescription costs facing people living with long-term and chronic conditions, including Crohn's Disease, 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.[19] However, the disadvantage is not specific to Risankizumab, and the value of an additional treatment option may remain beneficial as it will reduce the risk of loss of response.

[19] Prescription Charges Coalition (2017). Still Paying the Price Prescription Charges and People with Long-Term Conditions. still_paying_the_price_june_2017.pdf (prescriptionchargescoalition.org.uk)

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. As Crohn's Disease is often more severe when presenting in childhood, with major consequences for lifelong morbidity, there may be particular benefits for younger people of this treatment.

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

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The symptoms of Crohn's Disease, and their unpredictable nature, together with the side effects of medications, can have a profound and devastating impact on all aspects of a person's life. • There is significant unmet need within the moderate to severe cohort. 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). • Risankizumab may delay or prevent surgery in patients with Crohn's Disease. This is particularly important for patients who have exhausted all over treatment options and wish to avoid or delay surgery (e.g. to complete studies).

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]
A Single Technology Appraisal

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
Authors	**Maxwell S. Barnish**[1] **Jae Naik**[2] **Will Sullivan**[2] **Amanda Brand**[1] **Emma Hook**[2] **Justin Matthews**[1] **Mark Edmondson-Jones**[2] **Sophie Robinson**[1] **Jonathan Digby-Bell**[3] **G.J. Melendez-Torres**[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter [2] Delta Hat Limited, Nottingham [3] Royal Devon and Exeter Hospital, Exeter
Correspondence to	Dr Maxwell S. Barnish 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk
Date completed	01/09/2022
Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/56/25

Declared competing interests of the authors	None.
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows	Barnish MS, Naik J, Sullivan W, Brand A, Hook E, Matthews J, Edmondson-Jones M, Robinson S, Digby-Bell J, Melendez-Torres GJ. Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986] A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2022.
Copyright	

Author Contributions:

Maxwell S. Barnish	Project lead, lead for the ERG's appraisal of clinical evidence, drafted background and clinical sections of report, writing and editorial input.
Jae Naik	Health economic lead for the project. Led health economic review of the company's evidence submissions, implemented ERG adaptations to the company model, led writing of economic sections of this report.
Will Sullivan	Contributed to the critical appraisal of the cost effectiveness evidence and writing of the economic sections of the report.
Amanda Brand	Critical appraisal of the company submission, writing and editorial input.
Emma Hook	Contributed to the critical appraisal of the cost effectiveness evidence and writing of the economic sections of the report.
Justin Matthews	Critical appraisal of the company submission, writing and editorial input.
Mark Edmondson-Jones	Critical appraisal of the company submission, writing and editorial input.
Sophie Robinson	Critical appraisal of the literature search strategies.
Jonathan Digby-Bell	Clinical advice and review of draft report.
G.J. Melendez-Torres	Critical appraisal of the clinical and economic evidence, editorial review.

Table of Contents

List of key issues

List of tables

List of Figures

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to Section 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Broadly speaking the key clinical issues related to the appropriateness of how the network meta-analysis was conducted. There was also a decision problem key issue related to the subgroup analysis and an 'other' key issue related to differences in the method of administration for risankizumab between the clinical trials and intended clinical practice. In terms of cost effectiveness, the EAG noted key issues with various aspects of the company's modelling approach, including the appropriateness of a model structure based on Crohn's Disease Activity Index, assumptions regarding treatment effectiveness estimates and the estimation of health state utility values.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
#1	Feasibility of exploratory subgroup analysis by CD location	2.4
#2	Unexplored heterogeneity in network meta-analyses in relation to baseline risk	3.4.3
#3	Network structure in maintenance network meta-analyses should be connected	3.4.6

ID	Summary of issues	Report sections
#4	Appropriateness of the model structure	4.2.2
#5	Treatment duration and residual treatment effect assumptions	4.2.6
#6	Estimation and application of maintenance treatment effectiveness assumptions	4.2.6
#7	Health state utility value estimation	4.2.7
#8	Method of administration for risankizumab	2.3, 3.2.2.3, 4.2.4

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Maximum treatment duration on biologic therapy, and residual treatment effect following biologic therapy	Assume all patients discontinue biologic therapy at 52 weeks. From this point, assume patients move to conventional care. Assume all patients experience a 52-week residual treatment effect following biologic therapy.	Highlight uncertainty around a true maximum treatment duration and residual treatment effect for biologic therapies. Assume a 20-year maximum treatment duration for biologic therapy in the base case. Assume a 26-week residual treatment effect following biologic therapy in the base case.	4.2.2 and 4.2.6.7
Network structure in maintenance NMA, and placebo CDAI-remission rates	Separate treatments into two disconnected networks, to reduce the heterogeneity in the placebo arms of maintenance studies.	Use a single maintenance network, and model placebo CDAI-remission rates using trial date as a potential candidate for explaining between-trial heterogeneity	3.4.6 and 4.2.6
Transition matrix calibration and cycle-length adjustment	Calibrate transition probabilities for each comparator, by adjusting the remission | mild cut-point in the risankizumab ordered probit model, to match 52-week remission estimates from the maintenance NMA. Estimate per-cycle (2-week) transition probabilities from implied 26-week transition probabilities, using an exponential assumption.	Calibrate transition matrices by adjusting both the remission | mild and mild | moderate-to-severe ordered probit cut-points by the same amount. Apply a transition matrix cycle length adjustment approach which does not rely on the use of the approximate exponential assumption.	4.2.6.4

	Company's preferred assumption	EAG preferred assumption	Report Sections
Health state utility values	Estimate mean CDAI-based health state utility values using OLS regression.	Estimated mean CDAI-based health state utility values using a linear mixed model, which includes a random effect to account for repeated measures.	4.2.7.1

Abbreviations: CDAI, Crohn's Disease Activity Index; EAG, External Assessment Group; OLS, ordinary least squares; NMA, network meta-analysis.

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Affecting the expected Crohn's Disease Activity Index (CDAI) score of patients over time, and in doing so affecting the estimated distribution of patients in remission vs mild disease vs moderate-severe disease states over a lifetime perspective, with implications for patient health-related quality of life (HRQoL)
- A treatment-specific risk of adverse events, with implications for patient HRQoL

Overall, the technology is modelled to affect costs by:

- Introducing the acquisition cost of risankizumab to the treatment pathway for moderate-to-severely active CD
- Affecting the expected CDAI score of patients over time, and in doing so affecting the estimated distribution of patients in remission vs mild disease vs moderate-severe disease states over a lifetime perspective, with implications for the lifetime expected patient healthcare resource usage and associated costs
- A treatment-specific risk of adverse events, with implications for patient healthcare resource usage and associated costs

The modelling assumptions that have the greatest effect on the ICER are:

- The assumed maximum treatment duration for biologic therapies

- The estimation and application of long-term treatment effectiveness estimates; more specifically, assumptions regarding the separation of networks in the maintenance NMA and approach for calibrating and adjusting health state transition matrices
- The choice of model for estimating CDAI-based health state utility values

1.3. The decision problem: summary of the EAG's key issues

The EAG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issues for consideration by the committee.

Key Issue 1: Feasibility of exploratory subgroup analysis by CD location

Report sections	Section 2.4
Description of issue and why the EAG has identified it as important	The final NICE scope for this appraisal includes subgroup analysis by CD location. The company excluded this from its decision problem. Clinical advice to the EAG was that CD location was likely the key prognostic factor for clinical effectiveness in this population.
What alternative approach has the EAG suggested?	Due to the clinical significance of this subgroup analysis, the EAG considered that the company should as a minimum have retained the CD location subgroup analysis in the decision problem and stated that it was unable to provide data to conduct this analysis. However, the EAG did not consider that the company's rationale for being unable to conduct subgroup analysis by CD location to be clearly justified. The EAG agreed that the numbers of participants per subgroup were fairly low but noted that this was also the case for the subgroup analysis the company presented by age and did not consider that this would preclude conducting an exploratory subgroup analysis.
What is the expected effect on the cost-effectiveness estimates?	An increase in uncertainty in clinical effectiveness, and consequently cost effectiveness, estimates based on a failure to adequately profile a key prognostic factor.
What additional evidence or analyses might help to resolve this key issue?	Provision of exploratory subgroup analysis by CD location based on the NICE scope using available data, noting the limitations of available evidence

Abbreviations: CD, Crohn's disease; EAG, Evidence Assessment Group; NICE, National Institute for Health and Care Excellence

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 2: Unexplored heterogeneity in network meta-analyses in relation to baseline risk

Report sections	Section 3.4.3
Description of issue and why the EAG has identified it as important	The company asserts that the base case network meta-analyses (NMAs) use a risk difference metric to address heterogeneity in baseline risk. However, the EAG regards that this is not an adjustment per se, and that it does not account for differences in treatment histories between trials, particularly in the group that has already experienced a biologic failure (BF). The company additionally advocates use of a fixed effects model because a random effects model produces implausibly large confidence intervals, an argument that does not unto itself have face validity in the presence of heterogeneity.
What alternative approach has the EAG suggested?	The EAG suggests that baseline risk adjustment be explored for risk difference-metric meta-analyses, and that a random effects model using an informative prior be explored.
What is the expected effect on the cost-effectiveness estimates?	The expected effect is unclear, but is likely to manifest in wider credible intervals in probabilistic sensitivity analysis (due to a random effects meta-analysis) and differences in incremental QALYs arising from baseline risk adjustment.
What additional evidence or analyses might help to resolve this key issue?	The EAG regards that an updated meta-analysis incorporating the model specification above would resolve the issue.

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; NMA, network meta-analyses; QALY, quality-adjusted life year

Key Issue 3: Network structure in maintenance network meta-analyses should be connected

Report sections	Section 3.4.6
Description of issue and why the EAG has identified it as important	The company's base case NMA for maintenance treatments separates drugs into two disconnected networks, citing rationales relating to drug mechanism of action and half-life.
What alternative approach has the EAG suggested?	The EAG has suggested using a single, joined-up network for each maintenance NMA.
What is the expected effect on the cost-effectiveness estimates?	It is difficult to disentangle the impact of this from changes to the application of these NMAs (see Key Issue 2) below, but the EAG believes this is likely to produce more stable estimates.
What additional evidence or analyses might help to resolve this key issue?	At clarification the company provided joined-up maintenance NMAs, though it retained the disconnected networks as its base case. Furthermore, related to Key Issue 2 above, estimates from these NMAs may change.

Abbreviations: EAG, Evidence Assessment Group; NMA, network meta-analyses

1.5. The cost effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the economic model and cost-effectiveness evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 4: Appropriateness of the model structure

Report sections	Sections 4.2.2
Description of issue and why the EAG has identified it as important	The company's model structure defines health status by CDAI score (in particular, CDAI response and remission rates), yet the EAG is in receipt of expert advice that CDAI score is not used in NHS clinical practice for the management of CD, owing to its overcomplicated nature and poor correlation with endoscopy. Instead, advice to the EAG is that the Harvey Bradshaw Index and endoscopic response are used. As such, the EAG are concerned that company's model structure is not reflective of relevant patient outcomes. The company recognised this issue in their evidence submission, defending their approach in the context of limited endoscopic outcome data, which the company describe as only available from risankizumab and ustekinumab overall populations. Separately, the addition of risankizumab to the treatment options currently available would extend the plausible options available to treat each patient, yet the company assumes that after the initial therapy, patients move to conventional care, on every treatment arm. The EAG are concerned that this assumption does not reflect the treatment pathway as described by both the company and the EAG's clinical expert, which sees patients treated with every available and suitable option sequentially. Further, the modelled assumption that patients transition to conventional care after initial therapy discontinuation is at odds with the company's argument against providing a comparison to BSC, as requested in the Final Scope.
What alternative approach has the EAG suggested?	The EAG saw no alternative to the use of CDAI outcomes within the cost-effectiveness model to address the decision problem, given the data limitations described by the company. The EAG noted that it would have been possible for the company to have better captured the expected treatment pathway implications of risankizumab's proposed introduction, within a different model structure.
What is the expected effect on the cost-effectiveness estimates?	The effect of these issues upon cost-effectiveness estimates is unknown. The EAG are not able to explore the importance of these structural uncertainties within the scope of the company's cost-effectiveness model, and are not able to speculate on likely directional bias.
What additional evidence or analyses might help to resolve this key issue?	A considered, alternative approach to cost-effectiveness modelling that captures the expected pathway implications of the proposed introduction of risankizumab could serve to improve confidence in drawing cost-effectiveness conclusions in this appraisal.

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; EAG, Evidence Assessment Group; NHS, National Health Service

Key Issue 5: Treatment duration and residual treatment effect assumptions

Report sections	Section 4.2.6
Description of issue and why the EAG has identified it as important	The EAG had several concerns with the company's approach to treatment discontinuation assumptions. The company's analysis assumes treatment-specific, constant rates of biologic treatment discontinuation in the maintenance phase of the model, for the first 52 weeks of maintenance therapy, then assumes all patients discontinue. From this point, patients are assumed to move to conventional care, whereby the company assume there is a further 52-week residual treatment effect in absence of biologic treatment costs. The EAG's clinical adviser found it difficult to judge whether assuming different 1-year discontinuation rates across treatments based on observed data across trials was appropriate, given differences in inclusion criteria and study design across trials. Expert advice to the EAG suggests it is implausible that all patients discontinue at 52 weeks. The EAG's clinical adviser's perspective is that if maintenance therapy is working for a patient, there is every effort and incentive to maintain treatment. The company's own TTD data from the FORTIFY study are consistent with this advice. Expert advice to the EAG suggests a residual treatment effect is plausible, with such an effect linked to the half-life of the treatment discontinued. For ustekinumab, the EAG's expert advises it can take around 24 weeks for symptoms to return.
What alternative approach has the EAG suggested?	The EAG-preferred base case assumes a 20-year maximum treatment duration, across treatments. The EAG explores different maximum treatment duration assumptions in scenario analyses, ranging from 5 to 40 years. The EAG-preferred base case assumes a 6-month residual effect across treatments, given the similar half-lives across treatments and EAG expert advice on estimated time to symptomatic return for ustekinumab.
What is the expected effect on the cost-effectiveness estimates?	Applied collectively, EAG-preferred maximum treatment duration and residual treatment effect assumptions lead to an increase in total costs and total QALYs across all biologic therapies. As such, the expected impact on cost-effectiveness results is multifaceted, and conditional on other model inputs and assumptions (such as biologic discontinuation rates and the cost of biologic maintenance treatment). In the CCF population, for risankizumab versus infliximab SC, incremental costs decrease while incremental QALYs increase, resulting in an improvement in the ICER. However, in the BF population, for risankizumab versus vedolizumab SC, incremental costs increase while incremental QALYs decrease, resulting in a higher ICER.
What additional evidence or analyses might help to resolve this key issue?	Further follow-up of FORTIFY TTD data could better inform time to treatment discontinuation assumptions in the cost-effectiveness model. Post-hoc analysis of FORTIFY patient outcomes following risankizumab discontinuation could better inform residual treatment effect assumptions in the cost-effectiveness model.

Abbreviations: EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; TTD, time-to-treatment-discontinuation; SC, subcutaneous.

Key Issue 6: Estimation and application of maintenance treatment effectiveness assumptions

Report sections	Section 4.2.6
Description of issue and why the EAG has identified it as important	Beyond issues with the maintenance phase NMA covered in Key Issue 2 and Key Issue 3 the EAG recommends that the company expand the placebo remission model to allow for plausible causes of heterogeneity, in particular a temporal association with the time at which individual clinical trials were conducted. This is consistent with an apparent improvement in remission outcomes over time, as treatments have improved. In addition, the EAG has several concerns with the company's approach to capture treatment effectiveness implications of maintenance therapy based on combining results from this NMA and observed FORTIFY data, and the implications for cost-effectiveness predictions. The company use an ordered probit model fit to FORTIFY subsample data to estimate transition probabilities. Despite company responses to EAG requests for clarity, justification for the appropriateness of the subsample data, the use of an ordered probit model, and the ordered probit model structure is weak. Conversion of implied 26-week transition matrices to model cycle-length (2-week) matrices is subject to known approximations that the company do not adequately justify. For comparator transition matrix estimation, the company calibrated the transition matrices estimated from FORTIFY data, to ensure 52-week remission rates matched the NMA-predicted 52-week remission rates, before cycle length adjustment. However, the calibration approach used is apparently arbitrary, adjusting only the balance of transitions to remission and mild at 26-weeks, and alternative approaches with different implications for long-term projections are possible. In particular, it is not considered tenable to assume that a change in the proportion of patients reaching remission does not also impact the proportion of patients moving to/remaining in moderate-to-severe disease. Separately, the company assume dose escalation affects costs but not patient outcomes, in assuming that standard dose transition probabilities apply to patients subject to biologic dose escalation. This EAG view this as an assumption that very likely biases comparative cost-effectiveness estimates in favour of risankizumab, as dose escalation applies only to comparator biologics.
What alternative approach has the EAG suggested?	The EAG prefers that placebo remission rates are modelled to include a temporal effect, and that absolute remission rates in maintenance are then based on this anchor point. The EAG also recommends an alternative approach to changing cycle length which avoids the use of the approximate exponential assumption. Additionally, the EAG prefers a calibration approach which adjusts both of the estimated ordered probit cutpoints by the same amount.
What is the expected effect on the cost-effectiveness estimates?	The isolated effect of the EAG-preferred estimation and application of maintenance treatment effectiveness assumptions is uncertain, and conditional on other preferred assumptions. The isolated impact on cost-effectiveness (when compared with the company's preferred base case in which a 52-week maximum treatment duration for biologic therapies is applied) is lower than the combined effect when implementing the EAG-preferred assumptions described in key issue 5.

Report sections	Section 4.2.6
	When also applying the EAG-preferred assumptions described in key issue 5, the effect of the EAG-preferred estimation and application of maintenance treatment effectiveness assumptions leads to higher incremental costs and lower incremental QALYs for risankizumab versus infliximab SC (in the CCF population) and versus vedolizumab SC (in the BF population). The EAG has not amended company dose escalation assumptions, and not this as a limitation of both the EAG-preferred and company base case analyses, that may bias results in favour of risankizumab.
What additional evidence or analyses might help to resolve this key issue?	Further follow up of FORTIFY patient outcomes could better inform risankizumab maintenance effectiveness assumptions in the cost effectiveness model. In lieu of these data, and for effectiveness projections for comparator treatments, a more considered and more robustly justified approach to modelling maintenance treatment effectiveness, taking into account the EAG's critique, may reduce the uncertainty around this issue. Additionally appropriate imputation methods may improve estimation of transition matrices, where CDAI data are missing, and diagnostics to assess the fit of the ordered probit model should be undertaken. The company could better inform its dose escalation assumptions, and provide further exploratory analyses, to illustrate the importance of potential bias in the company's approach, for cost-effectiveness results.

Abbreviations: EAG, Evidence Assessment Group

Key Issue 7: Health state utility value estimation

Report sections	Section 4.2.6
Description of issue and why the EAG has identified it as important	The company estimated the effect of CDAI category upon patient HRQL in ADVANCE, MOTIVATE and FORTIFY patient-reported data using ordinary least squares estimation, in order to inform cost-effectiveness model health state utility assumptions.
What alternative approach has the EAG suggested?	In the context of within-patient repeated measures, the EAG prefer to use health state utility values based on the same data but estimated using a (linear) mixed model that includes a random effect to account for repeated measures.
What is the expected effect on the cost-effectiveness estimates?	Applying EAG-preferred health state utility values leads to decrease in the total lifetime estimated QALYs across all treatment arms, as the linear mixed model predicts lower health state utility values in the remission and mild health states compared with the ordinary least squares regression used in the company's base case. The expected effect on cost-effectiveness results is variable, and depends on other assumptions regarding treatment effectiveness estimates, which determine the proportion of patents in the remission, mild and moderate-to-severe health states over time. In the CCF population, when compared with infliximab SC, applying the EAG-preferred health state utility value improves cost-effectiveness outcomes for risankizumab. However, in the BF population, when compared with

Report sections	Section 4.2.6
	vedolizumab SC, cost-effectiveness estimates are worse for risankizumab when applying EAG-preferred health state utility values.
What additional evidence or analyses might help to resolve this key issue?	The EAG feels there is no additional evidence needed to resolve this key issue, as it is a choice between alternative methods.

Abbreviations: EAG, Evidence Assessment Group, SC, subcutaneous.

1.6. Other key issues: summary of the EAG's views

The EAG identified the following additional key issues for consideration by the committee.

Key Issue 8: Method of administration for risankizumab

Report sections	2.3, 3.2.2.3, 4.2.4
Description of issue and why the EAG has identified it as important	The method of administration for risankizumab in the included clinical trials differs from the intended method of administration for clinical practice. Risankizumab was administered by intravenous clinician-administered injection in ADVANCE and MOTIVATE and by subcutaneous clinician-administered injection in FORTIFY sub-study 1. In the CS, the company stated that the intention was for risankizumab to be administered in routine practice using an on-body device. Very limited information was provided on this method of administration in the CS. In response to a clarification question by the EAG, the company stated that: "Risankizumab 600 mg intravenous (IV) induction will be administered in a hospital setting whilst risankizumab 360 mg subcutaneous (SC) maintenance will be administered through the on-body-device (OBD) either at home or in clinic. The OBD is a self-injection device which takes up to five minutes to administer from when the OBD is placed on the body at the injection site. The OBD allows for at-home treatment (where agreed with the healthcare team). The device can be placed to the abdomen or thigh and then upon pressing the button the OBD delivers a steady injection. In terms of administration the OBD should be stored in the refrigerator (at 2–8°C) and just before injecting the medication should be left to come up to room temperature. Upon activating the OBD a beeping sound will be heard, and a flashing blue status light will appear. The OBD can be secured on the injection site and the grey injection button should then be firmly pressed and released to deliver the medication. The OBD will beep, and the status light will flash green as the injection is delivered. The patient may do moderate physical activities, such as walking, reaching and bending, during the injection. The status light will change from flashing green to solid green and the device will beep once the medication has been delivered, at this stage and then the OBD can be removed by peeling the adhesive OBD off the skin. The OBD and cartridge can then be disposed by placing them into a special disposal container".

Report sections	2.3, 3.2.2.3, 4.2.4
	EAG also noted that the company stated in its clarification response that it was the [redacted] The company captures the cost implications of this administration difference, but in the model presumes no impact on clinical effectiveness parameters. The EAG considered this to be a strong assumption in the absence of evidence. It was also unclear to the EAG whether the on-body device method of administration had been considered in regulatory review for safety. The company provides no transparent (non-CIC) information on this method of administration in the CS or the clarification response. As the method of administration is a fundamental part of the delivery of the intended technology, the EAG had concerns that this could preclude effective stakeholder consultation on this appraisal and whether it could preclude NICE showing the evidential basis for its decision, given the intended method of administration does not match that used in the trials included in the submission.
What alternative approach has the EAG suggested?	The company could have considered FORTIFY sub-study 4, which according to publicly available information from clinical trial registries used an on-body injector as the method of administration, as a potential means of sourcing or adjusting clinical effectiveness parameters for the model using the intended method of administration. However, clarification would be required as to whether the on-body injector referenced in publicly available information on FORTIFY sub-study 4 is the same as the on-body device referenced in the CS.
What is the expected effect on the cost-effectiveness estimates?	There is considerable uncertainty as to whether the clinical effectiveness inputs to the cost effectiveness model remain valid given they were assessed using a different method of administration.
What additional evidence or analyses might help to resolve this key issue?	Data from FORTIFY sub-study 4 could help address this uncertainty, provided the on-body injector referenced in publicly available information on FORTIFY sub-study 4 is the same as or similar to the on-body device referenced in the CS. Clarification as to whether the on-body device method of administration was considered in the regulatory review for safety would also be useful. Some descriptive results from FORTIFY sub-study 4 were provided in the clarification response but these were not numerical in nature and they were not used to source or adjust clinical effectiveness parameters for the model using the intended method of administration. The narrative results provided were not sufficient to allow the EAG to conduct any useful critique of FORTIFY sub-study 4 results.

Abbreviations: EAG, Evidence Assessment Group

1.7. Summary of EAG's preferred assumptions and resulting ICER

As there is more than one comparator of relevance to the decision problem, the cost-effectiveness results are ideally calculated by fully incremental, probabilistic analysis. However,

for clarity and ease of calculation within the company's model, the step-by-step impact of EAG corrections to the company base and EAG preferred assumptions are summarised using deterministic changes and in pairwise analyses, in Table 3 and Table 5, for the conventional care failure (CCF) and biologic failure (BF) populations, respectively. Furthermore, the design of the company's economic model and volume of Visual Basics for Applications (VBA) code is a limiting factor for exploring probabilistic analysis. The economic model includes one 'Markov trace' (calculation) sheet for the selected comparator, and therefore must cycle through the list of included comparators using automated processes to perform incremental analysis, while also drawing recalibrated transition matrices. The above factors and number of included comparators contribute to a PSA run-time of approximately 9 hours when sampling 1,000 iterations; as such, the EAG did not consider it feasible to produce probabilistic results for each EAG preferred assumption or exploratory analysis within the EAG report timeframe. Additionally, the EAG note the company's economic model presents probabilistic results only in graphical form. In clarification question B31, the EAG requested an executable version of the cost-effectiveness model that included fully incremental probabilistic analysis (in line with the company base case presented in CS B.3.10.1); however, such model was not provided by the company. Thus, the EAG present full incremental analysis results probabilistically for the EAG preferred base case only.

In the company's and EAG's CCF population base case, adalimumab biosimilar is the 'reference' (lowest cost) treatment, and infliximab SC is the optimal comparator in the incremental analysis at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained. Thus, Table 3 presents pairwise cost-effectiveness results for risankizumab versus infliximab SC, for the CCF population. Fully incremental results for the EAG's preferred CCF population base case are presented in Table 4. For ease of reference, the EAG have excluded original forms of infliximab and adalimumab from the CCF incremental analysis table, as biosimilars are assumed by the company to provide equal QALYs at a lower cost.

Table 3: Summary of EAG's preferred assumptions and ICER (CCF population), risankizumab versus infliximab SC

Scenario	Incremental cost	Incremental QALYs	ICER (stepwise change)
Company's base case (probabilistic)	[redacted]	[redacted]	Dominated, -£81,752
Company's base case (deterministic)	[redacted]	[redacted]	Dominated, -£84,028
EAG corrected company base case	[redacted]	[redacted]	Dominated, -£102,827 (-£18,800)

Scenario	Incremental cost	Incremental QALYs	ICER (stepwise change)
+ Maximum treatment duration of 20 years for all biologic treatments	[redacted]	[redacted]	£52,499 (+£155,326)
+ Residual treatment effect of 26 weeks for all biologic treatments	[redacted]	[redacted]	£57,503 (+£5,004)
+ Single maintenance network, with an estimated maintenance placebo remission proportion that is adjusted for a temporal effect	[redacted]	[redacted]	Dominated, -£76,611 (-£134,114)
+ Transition matrices estimated by adjusting both the remission | mild and mild | moderate-to-severe cut points, and without an exponential assumption to estimate 2-week transitions	[redacted]	[redacted]	Dominated, -£75,237 (+£1,374)
+ Health state utility values estimated using a mixed linear model	[redacted]	[redacted]	Dominated, -£88,792 (-£13,555)
EAG's preferred base case (deterministic)	[redacted]	[redacted]	Dominated, -£88,792
EAG's preferred base case (probabilistic)	[redacted]	[redacted]	Dominated, -£90,018

Abbreviations: BF, biological failure; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 4: Summary of EAG's preferred base case (CCF population), incremental analysis

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG preferred deterministic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£5,536	£5,536
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£56,481	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£52,086	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£1,349,539	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£4,358,832	Dominated
EAG preferred probabilistic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£6,744	£6,744
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£55,111	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£48,951	Dominated

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£867,497	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£91,825,236	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

In the company's BF population base case, all comparators are dominated by risankizumab; however, in the EAG's preferred base case, vedolizumab SC is the optimal treatment option in incremental cost-effectiveness analysis at a willingness-to pay threshold of £20,000-£30,000 per QALY gained. Table 5 therefore presents pairwise cost-effectiveness results for risankizumab versus vedolizumab SC. Fully incremental results for the EAG's preferred BF population base case are presented in Table 6.

Table 5: Summary of EAG's preferred assumptions and ICER (BF population), risankizumab versus vedolizumab SC

Scenario	Incremental cost	Incremental QALYs	ICER (stepwise change)
Company's base case (probabilistic)	[redacted]	[redacted]	Dominant, -£44,642
Company's base case (deterministic)	[redacted]	[redacted]	Dominant, -£43,738
EAG corrected company base case	[redacted]	[redacted]	Dominant, -£26,902 (+£16,836)
+ Maximum treatment duration of 20 years for all biologic treatments	[redacted]	[redacted]	£65,837 (+£92,739)
+ Residual treatment effect of 26 weeks for all biologic treatments	[redacted]	[redacted]	£66,781 (-£943)
+ Single maintenance network, with an estimated maintenance placebo remission proportion that is adjusted for a temporal effect	[redacted]	[redacted]	£55,959 (-£10,822)
+ Transition matrices estimated by adjusting both the remission | mild and mild | moderate-to-severe cut points, and without an exponential assumption to estimate 2-week transitions	[redacted]	[redacted]	£119,509 (+£63,550)
+ Health state utility values estimated using a mixed linear model	[redacted]	[redacted]	£143,088 (+£23,579)
EAG's preferred base case (deterministic)	[redacted]	[redacted]	£143,088
EAG's preferred base case (probabilistic)	[redacted]	[redacted]	£142,074

Abbreviations: BF, biological failure; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 6: Summary of EAG's preferred base case (BF population), incremental analysis

Treatment	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG preferred deterministic base case						
VDZ SC	[redacted]	[redacted]	-	-	-	-
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£2,198,195	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£252,156	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£143,088	£143,088
EAG preferred probabilistic base case						
VDZ SC	[redacted]	[redacted]	-	-	-	-
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£1,487,732	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£248,239	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£142,074	£142,074

Abbreviations: BF, biological failure; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Modelling errors identified and corrected by the EAG are described throughout Section 4, and summarised in Section 6.1. For further details of the exploratory and sensitivity analyses performed by the EAG, see Section 6.2. For further details of the EAG preferred base case, see Section 6.3. For additional exploratory scenarios around the EAG preferred base case, see Section 6.4.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the Evidence Assessment Group (EAG) provides a review of the evidence submitted by AbbVie in support of risankizumab for previously treated moderate to severe Crohn's disease.

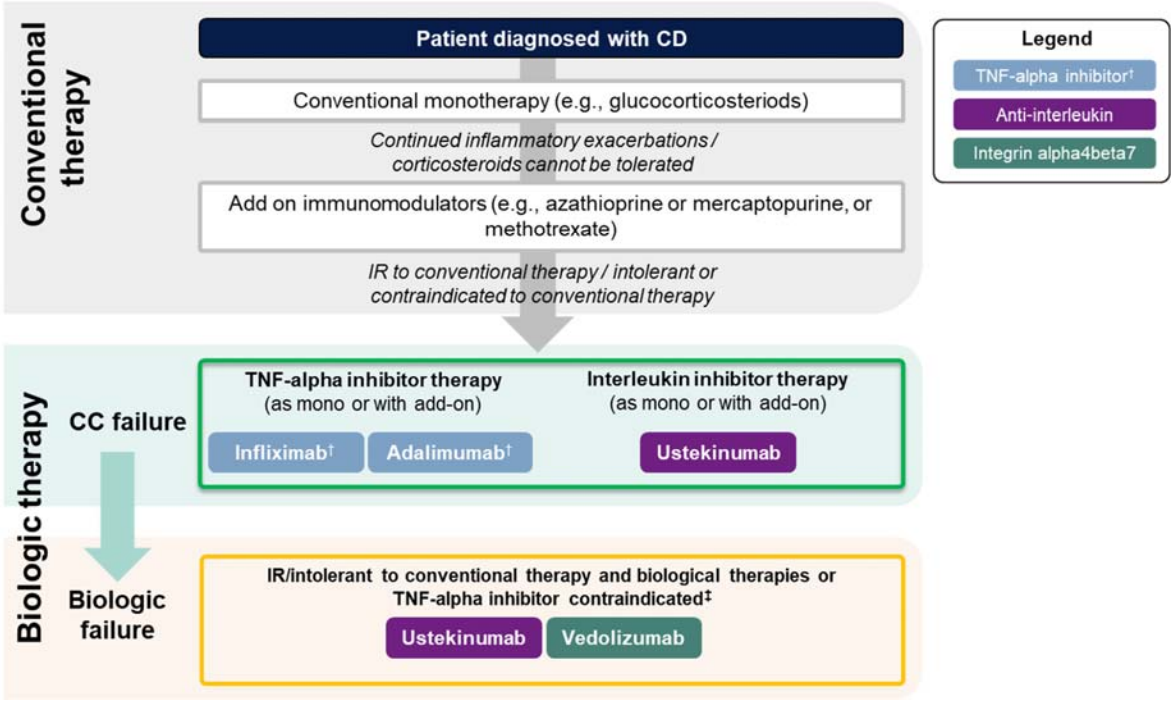
2.2. Critique of the company's description of the underlying health problem

The company's description of the underlying health problem, moderate to severe Crohn's disease (CD), is summarised in the CS Document B Section B.1.3.1. CD is a chronic relapsing systemic inflammatory bowel disease that can cause inflammation and mucosal ulceration to the entire gastrointestinal tract, but most commonly the distal small intestine. The pathogenesis of CD involves the complex interaction of immunological, microbiological, environmental and genetic factors.[1-3] Symptoms of CD can be heterogeneous, but include abdominal pain, diarrhoea, fatigue, weight loss, and blood or mucus in stools.[3, 4] Major extraintestinal manifestations for CD include ocular, renal, digestive, musculoskeletal, cardiovascular, dermatological and oral manifestations.[1] Symptoms can affect educational outcomes, work productivity, mental health and quality of life,[5-10] and result in extensive health service utilization.[6, 9-11] The prevalence of CD in the UK in 2021 was estimated to be 0.35% for males and 0.44% for females, leading to an estimated 185, 668 people aged 16 and over with CD in England.[12, 13] Around 40% of people with CD in the UK have been estimated to have moderate-to-severe disease, producing an estimated target population of 74,267 people with moderate-to-severe CD in England. The EAG considered the company's description of the underlying health problem to be adequate. Clinical advice to the EAG indicated that there was typically a dual peak in age distribution of patients encountered in routine clinical practice (late teens-early twenties and around the age of 50), that there was not considered to be an important difference in CD prevalence by gender, and that the key prognostic factors in this clinical population were age (the younger the patient is at diagnosis the less responsive the disease is likely to be), smoking status, and disease distribution (colonic disease is the most responsive to treatment and perianal disease the least responsive).

2.3. Critique of the company's overview of current service provision

The company's current care pathway is described in CS Document B Section 1.3.3. This is based on NICE Guideline NG129[14] and depicted in a flowchart. Clinical advice to the EAG was that each major centre has its own treatment pathway and that there are differences between centres, but in as much as there is a national standard of practice, the flowchart below is reasonably accurate in depicting this.

Figure 1. Treatment pathway based on CD management guidance by NICE



Risankizumab is humanised IgG1 monoclonal antibody that specifically binds with high affinity to the p19 subunit of human IL-23 cytokine blocking the binding of IL-23 to IL-23Rα without binding to IL-12.[15, 16] The recommended induction dose is 600 mg administered IV at Week 0, Week 4 and Week 8, followed by a maintenance dose of 360 mg administered SC at Week 12 and Q8W thereafter. Risankizumab was delivered IV in the risankizumab induction trials (ADVANCE and MOTIVATE) and SC in the risankizumab maintenance trial (FORTIFY) included in the CS. The EAG noted from publicly available information on clinical trials registries that an 'on-body injector' was used in FORTIFY sub-study 4, which was not included in the CS. In clinical practice, the company anticipates that risankizumab SC will be delivered using an on-body device. Clinical advice to the EAG indicated a low level of clinical familiarity with on-body injectors but identified both potential advantages and disadvantages of this approach. The EAG

considered that the description of the on-body device intended for clinical use in the CS was insufficiently detailed. The company provided further information in the clarification response QB3, as follows:

> *"Risankizumab 600mg intravenous (IV) induction will be administered in a hospital setting whilst risankizumab 360mg subcutaneous (SC) maintenance will be administered through the on-body-device (OBD) either at home or in clinic. The OBD is a self-injection device which takes up to five minutes to administer from when the OBD is placed on the body at the injection site. The OBD allows for at-home treatment (where agreed with the healthcare team). The device can be placed to the abdomen or thigh and then upon pressing the button the OBD delivers a steady injection. In terms of administration the OBD should be stored in the refrigerator (at 2–8°C) and just before injecting the medication should be left to come up to room temperature. Upon activating the OBD a beeping sound will be heard, and a flashing blue status light will appear. The OBD can be secured on the injection site and the grey injection button should then be firmly pressed and released to deliver the medication. The OBD will beep, and the status light will flash green as the injection is delivered. The patient may do moderate physical activities, such as walking, reaching and bending, during the injection. The status light will change from flashing green to solid green and the device will beep once the medication has been delivered, at this stage and then the OBD can be removed by peeling the adhesive OBD off the skin. The OBD and cartridge can then be disposed by placing them into a special disposal container".*

There are no additional tests or investigations associated with risankizumab use. Risankizumab currently holds marketing authorisation in the UK for the treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis. It has been recommended by NICE for the treatment of moderate-to-severe plaque psoriasis (TA596) and alone or in combination with methotrexate for the treatment of active psoriatic arthritis in adults who have had an inadequate response or been intolerant to one or more disease-modifying antirheumatic drugs.

2.4. Critique of company's definition of decision problem

The company statement regarding the decision problem is presented in the CS Section B.1.1, Table 1. The company position and the EAG response are provided in Table 7 below.

The EAG considered that the company's definition of the decision problem was generally acceptable. The EAG identified one key issue related to the decision problem: feasibility of exploratory subgroup analysis by CD location.

Table 7: 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 previously treated moderately to severely active CD	As per scope	NA	NA
Intervention	RZB	As per scope	NA	NA
Comparator(s)	• TNF-alpha inhibitors (IFX and ADA) • VDZ • UST For people for whom TNF-alpha inhibitors, VDZ and UST have been ineffective, are contraindicated or are not tolerated: • BSC	• TNF-alpha inhibitors (IFX and ADA) • UST • VDZ	The scope includes BSC as a comparator for those who have failed or are contraindicated to all currently available biologics (TNF-alpha inhibitors [ADA, IFX], UST and/or VDZ). BSC is not considered an appropriate comparator; in clinical practice, if a biologic therapy has failed or is contraindicated, the individual will be offered an alternative biologic therapy.	The EAG agreed that the exclusion of BSC as a comparator was likely appropriate given BSC would not be routinely used in clinical practice, based on clinical advice provided to the EAG. The EAG agreed that the focus on comparators applicable to UK practice was appropriate.
Outcomes	• Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Adverse effects of treatment • Health-related quality of life	As per scope	NA	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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 outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements in place for the intervention, comparator or subsequent treatment technologies will be taken into account.	• Cost per QALY • Lifetime horizon (suitably long to reflect differences) • NHS and PSS perspective on costs (base case) • PASs to be taken into account	N/A	The company present a non-reference case scenario analysis including societal costs
Subgroups	If evidence allows; location of CD (ileal, colonic and perianal)	• People who have had an inadequate response to conventional care (CCF) • People who have received ≥1 previous biologic and had an inadequate response (BF)	The trial design of RZB included the non-Bio-IR† and Bio-IR‡ populations, which were aligned in the model with CCF and BF populations. Separate analyses were conducted in these subpopulations as the comparators and clinical efficacy were different. Due to low	The EAG noted that the additional CCF and BF subgroup analyses in the company decision problem had not been specified in the NICE final scope for this appraisal. The company explained in the clarification response (A3) that the CCF and BF

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			subject numbers the analysis of outcomes by CD location was deemed untenable.	subgroups were consistent with previous TAs for ustekinumab (TA456) and vedolizumab (TA352). The EAG considered this potentially justifiable but a matter for the Committee to determine as it is not in line with the NICE scope. Regarding the exclusion of subgroup analysis by CD location, the EAG noted that it is reported in the CS that this was conducted. No details are reported. Without seeing the results of this analysis, the EAG is unable to agree that no meaningful conclusions could be drawn from this subgroup analysis. Clinical advice to the EAG identified location of CD as probably the key prognostic factor. Table 12 in the CS showed 155 patients with ileocolic CS, 76 patients with colonic CD and 55 patients with ileal CD in FORTIFY across both intervention and placebo arms. While noting power may be

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				suboptimal, the EAG considered that these numbers would likely be adequate for an exploratory subgroup analysis, noting that numbers were low in the presented subgroup analysis by patient age.
Special considerations including issues related to equity or equality	The availability and cost of biosimilars should be taken into consideration	• TNF-alpha inhibitors (ADA and IFX) are comparators which have biosimilars available	Cost of biosimilars have been taken into consideration where available i.e., for ADA and IFX.	Clinical advice to the EAG did not identify any equality concerns related to the potential introduction of risankizumab into the treatment pathway

Abbreviations: ADA, adalimumab; BF, biologic failure; BSC, best supportive care; Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; NA, not applicable; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PSS, Personal Social Services; QALY, quality-adjusted life year; RZB, risankizumab; TNcCF, tumour necrosis factor; UST, ustekinumab; VDZ, vedolizumab.; † Participants who had an inadequate response or intolerance to conventional therapy (defined as one or more of the following: aminosalicylates, oral locally acting steroids [e.g., budesonide, beclomethasone], systemic corticosteroids [prednisone or equivalent], or immunomodulators). This population may include patients who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response (IR) or intolerance (e.g., change in reimbursement coverage, well-controlled disease); ‡ Participants with documented intolerance or inadequate response (either failure to respond to induction treatment, or loss of response to maintenance therapy) to one or more biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab).

3. CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of risankizumab for previously treated moderate to severe Crohn's disease.

The EAG reviewed the details provided on:

- Methods implemented to identify, screen, data extract and assess the risk of bias in relevant evidence.
- Clinical efficacy of risankizumab.
- Safety profile of risankizumab.
- Assessment of comparative effectiveness of risankizumab against relevant comparators.

A detailed description of an aspect of the CS is only provided where the EAG disagreed with the company's assessment or proposal, or where the EAG identified a particular area of concern that the EAG considered necessary to highlight for the Committee.

The following clinical effectiveness key issues were identified:

- Unexplored heterogeneity in network meta-analyses in relation to baseline risk and use of fixed effect models
- Network structure in maintenance network meta-analyses should be connected

Additionally, the EAG considered that the following key issues had relevance to the clinical effectiveness evidence:

- Feasibility of exploratory subgroup analysis by CD location (decision problem key issue)
- Method of administration for risankizumab (other key issue)

3.1. Critique of the methods of reviews

The company undertook a global systematic literature review (SLR) to identify randomised controlled trials (RCTs) providing evidence for risankizumab (summarised in Section 3.2) and other relevant comparator therapies in people with moderately to severely active Crohn's disease. The company stated that included comparators to risankizumab may not all be relevant

to the UK due to the global approach that was used. Eligible RCTs were used to inform the company's indirect treatment comparison (Sections 3.3 and 3.4). An overview of the methods used in the SLRs is provided in Table 8 below.

Table 8: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Document B, Section B.2.1, Appendix D.1.1.	The EAG considered the company searches to be well executed overall. However, the RCT filter that was used by the company is not a recognised, validated filter such as the one from the Cochrane Handbook. In clarification the company stated that they used a mixture of different filters from SIGN and NICE; but this is not how these RCT filters are designed to be used and this makes the effectiveness of the search uncertain. In clarification, the company stated that no additional searches were carried out for adverse events as these were included in the overall clinical effectiveness search results. It is possible that exclusion of cohort, case-control, cross-sectional and case series as publication types in the literature searches (due to use of an RCT filter) meant that papers reporting adverse events have been missed.
Inclusion criteria	Inclusion criteria for clinical evidence: Appendix D.1.2. Table 2 (p.15-16) Inclusion criteria for studies included in the NMA: Appendix D.1.2. Table 3 (p.17-18)	The inclusion criteria for the clinical effectiveness review are considered broadly appropriate to the decision problem. Comparators not listed in the NICE scope, i.e. brazikumab, certolizumab pegol, estrasimod, etrolizumab, filgotinib, guselkumab, mirikizumab, ozanimod and upadacitinib were listed as eligible comparators, though the EAG noted that the company undertook a 'global' SLR. The EAG noted inclusion of adults with biologic-naïve, -exposed and –refractory CD, which is aligned with the population detailed in the company's scope as detailed in Table 7; however, no specific inclusion criteria were specified to identify trials in patients with specific locations for CD as per the NICE-scoped subgroups. The EAG noted the company's position that the number of patients per disease location made subgroup analyses untenable but considered that the company may have sufficient data to enable exploratory subgroup analyses by disease location, particularly since clinical advice to the EAG indicated that disease location is an important

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		prognostic factor. Therefore, inclusion criteria related to the location of CD for the purpose of subgroup analysis could have been useful. The additional inclusion criteria for the NMA were considered broadly reasonable by the EAG, though inclusion criteria related to the follow-up time for outcomes was considered to be potential source of heterogeneity (see Section 3.3.2.1), particularly in the induction NMAs. The EAG also noted that trials with 'treat-through' maintenance phases, as well as those re-randomising participants based on clinical remission, were excluded from the SLR. No explicit justification for this was provided, however, the EAG considered these exclusions to be appropriate given the likely impact this would have on the reduction of heterogeneity and intransitivity in the NMA (see Section 3.4.4).
Screening	Appendix D.1.2., p.16	Screening was conducted to appropriate standards to minimise selection bias, with duplicate, independent screening of identified studies and arbitration of discrepancies by a third reviewer. The EAG noted mention of the number of studies reviewed at the title and abstract screening stage as well as the full-text stage, though this staged approach was not explicitly reported.
Data extraction	Appendix D.1.2., p.16	Data extraction was conducted to appropriate standards to minimise selection bias, with extractions by a single reviewer into a pre-defined Excel-based template validated by a senior reviewer. Though data extraction was not done independently and in duplicate, the EAG noted that data validation by a second reviewer is permissible with the AMSTAR 2 critical appraisal tool.[17]
Tool for quality assessment of included study or studies	All studies included in the NMA: Appendix D.3	Quality assessments for ADVANCE, MOTIVATE and FORTIFY were conducted using the NICE clinical effectiveness quality assessment checklist for RCTs.[18] The tool was also used to assess the quality of all 13 other RCTs included in the company's NMA. The risk of bias of all 16 RCTs included in the NMA (ADVANCE, MOTIVATE and FORTIFY inclusive) was additionally assessed using the Cochrane risk of bias tool. The EAG considered these methods appropriate, though it was not clear why both methods were used, whether the outcomes of these assessments were considered together, or if the results of a

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		specific tool were selected. Furthermore, the EAG noted that the Cochrane risk of bias assessments included domains of the updated Cochrane risk of bias 2 tool,[19] but that no outcome-level assessments were conducted. The EAG considered this to be an inappropriate application of the tool. Various errors in algorithm results for this tool were identified, e.g. Domain 4 of several trials (ACCENT 1, CHARM, CLASSIC 1, GAIN, GEMINI 2 and GEMINI 3) should not be 'Low', and Domain 2 judgments for MOTIVATE and ADVANCE are incorrectly captured.
Evidence synthesis	Document B, Section B.2.9.1, Appendix D.1.3.3.	The company conducted several NMAs to evaluate the comparative efficacy of risankizumab with other available treatments within the CCF and BF subgroups; these were further stratified by induction and maintenance phases for each subgroup. This was considered reasonable by the EAG. The results within the maintenance phase for each subgroup were further divided into one of two treatment networks: risankizumab-ustekinumab or vedolizumab-TNFi. The EAG identified this grouping of treatment networks to be an area of uncertainty, as discussed in Section 3.4. The EAG also considered that further outcomes, particularly adverse events or treatment discontinuations, could have been evaluated; however, the company did not report feasibility assessment and therefore it is not possible to determine if these outcomes were considered but found not feasible for analysis. Statistical methods were appropriate, though the EAG highlighted concerns related to the way in which the maintenance networks were structured (see Section 3.4.6), potential heterogeneity in follow-up time (see Section 3.3.2.1) and potential effect modification due to patient characteristics (see Section 3.3.2.2). Given the company's preference for fixed effects analyses, the EAG regarded that random effects analyses using informative priors should have been considered.

Abbreviations: BF, biologic failure; CCF, conventional care failure; CD, Crohn's disease; CS, Company submission; EAG, Evidence Assessment Group; NMA, network meta-analysis; RCT, randomised controlled trial; SLR, systematic literature review; TNFi, tumour necrosis factor inhibitors

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The company presented evidence from three clinical studies: two pivotal induction studies (ADVANCE[20] and MOTIVATE[21, 22]) and one maintenance study (FORTIFY).[23, 24] These are analysed below.

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The CS included two pivotal induction studies (ADVANCE[20, 22] and MOTIVATE[21, 22]) and one maintenance study (FORTIFY).[23, 24] The pivotal induction studies were both placebo-controlled randomised multi-centre trials conducted internationally, including UK centres. The design of the included studies is summarised in Table 9. Only sub-study one from FORTIFY[23, 24] was included in the CS.

Table 9: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
ADVANCE (NCT03105128)[20, 22]	Phase 3 multicentre, randomised induction study	People aged 16 or older with moderate-to-severe CD and inadequate response or intolerance to prior biologic therapy (Bio-IR), or with inadequate response or intolerance to conventional therapy (non-Bio-IR)	Risankizumab, 600 mg or 1200 mg IV Q4W	Placebo	RCT
MOTIVATE (NCT03104413)[21, 22]	Phase 3 multicentre randomised induction study	People aged 16 or older with moderate-to-severe CD, with a documented inadequate response or intolerance to ≥1 biologic	Risankizumab, 600 mg or 1200 mg IV Q4W	Placebo	RCT

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
		therapy/therapies for CD (Bio-IR)			
FORTIFY (NCT03105102)[23, 24] Sub-study 1	Phase 3, multi-centre, partially randomised, double-blind, placebo-controlled, 52-week maintenance study with an ongoing open-label extension (OLE)	Participants who have entered and completed ADVANCE, MOTIVATE, or another AbbVie risankizumab Crohn's disease study and achieved clinical response during induction treatment with intravenous risankizumab or placebo	Randomised: participants with response to risankizumab 600 mg IV or 1200 mg IV during induction **randomised to risankizumab** 360 mg SC Q8W or 180 mg SC Q8W	Randomised: participants with response to risankizumab 600 mg IV or 1200 mg IV during induction **randomised to placebo** injection SC Q8W	RCT
			Non-randomised: participants with response to risankizumab 360 mg SC Q8W or 180 mg SC Q8W during induction continued on this dose	Non-randomised: participants with response to placebo IV during induction received placebo SC Q8W	NRS

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; IV, intravenous; n/a, not applicable; non-Bio-IR, conventional therapy inadequate response/intolerance; NRS, non-randomised study; OBI, on-body injector; OLE, open-label extension; Q4W, every four weeks; Q8W, every eight weeks; RCT, randomised controlled trial; SC, subcutaneous

3.2.2.2. Population

In the ADVANCE study,[20, 22] eligible participants were people aged 16 or older with moderate-to-severe CD who had inadequate response or intolerance to prior biologic therapy (Bio-IR), or with inadequate response or intolerance to conventional therapy (non-Bio-IR). Detailed inclusion and exclusion criteria were provided in the CS (Appendix M.1, Table 83). Participants were randomized to receive risankizumab 600 mg IV (n=336) or placebo (n=175).

In the MOTIVATE study,[25] eligible participants were people aged 16 or older with moderate-to-severe CD, with a documented inadequate response or intolerance to ≥1 biologic therapy/therapies for CD (Bio-IR). Detailed inclusion and exclusion criteria were provided in the CS (Appendix M.1, Table 83). Participants were randomized to receive risankizumab 600 mg IV (n=191) or placebo (n=187).

In the FORTIFY sub-study 1 (SS1),[23, 24] which is included in the company submission, eligible participants were people who had entered and completed either the ADVANCE or MOTIVATE study and achieved clinical response with risankizumab or placebo. This was defined as a ≥30% decrease in average daily stool frequency and/or a ≥ 30% decrease in average daily abdominal pain score; with both not worse than at baseline for the induction study at the last visit of ADVANCE or MOTIVATE. Detailed inclusion and exclusion criteria were provided in the CS (Appendix M.1, Table 83).

In both ADVANCE[20, 22] and MOTIVATE, the proportion of patients with exposure to ustekinumab was restricted to 20%. The EAG noted that these technologies had a similar mechanism of action. The company explained (clarification response A20) that this limit was based on prior experience in the adalimumab programme with participants exposed to infliximab. It was considered that there could be reduced efficacy in participants exposed to another technology designed to inhibit the same pathway. The EAG noted that in the company's response it was stated that a rationale for this 20% limit was to ensure 'probability of success for the co-primary endpoints'. Clinical advice to the EAG was that prescription of risankizumab to a patient who had not responded to ustekinumab was unlikely, so this was not a major issue.

FORTIFY SS1 included several analysis sets: three intention-to-treat (ITT) populations and one safety population. For the former, ITT1 included both randomised and non-randomised participants who received at least one dose of the study drug; ITT1A formed the primary population for efficacy analysis and included only randomised subjects in ITT1 who had a simple endoscopic score for Crohn's disease (SES-CD) of ≥ 6 (≥ 4 for isolated ileal disease) at baseline for either induction study; and ITT1C included only non-randomised subjects in the ITT1 set. The safety population, SA1, comprised all randomised participants who received at least one dose of study risankizumab in SS1. More details of these analysis sets are provided in CS in Table 8 (p.35) and Figure 6 (p.36).

A total of 141 participants receiving the licensed dose (360 mg SC Q8W) of risankizumab and 164 participants receiving placebo were included in the ITT1A population. Power calculations indicated that a sample size of 150 participants in each group would provide power (two-sided, α=0.05) of 87%, 93% and 99% for the co-primary endpoints of CDAI clinical remission, SF/APS clinical remission, and endoscopic response, respectively, at Week 52; the assumption of remission and response rates used in these calculations are reported in the supplementary appendix of Ferrante 2022.[24]

Baseline characteristics from the three included studies were provided in the CS Table 12 and reproduced below as Table 10.

Table 10. Characteristics of participants in the studies across treatment groups (ITT1A population)

	ADVANCE		**MOTIVATE**		**FORTIFY[¥]**	
Characteristic	RZB 600 mg IV N=336	PBO IV N=175	RZB 600 mg IV N=191	PBO IV N=187	RZB 360 mg SC N=141	PBO SC[††] N=164
Age, mean years (SD)	38.3 (13.3)	37.1 (13.4)	40.2 (13.6)	39.3 (13.5)	37.0 (12.8)	38.0 (13.0)
Age category, n (%)						
16 to <18 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18–40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40–65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	189 (56.3)	88 (50.3)	92 (48.2)	99 (52.9)	81 (57.4)	89 (54.3)
Female	147 (43.8)	87 (49.7)	99 (51.8)	88 (47.1)	60 (42.6)	75 (45.7)
Race						
White	258 (76.8)	134 (76.6)	176 (92.1)	162 (86.6)	111 (78.7)	126 (76.8)
Black or African American	9 (2.7)	9 (5.1)	7 (3.7)	7 (3.7)	8 (5.7)	10 (6.1)
Asian	65 (19.3)	31 (17.7)	8 (4.2)	15 (8.0)	20 (14.2)	28 (17.1)
American Indian/Alaska Native	0	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (0.6)	0	2 (1.1)	0	0
Multiple	4 (1.2)	0	0	1 (0.5)	2 (1.4)	0
Ethnicity						
Non-Hispanic/Latino	325 (96.7)	165 (94.3)	175 (91.6)	168 (89.8)	134 (95.0)	157 (95.7)
Hispanic/Latino	11 (3.3)	10 (5.7)	16 (8.4)	19 (10.2)	7 (5.0)	7 (4.3)
BMI (kg/m^2), mean (SD)	24.1 (5.6)	24.3 (5.8)	25.3 (6.4)	25.1 (5.8)	23.9 (5.4)	24.8 (6.3)
CD duration (years), mean (SD)	9.0 (8.8)	8.2 (7.1)	10.9 (7.7)	12.5 (9.7)	9.3 (8.1)	9.6 (8.8)

	ADVANCE		MOTIVATE		FORTIFY¥	
Disease location						
Ileocolic	180 (53.6)	90 (51.4)	96 (50.3)	98 (52.4)	72 (51.1)	83 (50.6)
Colonic disease	76 (22.6)	39 (22.3)	38 (19.9)	45 (24.1)	32 (22.7)	44 (26.8)
Ileal	62 (18.5)	37 (21.1)	49 (25.7)	33 (17.6)	25 (17.7)	30 (18.3)
Ileal - involving upper GI tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colonic disease - involving upper GI tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ileocolic - involving upper GI tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Faecal calprotectin (mg/kg), median (mean [SD])	n=141	n=284	n=150	n=146	n=114	n=140
	960 (1767.3 [2272.7])	1200 (2499.3 [4308.8])	1367 (2379.2 [3879.6])	987.5 (2648.9 [4831.2])	1543 (2182.5 [2471.7])	794.5 (1640.7 [2055.7])
Average daily SF, mean (SD)	5.8 (2.7)	6.1 (2.8)	6.2 (3.1)	6.4 (2.9) (n=186)	5.9 (2.6)	5.8 (2.7)
Average daily AP, mean (SD)	1.9 (0.6)	1.9 (0.6)	1.8 (0.5)	1.9 (0.5) (n=186)	1.8 (0.5)	1.9 (0.5)
CDAI, mean (SD)	311.2 (62.4)	319.2 (59.4)	310.7 (63.6)	319.6 (69.8) (n=186)	308.9 (61.1)	307.4 (64.9)
SES-CD, mean (SD)	14.7 (7.7)	13.8 (6.8)	14.4 (7.6)	15.0 (8.1)	14.3 (7.4)	14.0 (7.1)
Immunomodulator use, n (%)	88 (26.2)	42 (24.0)	36 (18.8)	40 (21.4)	40 (28.4)	40 (24.4)
Biologic failure, n (%)						
0	141 (42.0)	78 (44.6)	0	0	39 (27.7)	41 (25.0)
1	100 (29.8)	41 (23.4)	92 (48.2)	88 (47.1)	51 (36.2)	60 (36.6)
2	40 (11.9)	30 (17.1)	54 (28.3)	45 (24.1)	27 (19.1)	36 (22.0)
3	35 (10.4)	20 (11.4)	22 (11.5)	29 (15.5)	17 (12.1)	22 (13.4)
>1 (2-7)	95 (28.3)	56 (32.0)	99 (51.8)	99 (52.9)	51 (36.2)	63 (38.4)
TNF-alpha failure, n (%)	n=195†	n=97†			n=102†	n=123†

	ADVANCE		**MOTIVATE**		**FORTIFY¥**	
0	12 (6.2)	0	14 (7.3)	6 (3.2)	11 (10.8)	4 (3.3)
1	110 (56.4)	57 (58.8)	101 (52.9)	103 (55.1)	49 (48.0)	71 (57.7)
>1	73 (37.4)	40 (41.2)	76 (39.8)	78 (41.7)	42 (41.2)	48 (39.0)
Vedolizumab failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab failure, n (%)	n=195†	n=97†			n=102†	n=123†
	43 (22.1)	19 (19.6)	36 (18.8)	40 (21.4)	17 (16.7)	15 (12.2)
CD medication‡ at baseline§, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aminosalicylates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressants/immunomodulators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antibiotics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-diarrhoeal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AP, abdominal pain; Bio-IR, biologic inadequate response/intolerance; BMI, body mass index; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IV, intravenous; PBO, placebo; RZB, risankizumab; SC, subcutaneous; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF, tumour necrosis factor; WHO, World Health Organization.
†Bio-IR population; ‡generic name (WHO 2018Q1); §for FORTIFY, baseline refers to baseline of the induction study; ¥Data reported for randomised subjects only from FORTIFY SS1; †† The placebo SC (withdrawal) arm consisted of subjects who achieved SF/APS clinical response to IV risankizumab induction therapy in ADVANCE or MOTIVATE and were randomised to receive placebo in FORTIFY.

The CS reports that the risankizumab Crohn's disease study programme enrolled a total of [redacted] subjects at [redacted] UK centres, with UK participants representing [redacted]%, [redacted]% and [redacted]% of the study populations in ADVANCE, MOTIVATE and FORTIFY, respectively. Clinical advice to the EAG was that findings from overseas participants were likely to generalize reasonably well to the UK clinical practice setting, although usual caveats relating to treatment pathways and population similarity should be noted. The company was unable to provide baseline characteristics or results specifically for UK participants (clarification question A17), which increases uncertainty regarding generalizability to the target UK context.

3.2.2.3. Intervention

The intervention used in all included studies was risankizumab. Dosing and method of administration differed between the pivotal induction trials (IV administration in ADVANCE and MOTIVATE) and the maintenance trial (SC administration in FORTIFY). In both ADVANCE and MOTIVATE, risankizumab was administered intravenously at a dose of 600 mg (licensed dose) or 1200 mg Q4W.

In the FORTIFY sub-study 1, which is included in the company submission, the intervention is a maintenance dose of risankizumab; administered subcutaneously to participants randomised thereto as either 360 mg Q8W (licensed dose) or 180 mg Q8W risankizumab for 52 weeks following response to induction treatment with risankizumab in the ADVANCE or MOTIVATE induction trials. Non-randomised intervention arms in FORTIFY included participants who responded to non-licensed induction doses of risankizumab in ADVANCE or MOTIVATE, i.e. 360 mg Q8W (following 12 weeks of 600 mg risankizumab IV induction plus 12 weeks of 360 mg SC risankizumab) or 180 mg Q8W risankizumab.

3.2.2.4. Comparator

The comparator in the ADVANCE and MOTIVATE studies was placebo, which was not listed as a comparator in the NICE scope. The comparator used in SS1 of FORTIFY, the sub-study included in the CS, was also placebo; comprising succinic acid (0.5 mmol/L), disodium succinate hexahydrate (3.9 mmol/L), sorbitol (275 mmol/L), polysorbate 20 (0.16 mmol/L), and water for injection (Ferrante 2022).[24] In participants randomised thereto in FORTIFY SS1 following response to induction treatment with risankizumab in ADVANCE or MOTIVATE, placebo was administered as subcutaneous injection Q8W. Non-randomised participants with response to intravenously administered placebo during ADVANCE or MOTIVATE received subcutaneous placebo Q8W during FORTIFY SS1.

Clinical advice to the EAG was that placebo is not used in routine practice. The CS states that placebo was used due to FDA and EMA requirements. As such, no directly comparative trial evidence was provided linking risankizumab to scoped comparators. Therefore, a network meta-analysis was presented by the company (see Section 3.4) to link clinical effectiveness estimates for risankizumab from included trials with clinical effectiveness estimates for scoped comparators identified from the wider literature.

3.2.2.5. Outcomes

The outcomes reported in the included studies are summarised in the CS Table 9 and reproduced below as Table 11. The EAG noted that clinical remission was measured using CDAI. Clinical advice to the EAG was that this outcome measure is of limited utility and is not used in UK clinical practice and that use of the Harvey Bradshaw Index would have been preferable. The EAG noted that company's response (clarification question A18) that CDAI is commonly used in clinical trials and that its use improved comparability of results across trials. The company explained (clarification question A16) that in the original protocol for the risankizumab Crohn's disease studies, the definition of the co-primary endpoint was patient-reported outcomes 2-item (stool frequency/abdominal pain score) (PRO2 [SF/APS]) clinical remission and endoscopic response. However, subsequent discussions with the FDA led to the creation of a US-specific protocol, which defined the co-primary endpoint as CDAI clinical remission and endoscopic response. An outside-US (OUS) protocol was created which retained the original definition of the co-primary endpoint, i.e., using PRO2 (SF/APS) to assess clinical remission. Consequently, the co-primary endpoint for the OUS protocol was clinical remission (PRO2 [SF/APS]) and endoscopic response, while the co-primary endpoint for the US protocol was clinical remission (CDAI) and endoscopic response. Both co-primary endpoints were measured at all trial sites, regardless of region. The only differences between the protocols are the outcomes used to determine clinical remission for the co-primary endpoints, the ranking of secondary endpoints and the sample size power calculation based on the revised co-primary endpoint.

The EAG noted that the definitions of CDAI remission (defined as a CDAI score of ≤ 150 points) and CDAI clinical response (defined as a reduction of 100 or more points from baseline) effectively meant that a participant could be defined as in remission without being defined as having clinical response. The EAG considered this to be a limitation of the use of this measure.

Table 11. Overview of outcomes in included trials

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
Primary outcomes (including scoring methods and timings of assessments)	Definitions of coprimary endpoints: • CDAI clinical remission at Week 12: CDAI <150 • PRO2 (SF/APS) clinical remission at Week 12: average daily SF ≤2.8 and not worse than Baseline, and average daily AP score ≤1 and not worse than Baseline • Endoscopic response at Week 12: decrease in SES-CD >50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline), as scored by central reviewer Assessments: • CDAI clinical remission: CDAI scores were calculated using a central laboratory Hct value from the same visit for all visits (Week 4, 8, 12/premature discontinuation, 16, 20, 24 or any unscheduled visit) except Baseline, where the most recent Screening Hct value was used‡‡ • PRO2 (SF/APS): Average daily SF, average daily AP score, and well-being were calculated from the subject diary at all visits (Baseline, Week 4, 8, 12/premature discontinuation, 16, 20, 24 or any unscheduled visit). The Screening period was a minimum of 7 days to calculate the Baseline scores. • Endoscopic response: an endoscopy was performed during screening,†† Week 12/premature discontinuation, Week 24 - The same endoscopist, where possible, performed all endoscopies		Definitions of co-primary endpoints: • CDAI clinical remission at Week 52: CDAI <150 • PRO2 (SF/APS) clinical remission at Week 52: average daily SF ≤2.8 and not worse than Baseline of the induction study, and average daily AP score ≤1 and not worse than Baseline of the induction study • Endoscopic response at Week 52: decrease in SES-CD >50% from Baseline of the induction study (or for subjects with isolated ileal disease and a SES-CD of 4 at Baseline of the induction study, at least a 2-point reduction from Baseline of the induction study), as scored by central reviewer Assessments: • The CDAI was calculated at each visit (Week 24, 52/premature discontinuation, any unscheduled visit, or rescue therapy visit). The scores calculated at the final visit in ADVANCE or MOTIVATE served as the Week 0 scores‡‡ • PRO2 (SF/APS): Average daily SF, average daily AP score, and well-being were calculated from the subject diary at each visit (Week 8, 16, 24, 32, 40, 48, 52/premature discontinuation, any unscheduled visit or rescue therapy visit). The scores calculated at the final visit in ADVANCE or MOTIVATE served as the Week 0 scores • Endoscopic response: An endoscopy was performed at Week 52/premature discontinuation

Trial no. (acronym)	M16-006 (ADVANCE)	M15-991 (MOTIVATE)	M16-000 Sub-Study 1 (FORTIFY)
	- Where possible, the Investigator or sub-Investigator was an endoscopist. All endoscopies were reviewed by a blinded central reviewer		- An endoscopy may have been performed at unscheduled visits to confirm inadequate response if hs-CRP and FCP are not elevated - The same endoscopist, where possible, performed all endoscopies - Where possible, the Investigator or sub-Investigator was an endoscopist. All endoscopies were reviewed by a blinded central reviewer
Other outcomes used in the economic model/specified in the scope	• Endoscopic remission at Week 12 • CDAI clinical response at Week 4 or Week 12 • EQ-5D-5L at Week 4 or Week 12		• Endoscopic remission at Week 52

Abbreviations: APS, abdominal pain score; CDAI, Crohn's disease activity index; FCP, faecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; PRO2, patient reported outcome 2-item; SES-CD, simple endoscopic score for Crohn's disease; SF, stool frequency;

Notes: †† An endoscopy performed before the Screening visit, independently of the study, may have been used as the Screening endoscopy, with the approval of the AbbVie TA MD, if the following conditions were met: 1. Biopsy confirmation of the diagnosis was available according to section "Biopsy During Endoscopy" below, as applicable, 2. The endoscopy took place within 45 days prior to Baseline visit, 3. The endoscopy was recorded in a video format as the endoscopic eligibility will be determined by the central reviewers; ‡‡ The final CDAI for all other visits was calculated once the Hct value was received from the central lab. If the Hct was missing due to technical issues, the Hct value from the preceding visit may have been used.

3.2.2.6. Critical appraisal of the design of the studies

The company's approach to the critical appraisal of included trials was reported in the CS (Appendix D.3., Tables 26 and 27). Quality assessments for ADVANCE[20, 22]and MOTIVATE,[21, 22] the two risankizumab induction trials, as well as for FORTIFY,[23, 24] the maintenance trial for risankizumab, were conducted using the NICE clinical effectiveness quality assessment checklist for RCTs.[18] The EAG noted that the declaration of conflicts of interest was not assessed as part of the NICE guidance for quality appraisal.

The risk of bias of these trials was additionally assessed using the Cochrane risk of bias tool. The EAG considered these methods appropriate, though it was not clear why both methods were used, whether the outcomes of these assessments were considered together, or if the results of a specific tool were selected. The EAG also noted that the Cochrane risk of bias assessments included domains of the updated Cochrane risk of bias 2 tool,[19] but that no outcome-level assessments were conducted. In addition, the final question for domain 2, i.e. '2.7. If No/Probably No/No Information to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?' was entirely omitted. The EAG considered this to be an inappropriate and incomplete application of the tool that may have altered the overall risk of bias judgment of the assessed trials; however, given that this information is not used to inform any sensitivity analyses in the CS the impact is likely limited.

ADVANCE

Using the NICE guidance for quality appraisal of RCTs, the company appraised this trial as having no methodological concerns. No substantiation of these judgements were provided. The EAG considered the company's judgments related to randomisation, allocation concealment and baseline equivalence to be reasonable, given that patients were randomly assigned using interactive response technology as well as the unimportant differences between randomised groups at baseline (D'Haens 2022).[22] Furthermore, the EAG agreed with the company's judgments related to the lack of selective reporting, given the agreement between the primary publication (D'Haens 2022)[22] and the trial registry (NCT03105128), as well as the analytical approach, given that intention-to-treat analyses were conducted and conservative assumptions applied to the imputation of missing data. The EAG did not agree with the company's judgment related to blinding, since outcome assessors were not indicated as having been blinded, and considered 'No' to be a more appropriate judgment for this domain. The EAG also did not agree

with the company's judgment related to imbalances in loss to follow-up: while the overall attrition is acknowledged to be reasonably low at 7% (disregarding reasonable exclusions related to non-compliance of sites and low SES-CD participants), differential attrition was suggested by loss to follow-up of 5% and 4% in the risankizumab 600 mg and 1200 mg groups, respectively, versus loss to follow-up of 14% in the placebo group. As a result, the EAG considered 'Yes' to be a more appropriate judgment for this domain.

Using the Cochrane Risk of Bias tool, the company also appraised this trial as having no methodological concerns. As for the NICE quality appraisal, no substantiations accompanied these judgments. The EAG considered the judgments for domain 1 (Randomisation), domain 3 (Missing outcome data) and domain 5 (Selection of the reported result) to be reasonable, in line with the discussion related to the appraisal using the NICE guidance. It is not clear to the EAG, however, why the company indicated that carers and people delivering interventions were probably aware of assignment under question 2.2; particularly given the difference in the judgement for MOTIVATE, which was reported in exactly the same way. Furthermore, the answers to domain 2 (Deviations from intended interventions) represent an incorrect progression of the algorithm which could not have resulted in a domain-level judgment, unless this was overridden by the Assessor's judgment. The EAG considered that such a step should have been noted and justified. As was the case for the NICE guidance, there is no substantiating evidence to show that outcome assessors were blinded and therefore the EAG also considers that question 4.3 under domain 4 (Measurement of the outcome) was incorrectly assessed.

MOTIVATE

Using the NICE guidance for quality appraisal of RCTs, the company appraised this trial as having no methodological concerns. No substantiation of these judgements were provided. The EAG considered the company's judgments related to randomisation, allocation concealment and baseline equivalence to be reasonable, given that patients were randomly assigned using interactive response technology as well as the unimportant differences between randomised groups at baseline (D'Haens 2022).[22] Furthermore, the EAG agreed with the company's judgments related to the lack of selective reporting, given the agreement between the primary publication[22] and the trial registry (NCT03104413), as well as the analytical approach, given that intention-to-treat analyses were conducted and conservative assumptions applied to the imputation of missing data. The EAG did not agree with the company's judgment related to

blinding, since outcome assessors were not indicated as having been blinded, and considered 'No' to be a more appropriate judgment for this domain. The EAG also did not agree with the company's judgment related to imbalances in loss to follow-up: while the overall attrition is acknowledged to be reasonably low at 6% (disregarding reasonable exclusions related to non-compliance of sites and low SES-CD participants), differential attrition was suggested by loss to follow-up of 3% and 4% in the risankizumab 600 mg and 1200 mg groups, respectively, versus loss to follow-up of 14% in the placebo group. As a result, the EAG considered 'Yes' to be a more appropriate judgment for this domain.

Using the Cochrane Risk of Bias tool, the company also appraised this trial as having no methodological concerns. As for the NICE quality appraisal, no substantiations accompanied these judgments. The EAG considered the judgments for domain 1 (Randomisation), domain 3 (Missing outcome data) and domain 5 (Selection of the reported result) to be reasonable, in line with the discussion related to the appraisal using the NICE guidance. The EAG noted that the answers to domain 2 (Deviations from intended interventions) represent an incorrect progression of the algorithm which could not have resulted in a domain-level judgment, unless this was overridden by the Assessor's judgment; a step that should have been noted and justified, if this is the case. The company provided no substantiating evidence to show that outcome assessors were blinded during this trial, and therefore the EAG also considers that question 4.3 under domain 4 (Measurement of the outcome) was incorrectly assessed.

FORTIFY

Using the NICE guidance for quality appraisal of RCTs, the company appraised this trial as having no methodological concerns. No substantiation of these judgements were provided. The EAG considered the company's judgments related to randomisation, allocation concealment and baseline equivalence to be reasonable, given that patients were randomly assigned using interactive response technology as well as the unimportant differences between randomised groups at baseline[24]. The EAG agreed with the company's judgments related to blinding, given the quadruple blinding (participant, care provider, investigator and outcome assessor) reported in the trial registry (NCT03105102). Furthermore, the EAG agreed with the company's assessment regarding a lack of selective reporting, given the agreement between the primary publication[24] and the trial registry (NCT03105102), as well as the analytical approach, given that intention-to-treat analyses were conducted and conservative assumptions applied to the imputation of missing data. The EAG noted the company's judgment related to imbalances in

loss to follow-up: it considered overall attrition as fairly high at 11%, even when disregarding reasonable exclusions related to non-compliance of sites, low SES-CD participants and those with ineligible induction periods. However, no differential attrition was suggested by loss to follow-up of 8% and 12% in the risankizumab 180 mg and 360 mg groups, respectively, versus loss to follow-up of 12% in the placebo group. As a result, 'Yes' may possibly be a more appropriate judgment for this domain; however, the EAG accepted the company's judgment since no numerical cut-off value for 'high attrition' was stated in the CS.

Using the Cochrane Risk of Bias tool, the company also appraised this trial as having no methodological concerns. As for the NICE quality appraisal, no substantiations accompanied these judgments. The EAG considered the judgments for all domains to be reasonable, in line with the discussion related to the appraisal using the NICE guidance, and found no errors in the algorithm progression for this trial.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Disease activity (remission, response, relapse)

In ADVANCE, the co-primary endpoints of clinical remission (CDAI and PRO2 [SF/APS]) and endoscopic response were met for the risankizumab 600 mg IV arm when compared with the placebo IV arm. At week 12, a significantly greater proportion of participants in the risankizumab 600 mg IV arm achieved the co-primary endpoint of CDAI clinical remission versus the placebo IV arm (45.2% vs 24.6%, respectively; p<0.001). At week 12, a statistically significantly greater proportion of subjects in the risankizumab 600 mg IV arm achieved endoscopic response compared with the placebo IV arm (40.3% vs 12.0%, respectively; p<0.001). At week 4, significantly more participants in the riskankizumab arm achieved CDAI clinical response than those in the placebo arm (40.8% vs 25.2%, respectively; p<0.001).

In MOTIVATE, the co-primary endpoints of clinical remission (CDAI) and endoscopic response were met for the risankizumab 600 mg IV arm when compared with the placebo IV arm[21, 22]. At week 12, a significantly greater proportion of participants in the risankizumab 600 mg IV arm achieved the co-primary endpoint of CDAI clinical remission versus the placebo IV arm (42.0% vs 19.8%, respectively; p<0.001). At week 12, a statistically significantly greater proportion of participants in the risankizumab 600 mg IV arm achieved endoscopic response compared with the placebo IV arm (28.8% vs 11.2%, respectively; p<0.001). At week 4, significantly more

participants in the risankizumab arm achieved CDAI clinical response than those in the placebo arm (36.6% vs 20.9%, respectively; p=0.001).

In FORTIFY SS1, the co-primary endpoints of clinical remission (CDAI) and endoscopic response were met for the risankizumab 360 mg SC arms when compared with the SC placebo (withdrawal) arm according to the CSR[23] and primary publication[24] of this study (35.8% vs 15.9%, respectively; nominal p <0.001). The CS indicates that this result did not achieve statistical significance (NS) based on the pre-specified graphical testing procedure for the US-specific protocol, though the EAG noted the small nominal p-value. At week 52, a statistically significantly greater proportion of participants in the risankizumab 360 mg SC arm achieved CDAI clinical remission (as defined in Table 11) when compared to SC placebo (withdrawal) (52.2% vs 40.9%, respectively; p=0.005).

Among participants in FORTIFY SS1 who had CDAI clinical remission at week 0, a greater proportion in the risankizumab 360 mg SC arm achieved CDAI clinical remission at week 52 when compared to those re-randomised to SC placebo (withdrawal); however, statistical significance was not met according to the pre-defined testing procedure ([redacted] vs [redacted], respectively; nominal [redacted])

In FORTIFY SS1, a greater proportion of participants in the risankizumab 360 mg SC arm achieved SF remission at week 52 when compared to those receiving SC placebo (withdrawal); statistical significance was not met (57.0% vs 44.5%, respectively; nominal p=0.004). Similarly, a greater proportion of participants in the risankizumab 360 mg SC arm achieved AP remission at week 52 when compared to those receiving SC placebo (withdrawal), though statistical significance was also not reached (56.5% vs 46.3%, repesctively; nominal p=0.014).

A total of 29.1% of participants receiving risankizumab 360 mg SC achieved deep remission at week 52 of FORTIFY SS1 compared with 10.4% of those re-randomised to SC placebo (withdrawal) (difference of 18.8; nominal p<0.001). The CS indicates that this result did not achieve statistical significance (NS) based on the pre-specified graphical testing procedure for the US-specific protocol, though the EAG noted the small nominal p-value.

A total of 39% of participants treated with risankizumab 360 mg SC achieved endoscopic remission at week 52 of FORTIFY SS1 compared with 12.8% of those receiving SC placebo (withdrawal) (difference of [redacted]; nominal p<0.001). The CS indicates that this result did not

achieve statistical significance (NS) based on the pre-specified graphical testing procedure for the US-specific protocol, though the EAG noted the small nominal p-value.

As described in Appendix M.5.9. (p.383), participants entering FORTIFY SS1 who were treated with steroids (to a maximum of ≤20 mg/day prednisone or equivalent or ≤9 mg/day budesonide) were initiated on a mandatory steroid taper. Discontinuation of corticosteroid use in participants who were taking steroids at the baseline of ADVANCE or MOTIVATE is presented in Figure 18 of Appendix M.5.9. (p.384). The rates of steroid-free CDAI clinical remission were significantly higher with risankizumab 360 mg SC when compared to SC placebo (withdrawal) (vs , respectively; ; Figure 19, Appendix M.5.9., p.385); as were steroid-free SF/APS remission (vs , respectively; ; Figure 19, Appendix M.5.9., p.385), and steroid-free endoscopic remission (vs , respectively; ; Figure 20, Appendix M.5.9., p.385).

A greater proportion of participants who received risankizumab 360 mg SC in FORTIFY SS1 achieved CDAI clinical response at week 52, when compared to those receiving SC placebo (withdrawal) (61.6% vs 48.2%, respectively; nominal p=0.002). The CS indicates that this result did not achieve statistical significance (NS) based on the pre-specified graphical testing procedure for the US-specific protocol, though the EAG noted the small nominal p-value.

At week 52, a statistically significantly greater proportion of participants in the risankizumab 360 mg SC arm achieved endoscopic response (as defined in Table 11) when compared to SC placebo (withdrawal) (46.5% vs 22.0%, respectively; p<0.001). Rates of steroid-free endoscopic response were significantly higher with risankizumab 360 mg SC when compared to SC placebo (vs , respectively; ; Figure 20, Appendix M.5.9., p.385).

No relapse data were presented for any of the included studies.

Mucosal healing

No data for mucosal healing were presented in the CS, but were presented in data on file supplied in the company's reference pack. The proportions of participants with mucosal healing at week 12 on risankizumab 600 mg IV were in ADVANCE and in MOTIVATE, while on placebo IV it was in ADVANCE and in MOTIVATE. In the maintenance trial FORTIFY SS1, at week 52, these proportions were on risankizumab 360 mg SC and on SC placebo (withdrawal).

Surgery

No clinical data from the risankizumab trials are provided for surgery or colectomy in the CS or other supplied documents. The EAG noted that the CS stated that trial outcomes were reported according to the NICE scope, and its decision problem (Document B, Table 1) included surgery as an outcome. HRQoL and cost-effectiveness implications of surgery were factored into the economic model, though the EAG noted these values were based on Hospital Episode Statistics data, reported in a prior appraisal, as well as various assumptions.

Health-related quality of life

In ADVANCE, the risankizumab 600 mg IV arm was associated with statistically significant improvements in EQ-5D-5L at week 4 and week 12 compared with the placebo IV arm. For EQ-5D-5L Index Value scores, participants in the risankizumab 600 mg IV arm had a greater improvement from baseline (least squares [LS] mean) when compared with the placebo IV arm at week 4 ([redacted]) and week 12 ([redacted]). Similar results were observed for EQ-5D visual analogue scale (VAS) scores; participants in the risankizumab 600 mg IV arm had a greater improvement from baseline (LS mean) when compared with the placebo IV arm to week 4 ([redacted]) and week 12 ([redacted]).

In MOTIVATE, the risankizumab 600 mg IV arm was associated with statistically significant improvements in EQ-5D-5L from as early as week 4 and also at week 12 compared with the placebo IV arm. For the EQ-5D Index Value scores, participants in the risankizumab 600 mg IV arm had a greater improvement from baseline (LS mean) when compared with the placebo IV arm at week 4 ([redacted]) and week 12 ([redacted]).

In FORTIFY SS1, participants receiving risankizumab 360 mg SC had similar improvements in EQ-5D-5L Index Value scores from baseline of the induction study (LS mean from a mixed-effect model repeat measurement (MMRM)) to week 52 when compared to those receiving SC placebo (withdrawal). No significant differences in changes EQ-5D-5L Index Value scores from baseline to week 52 were found between these two trial arms ([redacted] vs [redacted], respectively; [redacted]). Participants receiving risankizumab 360 mg SC had a greater, but non-significant, improvement in EQ-5D-5L VAS scores from baseline of the induction study (LS mean from MMRM) to week 52 when compared to those receiving SC placebo (withdrawal). No significant

differences in changes EQ-5D-5L Index Value scores from baseline to week 52 were found between these two trial arms ([redacted] vs [redacted], respectively; [redacted]).

Participants receiving risankizumab 360 mg SC in FORTIFY SS1 had a numerically greater improvement in the Inflammatory Bowel Disease Questionnaire (IBDQ) total score from baseline of the induction study (LS mean from analysis of covariance (ANCOVA)) to week 52 when compared to those re-randomised to SC placebo (withdrawal); the difference in change from baseline between the two trial arms was not significant ([redacted] vs [redacted], respectively; [redacted]).

Similar changes were observed in the risankizumab 360 mg SC and SC placebo (withdrawal) arms of FORTIFY SS1 for the Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score with regards to change from baseline of the induction study (LS mean from ANCOVA) to week 52; the difference in change from baseline between the two trial arms was not significant ([redacted] vs [redacted], respectively; [redacted]).

Similar changes were observed in the risankizumab 360 mg SC and SC placebo (withdrawal) arms of FORTIFY SS1 for the Short Form 36-item health questionnaire (SF-36) physical component score with regards to change from baseline of the induction study (LS mean from ANCOVA) to week 52; the difference in change from baseline between the two trial arms was not significant ([redacted] vs [redacted], respectively; [redacted]).

Subgroup analyses

The company presented subgroup analysis (Appendix E) for participants who had prior TNF-alpha inhibitor failure and also for participants aged 16-17.

In ADVANCE, at week 12, a greater proportion of participants with prior TNF-alpha inhibitor failure, either participants who failed one inhibitor or those who failed >1 inhibitor, achieved CDAI clinical remission (CDAI <150) when compared with the placebo. The difference in response rate versus placebo was greater for participants who failed >1 inhibitor compared with those who failed 1 inhibitor ([redacted]% vs [redacted]%, respectively). Moreover, a greater proportion of participants with prior TNF-alpha inhibitor failure, either participants who failed one inhibitor or those who failed >1 inhibitor, achieved endoscopic response (decrease in SES-CD >50% from baseline [or for participants with isolated ileal disease and a baseline SES-CD of 4, ≥2-point reduction from baseline]) when compared with the placebo arm. The difference in response rate versus placebo was greater for participants who failed one inhibitor compared with those who failed >1 inhibitor ([redacted]% vs [redacted]%, respectively).

In MOTIVATE, at week 12, a greater proportion of participants with prior TNF-alpha inhibitor failure, either participants who failed one inhibitor or those who failed >1 inhibitor, achieved CDAI clinical remission (CDAI <150) when compared with the placebo arm. The difference in response rate versus placebo was greater for participants who failed one inhibitor compared with those who failed >1 inhibitor ([redacted]% vs [redacted]%, respectively). At week 12, a greater proportion of participants with prior TNF-alpha inhibitor failure, either participants who failed one inhibitor or those who failed >1 inhibitor, achieved endoscopic response (decrease in SES-CD >50% from baseline [or for participants with isolated ileal disease and a baseline SES-CD of 4, ≥2-point reduction from baseline]) when compared with the placebo arm. The difference in response rate versus placebo was greater for participants who failed >1 inhibitor compared with those who failed one inhibitor ([redacted]% vs [redacted]%, respectively).

In FORTIFY, at week 52, a greater proportion of participants with prior TNF-alpha inhibitor failure, either participants who failed one inhibitor or those who failed >1 inhibitor, achieved CDAI clinical remission (CDAI <150) when compared with the placebo arm. The difference in response rate versus placebo was similar for participants who failed one inhibitor compared with those who failed >1 inhibitor ([redacted]% vs [redacted]%, respectively). At week 52, a greater proportion of participants with prior TNF-alpha inhibitor failure, either participants who failed one inhibitor or those who failed >1 inhibitor, achieved endoscopic response (decrease in SES-CD >50% from baseline [or for participants with isolated ileal disease and a baseline SES-CD of 4, ≥2-point reduction from baseline]) when compared with the placebo arm. The difference in response rate versus placebo was marginally greater for participants who failed >1 inhibitor compared with those who failed one inhibitor ([redacted]% vs [redacted]%, respectively).

The company noted that there were low numbers of participants aged 16-17 in the included studies and cautions against drawing conclusions from the data. The EAG agreed that the subgroup analysis for participants aged 16-17, presented in Appendix E of the CS, does not offer robust results.

The company also presented analyses separated by Bio-IR vs Non-Bio-IR. These were presented in the main results section of the CS. However, the EAG presents these results in the subgroup analysis section, aligned with the decision problem.

In ADVANCE, CDAI clinical remission at week 12 was achieved by numerically more patients in the Non-Bio-IR group than the Bio-IR group (response rate difference vs placebo 25.8 vs 16.7, 95% CI 13.3, 38.3 vs 5.5, 27.8), although the confidence intervals overlapped. Similarly, there

was a numerically greater endoscopic response in the Non-Bio-IR group than the Bio-IR group (response rate difference vs placebo 37.7 vs 21.5, 95% CI 26.5, 48.8 vs 12.3, 30.7), although the confidence intervals overlapped. CDAI clinical response at week 12 was similar in the two groups (response rate difference vs placebo Bio-IR 24.2 vs Non-Bio-IR 21.7, 95% CI 12.4, 35.9 vs 8.2, 35.3). Endoscopic remission at week 12 was slightly higher numerically in the Non-Bio-IR group than the Bio-IR group (response rate difference vs placebo 17.9 vs 13.3, 95% CI 7.0, 28.8 vs 6.3, 20.3) and the confidence intervals overlapped.

In MOTIVATE, CDAI clinical remission at week 12 was numerically higher in those who had failed ≤1 prior biologics compared to those who failed >1 prior biologics (response rate difference vs placebo [redacted] vs [redacted], 95% CI 12.0, 38.4 vs 7.0, 31.7), although the confidence intervals overlapped. Endoscopic response at week 12 was slightly higher numerically in those who had failed ≤1 prior biologics compared to those who failed >1 prior biologics (response rate difference vs placebo [redacted] vs [redacted], 95% CI 7.6, 32.5 vs 5.5, 24.8) and the confidence intervals overlapped.

In FORTIFY sub-study 1, CDAI clinical remission at week 52 was numerically higher in the Bio-IR group than the Non-Bio-IR group (response rate difference vs placebo 12.7 vs 5.6, 95% CI -0.2, 25.6 vs -15.7, 26.9), while the confidence intervals overlapped. Endoscopic response was higher in the Non-Bio-IR group than the Bio-IR group (27.0 vs 23.4, 95% CI 6.3, 47.7 vs 11.4, 35.4).

Across studies, patients without prior biologic failure did better numerically, but the difference was not statistically significant with wide and overlapping confidence intervals indicating a lack of precision.

Adverse effects

Information on adverse events (AEs) is presented in the CS Section B.2.10. The EAG had no major concerns with the presentation of AE data.

The EAG agreed that risankizumab IV 600mg was generally well tolerated in both ADVANCE and MOTIVATE. The overall incidence of treatment-emergent adverse events (TEAEs) during the 12-week induction period was similar between the risankizumab 600 mg IV and placebo IV treatment arms (56.3% vs 56.5% in ADVANCE and 47.6% vs 66.2% in MOTIVATE). The rates of serious AEs (SAEs), severe AEs and AEs leading to discontinuation were numerically higher in the placebo IV arm than the risankizumab 600 mg IV arm. Two deaths occurred during

induction (ADVANCE), both of which were in the placebo IV arm. No deaths occurred in the risankizumab 600 mg IV arm.

The EAG agreed that risankizumab 360 mg SC as maintenance treatment for 1 year was generally well tolerated in FORTIFY sub-study 1. The incidence of TEAEs was 72.1% in the risankizumab 360 mg SC arm and 73.4% in the placebo SC (withdrawal) arm. The percentage of subjects with SAEs, severe AEs and AEs leading to discontinuation were comparable in risankizumab 360 mg SC and placebo SC (withdrawal) arms. There were no deaths reported during the maintenance study.

The EAG noted that publicly available information from clinical trial registries stated that an on-body injector was used for FORTIFY sub-study 4. This method of administration was not included in the CS, although the company stated that it intended that an on-body device would be intended to be used in clinical practice. It would be valuable to verify that this method of administration was covered in regulatory review.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company included 16 trials in its network meta-analyses (NMAs), covering a range of positions in the treatment pathway: this included nine induction, five maintenance and two induction/maintenance trials (CS Appendix D.1.3., Table 6). The CS included a summary of each (CS Appendix D.1.3.2). Most studies were multisite and international, though Watanabe (2012)[26] and Watanabe (2020)[27] were carried out in Japan only. Participants in included trials were CCF, BF or both (CS Appendix D.1.3.1.2., Table 9). The EAG noted that where trials presented findings for both CCF and BF, but did not stratify by these groups, they were reportedly excluded from analyses; however, it is not clear how many trials were excluded on this basis. A number of other exclusions are worth mentioning. One trial represented by two records was excluded on the basis of a treat-through design (i.e. without re-randomisation), and a further study was excluded on the basis of re-randomising based on remission rather than response. The EAG regarded that these exclusions were appropriate to reduce heterogeneity in the network.

Outcomes included in trials were CDAI remission and CDAI-100 response (CS Appendix D.1.3.1.2., Table 8). Doses varied as shown in CS Appendix D.1.3.1.1., Table 7; in particular, risankizumab doses are indicated as 600 mg IV for induction and 360 mg SC for maintenance.

The EAG presents two key domains for considering included trials: risk of bias of included trials, and differences across trials in design and patient population.

3.3.1. Risk of bias in included trials

The CS reported low risk of bias in all domains for included trials (CS Appendix D.3., Table 27), and largely acceptable assessments of trial quality (CS Appendix D.3., Table 26), the main limitation being several trials in which blinding was not achieved over all roles in the trial. The EAG was unable to independently replicate all assessments in the presented appraisals but noted that judgments relating to risk of bias domains followed from the presented judgments. There was no clear sign of imbalance across included treatments on risk of bias judgments.

3.3.2. Differences across trials in design and patient population

Included trials differ in a number of ways: these differences relate to design in terms of time of follow-up, and patient populations.

3.3.2.1. Time of follow-up

CS Appendix D.1.3.1.2., Table 9 details the week in which outcome data were collected for induction and maintenance. Maintenance outcome data were collected between week 44 and week 60, though networks were too sparse to comment on imbalance in time to follow-up. However, induction outcome data were collected between four and 12 weeks post-baseline. There is some evidence of imbalance in the distribution of follow-up times, with both risankizumab trials establishing post-induction outcomes at 12 weeks, while adalimumab and infliximab trials establish post-induction outcomes at four weeks. This variation is a potential source of heterogeneity, though the sparseness of networks precludes any formal meta-regression.

3.3.2.2. Patient populations

Another important way in which included trials differ is in included patient populations. The consequences of this are discussed below in Section 3.4.3 and 3.4.4. Trials varied across a range of effect modifiers. The company describes assessing included trials on the basis of these effect modifiers to establish transitivity of networks, and presented tabulated data relating to relevant effect modifiers in response to clarification question 12. The EAG regarded that there were no obvious sources of imbalance on the basis of these effect modifiers, which included

age, weight, duration of disease, CDAI score, inflammatory bowel disease questionnaire score, biomarkers and location of disease.

However, there were two important remaining sources of effect modification. The first is overall comparison group risk, which differed systematically by trial. This is important because imbalances in baseline risk across the network, which were evidence in included NMAs, creates likely effect modification. The second is that stratification by CCF and BF, while useful to distinguish between two clinically relevant subgroups, does not solve the issue of treatment history heterogeneity in the BF group. Specifically, the overall population implied by NMAs for the BF population would not strictly be at risk of every treatment of the network. This is because by definition, experiencing the failure of one biologic treatment suggests that not all subsequent treatments are appropriate treatment choices. The implication of this for NMA estimates is unclear, and the specific provenance of the BF subgroups in the analysis is unclear; that is, whether all trials contributing to the BF NMA defined the subgroup similarly.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

3.4.1. General approach

Analysis of NMAs was carried out in a Bayesian framework by two binomial methods: 'standard' logit link and risk-difference (RD). The binary outcomes assessed were CDAI clinical remission and CDAI-100 response (defined in Document B, Table 35). The former is an absolute measurement while the latter a change in score over baseline level: alternative analysis, treating these as ordinal measurements, is therefore not appropriate. In the RD case extra steps were required and taken to ensure risk estimates are bounded between [0,1] following Warn et al. (2002). In the view of the EAG, these binomial analyses are appropriate and, depending on circumstances, recommended by TSD2.

The company provided a copy of their NMA code: logit-link analysis was carried out with *bnma* package in R; baseline modelling and RD analysis with WinBugs (driven from R). Data and control parameters were not supplied initially, resulting in the EAG requesting complete code in clarification question A7. The code provided at following clarification appeared clear and well-programmed, although on attempting to run errors were encountered with undefined variables being referenced. Furthermore, the code as configured did not replicate the results used in the model without amendment.

The CS reported difficulties with the risk-adjusted logit link analyses (section B.2.9.3.1), and in clarification question A4 the company further explained that the adjusted logit-link random-effects (RE) model failed to converge, while in the adjusted logit-link fixed-effect (FE) model the regression term was not significantly different to zero (that is, an unadjusted model was not rejected). Given the problematic adjusted logit-link analysis, the company went on to argue that the RD analysis (which the EAG believes to be unadjusted) is preferred to the unadjusted logit-link analysis (B.2.9.3.1, CQ A4). The EAG is not aware of any strong rationale for or against this point of view. This is discussed further in Section 3.4.5.

Following this reasoning, the CS only gives NMA effect estimates for the RD approach. The estimated risk differences between treatment and placebo are combined with a baseline risk to give absolute risks under treatment (see Appendix P1.1. tables). These risks are inputs to the cost-effectiveness model.

The EAG found the CS somewhat unclear about why all parts of the reported analyses were not applied, where relevant, to each of the unadjusted and adjusted logit-link and the RD analyses. The EAG understands that only in the unadjusted logit-link analyses was there an assessment of consistency, and only for the logit-link model an attempt to adjust by regression for varying baseline risk.

In the CS, network nodes were defined by treatment and dose (e.g. ADA160/80 and ADA80/40 are separate nodes). The EAG agreed with this approach to setting up nodes, which is in line with the recommendations of Dias et al. (2018). Separate networks were used for CCF and BF subgroups (also referred to as non-Bio IR and Bio IR, respectively, in the trials) and induction and maintenance phases. The company further chose to separate the maintenance phase into two networks ‘based on biologic half-life, induction duration, and study heterogeneity’ (reported in Document B, Section B.2.9.1.4): risankizumab and ustekinumab vs TNFi (adalimumab and infliximab) and vedolizumab. The EAG was not convinced by this rationale and queried this decision; this is further covered in Section 3.4.6 below.

With respect to between-trial heterogeneity, an FE framework was used in the company base case and an RE model in a scenario analysis. The company argued that the FE model was preferred given similar deviance information criterion (DIC) values with the RE models and for ease of interpretation. In clarification question A5 the company further explained that under an RE model credible intervals included values that favoured placebo over biologics, and the company concluded that the RE model therefore lacked face validity. The EAG disagrees,

however, that an RE model should have been discarded given the manifest heterogeneity in the analysis, noting that informative priors should have been considered to produce more plausible results.

The CS presents results for logit-link FE NMAs compared with an inconsistency ('Unrelated Mean Effects') model in the CS (Document B, Tables 44 and 45). The differences in residual deviance where available are small (<1) implying no evidence of inconsistency, though there are few loops in the networks to do so. The EAG further notes that the residual deviances are of similar magnitude to the number of data points, indicating an acceptable model fit.

NMAs are susceptible to bias when there is variation in effect modifiers across the network. The CS lists potential effect modifiers, and the company supplied a summary of these in clarification. Some potential effect modifiers were controlled by design (for example, all trials used outcomes on the CDAI scale). The EAG believes that potentially the most problematic are variations in previous treatments between trials and associated differences in patient populations. Section 3.4.4 contains further discussion of effect modification. The CS indicated that an adjustment was made for baseline risk, where baseline risk was a proxy for an unspecified set of effect modifiers. The EAG agreed that this step could help protect against bias, but concluded that it was not carried out in the RD NMAs (see section 3.4.5 below for further discussion).

3.4.2. NMA results

The CS presents results for the company's base case network configuration RD model with FE in Document B and with RE in Appendix P1.2. These results are discussed in the induction setting below. For the maintenance setting, the EAG preferred a different network configuration; these results were presented in clarification response. As per the CS, 'significance' denotes credible intervals not crossing zero.

3.4.2.1. Induction

CS results in Document B were provided as RDs. In the following text, the EAG used a RD threshold of [redacted] as an indication of 'substantial' magnitude (unrounded figures will be found in the tables) with the strong caveat that precision of the estimates is generally low.

Under induction, risankizumab and most comparator drugs showed statistically significant improvement over placebo with substantial point RDs. In the BF subgroup, risankizumab was substantially favoured (i.e. with point magnitude RD [redacted]) over three of four comparators, with evidence of a statistical difference for two of these (VDZ300 and UST6) but not for ADA80/40. In

the CCF subgroup, there was not statistical evidence of a difference between risankizumab and any comparators, though several point magnitudes were substantial, favouring risankizumab over VDZ300 and ADA80/40, but favouring IFX5 over risankizumab.

Table 12: Summary of treatment effect estimates (RD) with CrIs under induction on CDAI remission of risankizumab versus comparators from FE NMA

	CCF[a]	BF[b]
	RZB600	**RZB600**
PBO	[redacted]	[redacted]
ADA80/40	[redacted]	[redacted]
VDZ300	[redacted]	[redacted]
UST6	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]
IFX5	[redacted]	NA

Abbreviations: ADA, adalimumab; BF, biologic care failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CrI, credible interval; FE, fixed effect; IFX, infliximab; NA, not applicable; NMA, network meta-analysis; PBO, placebo; RD, risk difference; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

Sources: CS Document B, [a] Table 36; [b] Table 37

NMA results comparing risankizumab against comparators for CDAI-100 over induction under the FE model are shown in Table 13. These results were extracted from full tables in the CS. The RD estimates significantly favoured risankizumab over placebo in both CCF and BF subgroups, with substantial point magnitude in both. In BF, risankizumab was significantly favoured, with substantial point magnitudes, over all but one (ADA80/40) of its comparators. In CCF, differences from other comparators were not statistically significant, but point magnitudes were approaching substantial in one case, favouring risankizumab over VDZ300.

Results for the RD models with RE rather than FE are given in CS Appendix P.1. Confidence intervals were wider and point estimates similar, as anticipated.

Table 13: Summary of treatment effect estimates (RD) with CrIs on CDAI-100 clinical response of risankizumab versus comparators from FE NMA over induction

	BF[a]	CCF[b]
	RZB600	**RZB600**
PBO	[redacted]	[redacted]
VDZ300	[redacted]	[redacted]
UST6	[redacted]	[redacted]

	BF[a]	CCF[b]
ADA160/80	[redacted]	[redacted]
ADA80/40	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic care failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CrI, credible intervals; FE, fixed effect; NMA, network meta-analysis; PBO, placebo; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

Sources: CS Document B, [a] Table 39; [b] Table 38

3.4.2.2. Maintenance

The NMA results for reconfigured maintenance networks were provided in the response to clarification question A15. The EAG preference is for a single maintenance network (issue detailed in Section 3.4.6). The single network results for CDAI remission in CCF and BF populations are reproduced here in Table 14 and Table 15, respectively. Note these results were received as absolute risks, whereas the induction results (Section 3.4.2.1) are risk differences.

Table 14 : Single maintenance NMA network results for CDAI remission: CCF population

Treatment	Median	Lower CrI	Upper CrI
ADA 40 QW	[redacted]	[redacted]	[redacted]
ADA 40 Q2W	[redacted]	[redacted]	[redacted]
IFX 5/10 Q8W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]
IFX5 Q8W	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]
RZB Q8W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CCF, conventional care failure; CrI, credible interval; IFX, infliximab; IV, intravenous; PBO, placebo; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab

Source: Company clarification response, Table 24

Table 15: Single maintenance NMA network results for CDAI remission: BF population

Treatment	Median	Lower CrI	Upper CrI
ADA 40 QW	[redacted]	[redacted]	[redacted]
ADA 40 Q2W	[redacted]	[redacted]	[redacted]

Treatment	Median	Lower CrI	Upper CrI
VDZ SC Q2W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
RZB Q8W	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biologic failure; CrI, credible interval; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Source: Company clarification response, Table 25

Remission on risankizumab is relatively low among the comparators in CCF ([redacted]) and in BF ([redacted]). Adalimumab has the highest median remission rates in both CCF and BF, and is the only treatment significantly better than placebo regardless of dose. All comparators perform better than placebo, though the difference is not always significant.

3.4.3. Baseline risk

The company modelled *'the reference treatment (placebo in all instances) …using a baseline natural history model that was constructed independently from the model of relative treatment effects'* (D1.3.3.10). The EAG agrees that the separation of modelling is as advised by TSD5.

The EAG consulted a clinician on whether or how the trial placebo arm mapped to a pathway/health state in UK clinical practice. The trial concept of placebo is active treatment withheld for the duration of the trial or withheld altogether. Clinical advice to the EAG was that withholding/delaying comparator treatments to risankizumab would be an unsatisfactory clinical practice usually only necessitated when patients are seriously ill or steroid-dependent. Also, in clinical practice, if patients did not respond overall to any of the comparator drugs they are not returned to standard care, but alternative strategies are sought (new drugs via trials, repeat TNFis or combinations of drugs). Further details on trials for comparator drugs were provided in CS Appendix D1.3.2 – this seems to indicate that patients were generally permitted concomitant medication (aminosalicylates, immunomodulators, corticosteroids, antibiotics).

Because there is no real-world 'placebo' treatment and because trial placebo arm participants generally receive conventional care medicines, the EAG believes that trial control arms, as

opposed to observational studies, are the most likely and perhaps only source of data for baseline risk, as has been used in the CS.

The posterior baseline risks estimated by the company model are summarised in Table 16. In each case, the placebo arms of every trial in the NMA contribute data for these estimates. The question arises whether a subset of these trials would give better a representation of UK clinical practice. For example, the trials by Watanabe et al (2012) [26]and (2020) [27]were carried out in Japan only.

The trial-level proportion of patients in response or remission are shown in Figure 2, based on data supplied at clarification (CQ A7). Apart from CDAI-remission at maintenance, there is considerable variation. The CS base case approach used a FE model (Appendix D D1.3.3.10), but with this level of heterogeneity the EAG prefers a RE model.

Table 16: Placebo response rates collated by EAG

Comparators in network	Treatment phase	Population	Outcome	Estimate of % attaining outcome under 'placebo'	CrI
RZB, UST, ADA, IFX, VDZ, PBO	Induction	CCF	CDAI remission	[redacted]	[redacted]
		BF		[redacted]	[redacted]
		CCF	CDAI-100 response	[redacted]	[redacted]
		BF		[redacted]	[redacted]
RZB, UST, PBO	Maintenance	CCF	CDAI remission	[redacted]	[redacted]
		BF		[redacted]	[redacted]
ADA, IFX, VDZ, PBO	Maintenance	CCF	CDAI remission	[redacted]	[redacted]
		BF		[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF: biologic failure; CCF, conventional care failure; CrI, credible interval; IFX, infliximab; PBO, placebo; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab

Sources: Tables 113-120, Appendix P.1.1.

Arguments regarding placebo heterogeneity, in particular in the maintenance trial data, are not convincing, and the use of two different proportions reaching remission according to comparators under consideration is problematic. The maintenance trial data shown in Figure 2 have been supplemented with the trial start date (sourced from www.clinicaltrials.gov) for both the biologic failure and conventional care failure subgroups and illustrated in Figure 3 and

Figure 4 respectively. Both figures suggest that the observed heterogeneity can be largely attributed to a temporal effect, with improvements in available concomitant treatment options. Such a model is preferred for estimation of a single maintenance placebo remission proportion at a suitable timepoint, which would be the basis for absolute estimates for use in the cost-effectiveness model generated in combination with relative effects estimated from a single maintenance network.

Figure 2: Proportion responding or remitting in the placebo arm of each trial in the NMAs (EAG plot).

Abbreviations: BF, biologic failure; CCF, conventional care failure; IND, induction; MAINT, maintenance
Sources: Data supplied in company's response to clarification questions A7

Figure 3: Proportion of placebo arm patients achieving remission following biologic failure (EAG plot)

Abbreviations: BF: Biologic failure
Sources: Data supplied in company's response to clarification questions A7; www.clinicaltrials.gov

Figure 4: Proportion of placebo arm patients achieving remission following conventional care failure (EAG plot)

Abbreviations: CCF: Conventional care failure
Sources: Data supplied in company's response to clarification questions A7; www.clinicaltrials.gov

3.4.4. Effect modifiers

Differences in effect modifiers across trials can lead to bias in NMA estimates. The CS identified potential effect modifiers in Appendix D (pp.56-57).

Some potential effect modifiers were addressed with varying success by the design of the NMAs: the outcomes scale was homogeneous (CDAI used throughout); CCF vs BF subgroups were analysed separately; and follow-up periods were at some variance: between 4 and 12 weeks for induction studies and, more consistently, between 44 and 60 weeks for maintenance studies (App D Table 9). The separate analysis of CCF and BF patients in the CS has the effect of creating a crude subgrouping by prior treatment. Nevertheless, CCF may have included patients who had biologic treatment in the past and stopped for reasons other than inadequate response/failure (Appendix D1.3.3.3). BF patients will have received one or more biologics

previously and had inadequate response/treatment failure, but the line of treatment and their composition may be heterogeneous.

Maintenance trial study design was a potential effect modifier, but in all included maintenance trials, patients were randomised at maintenance (and perhaps also at induction). Another design potentially applied in maintenance trials is a 'treat-through' design in which patients are randomised prior to induction only: this was excluded by the company's SLR (Appendix D Table 5, records 226-227), resulting in exclusion of 2 records, both reporting on the SEAVUE trial comparing adalimumab and ustekinumab. In most of the maintenance trials, the participants were responders to induction treatment. In the CHARM study all patients, regardless of response, were randomized to one of three maintenance treatment groups (adalimumab 40 mg Q2W, adalimumab 40 mg QW, or placebo) for an additional 52 weeks following a 4-week induction phase; however, randomisation was stratified by response status at week 4. The EAG also noted the exclusion of the CLASSIC II trial, where participants were re-randomised based on clinical remission instead of response. Overall this aspect of design heterogeneity was judged by the EAG to be well-controlled by the company's SLR and exclusions were considered to reduce heterogeneity and intransitivity in the NMA.

Trial-level values of potential effect modifiers were supplied in response to CQ A12 (Tables 9-14). The EAG observed consistency in a number of the variables, including weight (usually averaging around 70 kg, though a study in Japan (Watanabe et al 2012) [26] was clearly different averaging around 55 kg), and age (averaging 30 to 40 years). Clinical advice to the EAG suggested that age, duration of disease, C-reactive protein (CRP) and gastrointestinal areas involved are effect modifiers for response to treatment. Of these, most showed considerable variability: duration of disease ranged 4.4 to 12.7 years; CRP levels from 7.8 to 30 mg/L; ileal involvement from 9 to 75%; colonic involvement from 14 to 68% and ileo-colonic involvement from 9 to 70%. Only age was considered to be homogeneous enough to have limited implications for effect modification.

Prior treatment was by necessity recorded only crudely in the summary tables, but appeared to be rather variable. There is also variability in the exclusion criteria of the NMA trials (see D1.3.2): for example, CLASSIC excludes patients if TNFi previously received, while GEMINI2 excludes patients previously on vedolizumab, natalizumab, efalizumab or rituximab. In the summary tables a division is clearly seen between trials with no history or no failures of TNFi

recorded as zero or perhaps NR, perhaps due to exclusion criteria (e.g. ACCENT 1), and others with counts over zero.

An example of variation in prior treatment history across a network is seen when comparing RZB with placebo with ustekinumab (Document B, Figure 8). Patients previously receiving IL-12 or IL-23 antagonists in the IM-UNITI trials were excluded, while in contrast up to 20% patients entering induction via the ADVANCE and MOTIVATE trials and prior to the maintenance period of the FORTIFY trial might receive ustekinumab, an IL-23/IL-12 inhibitor.

3.4.5. Adjustment for baseline risk

The analysis of the CS aims to adjust for risk in the placebo arm (D1.3.3.6), this acting as a proxy for the combined influence of known and unknown effect modifiers. The EAG agrees with this aim, because the baseline risk is a logical proxy and because it is known to be heterogeneous (see Figure 2, Section 3.4.3).

The logit-link NMA adjusted for baseline-risk using 'standard' code supplied by Dias et al/TSDs (coded in R with package '*bnma*'). The baseline-risk adjusted model for logit-link contains a coefficient to represent a linear change in risk with trial-level difference from overall average (treatment x covariate interaction, with baseline risk as the covariate). This regression term is coded for using the *bnma* package, and also referred to in Appendix D1.3.3.6, equation 6, with respect to the logit-link analysis. The CS indicated the use of a 'common baseline' model as a response to the sparsity of the network (CQ A6) – the EAG accepts this reasoning.

No analogous regression modelling of baseline risk appears to have been used in the risk difference model. The EAG believes the RD model *does not* adjust for baseline risk, because there is no regression term of a form similar to beta * (x – mx) (see Dias 2018- [28] p243 ff.) in the company RD code. The CS argues (B.2.9.3.1) *'absolute probabilities of treatment response were subtracted across interventions in RD models, minimising potential impacts of overly low or high placebo efficacy. This may help minimise bias when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network'.* The EAG agrees that RD model *does account* for differences in baseline risk in the usual way because there is an uninformative prior on baseline risk, but it *does not adjust* for baseline risk via meta-regression.

The CS indicates that *"The NMAs used in this submission utilised the RD method, which was used in this instance as it is recommended where baseline risk-adjusted models are deemed*

inappropriate due to lack of convergence or face validity" referring to TSD2. The EAG was not able to locate this recommendation in TSD2, though it is a logical response to the difficulties. Additionally, CS section B.2.9.3.1 says *"TA521 concluded that baseline-risk adjusted models and risk difference NMAs should yield less biased estimates of effect than the unadjusted NMA analyses on the relative scale"*. The EAG identified the following passage in TA521 that makes the following argument*: "We also presented an alternative approach to adjust for cross-trial differences using risk differences, as opposed to relative effects. Rather than divide by low placebo response rates, which inflate relative effects, differences in absolute probabilities across treatments are subtracted (i.e., treated as risk differences). This may help minimize bias when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network*." (response to clarification 7(f), Committee Papers pp196-197). The EAG did not find this argument wholly persuasive, since the logit-link transforms to a linear scale in which treatments effects are also additive. The EAG accepts the company point that in the comparison of RD versus logit-link results on an OR scale presented in response to clarification question A10, there are some 'extreme' variances for logit-link estimates on the OR scale, though the EAG also notes that the RD variances can also be very large (e.g. IFX IV vs PBO [redacted], clarification question response, Table 2).

The EAG concludes that both logit-link and RD models take account of varying baseline risk in the standard way, with the inclusion of modelling terms for the control arm risk and accompanying uninformative priors. However, while *adjusting* for baseline-risk as a proxy for various effect modifiers would be desirable, this adjustment has *not* been included in the company's base case RD model. Baseline-risk adjustment *was* carried out using the logit-link model (D.1.3.3.6) but analysis was problematic (B2.9.3.1 and CQ A4 and A10) and not reported in the CS.

3.4.6. Separation of maintenance network

The CS separated the maintenance evidence into two networks risankizumab/ustekinumab vs adalimumab/infliximab/vedolizumab) *'based on biologic half-life, induction duration, and study heterogeneity'* (B2.9.1.4). The EAG disagrees with this approach in general because network formation is recommended on the basis of comparator connections (Dias et al 2018, section 1.6.1), not drug characteristics. On top of this, the EAG noted in clarification question A15 the similarity in the half-life and induction period between vedolizumab and ustekinumab, and that they are seen as similar therapy options.

In response to clarification question A15 the company argue that vedolizumab has a different biological mechanism to IL inhibitors, ustekinumab and risankizumab, and is therefore not appropriate to include in that network. The EAG finds the argument inconsistent because the alternative network is made up of the TNFis, infliximab and adalimumab, which also have different biological mechanism.

In clarification question A15 and CS B2.9.3.2 the company argues that their chosen separation of the networks, grouping vedolizumab with adalimumab and infliximab, mitigates placebo arm heterogeneity. However, the EAG notes from the data plotted in Figure 2 that the placebo arm remission rate for the VISIBLE2 trial (VDZ vs PBO) is actually rather high, and closer to placebo rates in FORTIFY (RZB vs PBO) and IM-UNITI (UST vs PBO). The EAG considered this lack of placebo arm dissimilarity as further evidence that the networks should be combined.

A final argument made by the company in favour of its base case separated networks is that "*the single maintenance NMA network does not stand up to basic face validity as the outputs suggest that in some cases placebo is more effective than ustekinumab, vedolizumab and risankizumab; this observation goes against the results presented in the Phase 3 clinical trials of the respective biologic therapies"*. The EAG noted that the company's preferred NMA base case, comprising two disconnected networks, also had cases where active treatments were not significantly better than placebo. It considered that this, by the company's reasoning, also lacks face validity when compared to individual trial results. As such, the EAG considered these findings for both the disconnected and combined network to be methodologically driven, and not an issue of face validity.

The EAG requested (clarification question A15) further analyses (1) grouping vedolizumab in the network with risankizumab and ustekinumab instead of the TNFis, and (2) grouping all treatments (TNFis, vedolizumab, ustekinumab and risankizumab) together in a single network. The single-network results are outlined in 3.4.2.2 and forms the EAG's preferred base case.

3.5. Additional work on clinical effectiveness undertaken by the EAG

None.

3.6. Conclusions of the clinical effectiveness section

The EAG considered that the company's SLR had generally been conducted adequately, although certain limitations were noted, particularly with regard to the assessment of risk of bias. The company's decision problem generally aligned with the NICE scope, but the EAG noted in

particular that subgroup analysis by CD location had been excluded from the company decision problem. The EAG did not consider that this exclusion was suitably justified. The EAG also noted that no results were presented for surgical outcomes. The EAG considered that generally the company's SLR and included trials were adequately described, although certain information was not described in sufficient detail.

Three clinical trials were included in the CS. There were two phase 3 multicentre, randomised placebo-controlled induction trials (ADVANCE and MOTIVATE) plus one Phase 3, multi-centre, partially randomised, double-blind, placebo-controlled, 52-week maintenance study with an ongoing open-label extension (FORTIFY). Only sub-study one from FORTIFY was included in the CS. In ADVANCE and MOTIVATE, riskankizumab was administered intravenously 600 mg or 1200 mg Q4W by a clinician. In FORTIFY sub-study one, risankizumab was administered subcutaneously 360 mg Q8W or 180 mg Q8W by a clinician. The EAG noted that the proposed method of administration for clinical practice using an on-body device differed from the method of administration used in the included trials. However, publicly available information from clinical trials registries stated that an on-body injector was used in FORTIFY sub-study four, which was not used in the CS. No studies in the CS directly compared riskankizumab with any scoped comparators. The EAG was satisfied that based on the included trials in the CS there was evidence for a benefit for risankizumab against placebo for remission, response, mucosal healing and health-related quality of life.

NMA methods were broadly appropriate, though the EAG regarded that RE models would have been more suitable, and highlighted challenges with the body of evidence (prior history of treatments, baseline risk) that challenge interpretation of analysis. The EAG considered the use of a single, connected maintenance network to be preferable to the split networks provided as the company base case NMA, as it was unconvinced by the company's clinical rationale for splitting the network. In induction meta-analyses, risankizumab was not significantly better than any other active comparator for remission in the CCF population, though risankizumab was numerically superior to most. In the BF population, risankizumab was numerically superior to all comparators and significantly better than several of them. In the maintenance meta-analyses of the connected network, risankizumab was numerically superior only to placebo in the CCF population and only placebo and ustekinumab Q12W in the BF population for remission; it was not significantly better than any comparator in either of these populations.

The EAG considered the methods used to assess the quality of the three risankizumab trials (ADVANCE, MOTIVATE and FORTIFY), as well as trials included in NMA, to be an appropriate selection of methodological approach. However, the application of the Cochrane risk of bias tool was considered to have limitations (see Section 3.2.2.6). The EAG noted that these may have altered the overall risk of bias of assessed trials, though the impact was judged to be minimal since no approaches assessing the robustness of effectiveness results (e.g. sensitivity analyses) were informed by methodological quality of the included trials. In terms of specific trial-level judgments the EAG was mostly in agreement with the company's appraisal, though it disagreed with the assessment of risk of bias related to blinding for ADVANCE and MOTIVATE and considered that attrition may also have been of concern for these induction trials; it also flagged uncertainty around the judgment of attrition bias in FORTIFY. The EAG did not assess quality assessments of other trials included in the NMA independently (see Section 3.3.1).

The following clinical effectiveness key issues were identified:

- Unexplored heterogeneity in network meta-analyses in relation to baseline risk
- Network structure in maintenance network meta-analyses should be connected

Additionally, the EAG considered that the following key issues also had relevance to the clinical effectiveness evidence:

- Feasibility of exploratory subgroup analysis by CD location (decision problem key issue)
- Method of administration for risankizumab (other key issue)

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

Appendices G, H and I of the CS detail systematic searches of the literature used to identify cost effectiveness, health-related quality of life, healthcare resource use and costs evidence, critique is provided in Table 17, Table 18, and Table 19. Searches and eligibility criteria were appropriate and therefore it is unlikely that relevant studies were missed.

Table 17. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix G, Table 40.	The company literature search appears to be well conducted. The cost effectiveness filter that was used does not appear to be a tested filter;[29] this makes the effectiveness of the search uncertain and it is possible that some relevant papers may have been missed.
Inclusion criteria	Appendix G, Table 41	The inclusion criteria were broad and therefore likely to have captured the available evidence. The company included a total of 69 studies of which seven analyses were relevant to the UK.[30-36] A summary was provide in Table 55 of the CS (Document B). None of the identified cost-effectiveness analyses evaluated Risankizumab. The company made reference to two previous NICE technology appraisals – TA352 and TA456.
Screening	Appendix G, Section G.1.2	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by the two reviewers and disagreements resolved in the same way.
Data extraction	Appendix G, Section G.1.2	Data extraction was completed by one reviewer with a senior reviewer checking the extraction and disagreements resolved through discussion.
QA of included studies	Appendix G, Section G.2	The methodological quality of included full text publications was assessed using the Drummond checklist for cost-effectiveness studies.[37]

Abbreviations: CS, Company Submission; EAG, Evidence Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 18. Summary of EAG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix H, Table 46.	The company literature search appears to be well conducted and a good range of sources were searched.
Inclusion criteria	Appendix H, Table 47	The inclusion criteria were broad and therefore likely to have captured the available evidence. A total of 142 studies (reported in 204 publications) were included. The majority of studies were conducted in US, Canada, EU-5, Australia and Japan, and were selected for data extraction. The remaining studies were not extracted as the geography was not relevant.
Screening	Appendix H, Section H.1.2	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by the two reviewers and disagreements resolved in the same way.
Data extraction	Appendix H, Section H.1.2	Data extraction was completed by one reviewer with a senior reviewer checking the extraction and disagreements resolved through discussion.
QA of included studies	Appendix H, Section H.2	The methodological quality assessment for utility studies was performed using the NICE checklist, while the quality assessment for HRQoL studies was performed using the Efficace checklist.[38]

Abbreviations: CS, Company Submission; EAG, Evidence Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 19. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix I.1	The company literature search appears to be well conducted and a good range of sources were searched. The same literature search strategy was used for the cost effectiveness searches, see Table 17
Inclusion criteria	Criteria reported in Appendix G, Table 41 – healthcare resource use and cost outcomes were collected in the review for economic evaluations	The inclusion criteria were broad and therefore likely to have captured the available evidence. A total of 91 studies (91 records), were included that reported cost and healthcare resource use (HCRU) outcomes relevant to the UK were identified. A total of 14 records were found to be relevant to the UK.[30, 39-51]

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Screening	Referred to Appendix G, Section G.1.2	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by the two reviewers and disagreements resolved in the same way.
Data extraction	Referred to Appendix G, Section G.1.2	Data extraction was completed by one reviewer with a senior reviewer checking the extraction and disagreements resolved through discussion.
QA of included studies	Referred to Appendix G, Section G.2	The methodological quality of included full text publications was assessed using the Drummond checklist for cost-effectiveness studies.[37]

Abbreviations: CS, Company Submission; EAG, Evidence Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 20: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓ Not explicitly stated in the company submission
Perspective on costs	NHS and PSS	✓ The company presented a non-reference case scenario analysis including societal costs
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	✓ No comments
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓ A lifetime horizon is suitable for decision making, owing to plausibly lifetime implications of the intervention upon patient health outcomes and NHS and PSS costs
Synthesis of evidence on health effects	Based on systematic review	✓ No comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	✓ No comments

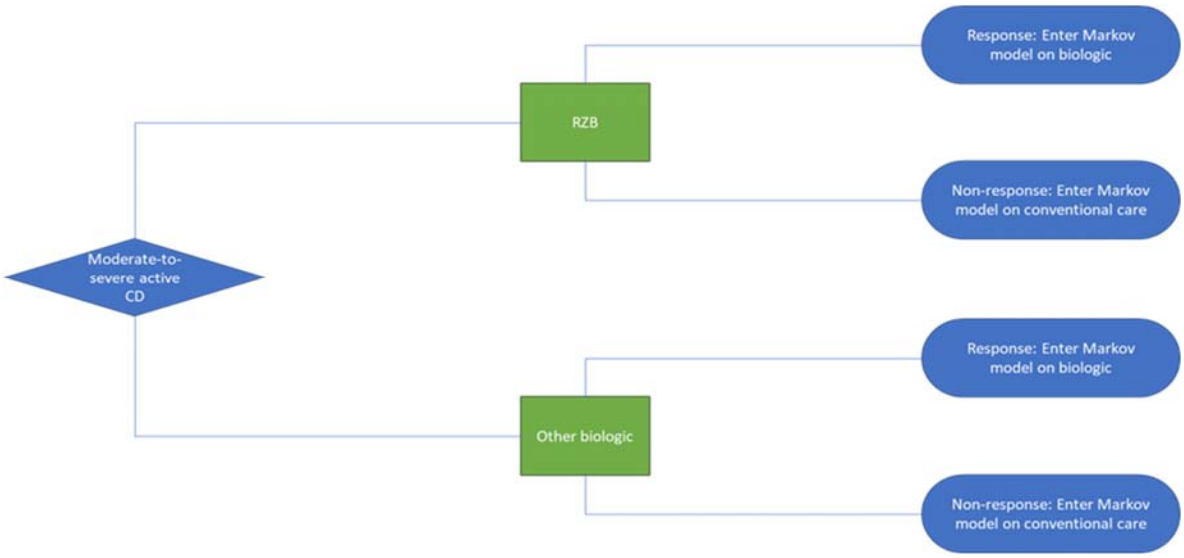
Attribute	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	✓ No comments
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	✓ No comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓ No comments
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✓ No comments
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ No comments

Key: CD, Crohn's disease; EQ-5D, EuroQol 5 dimension; HRQoL, health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal
Note(s):
Source(s):

4.2.2. Model structure

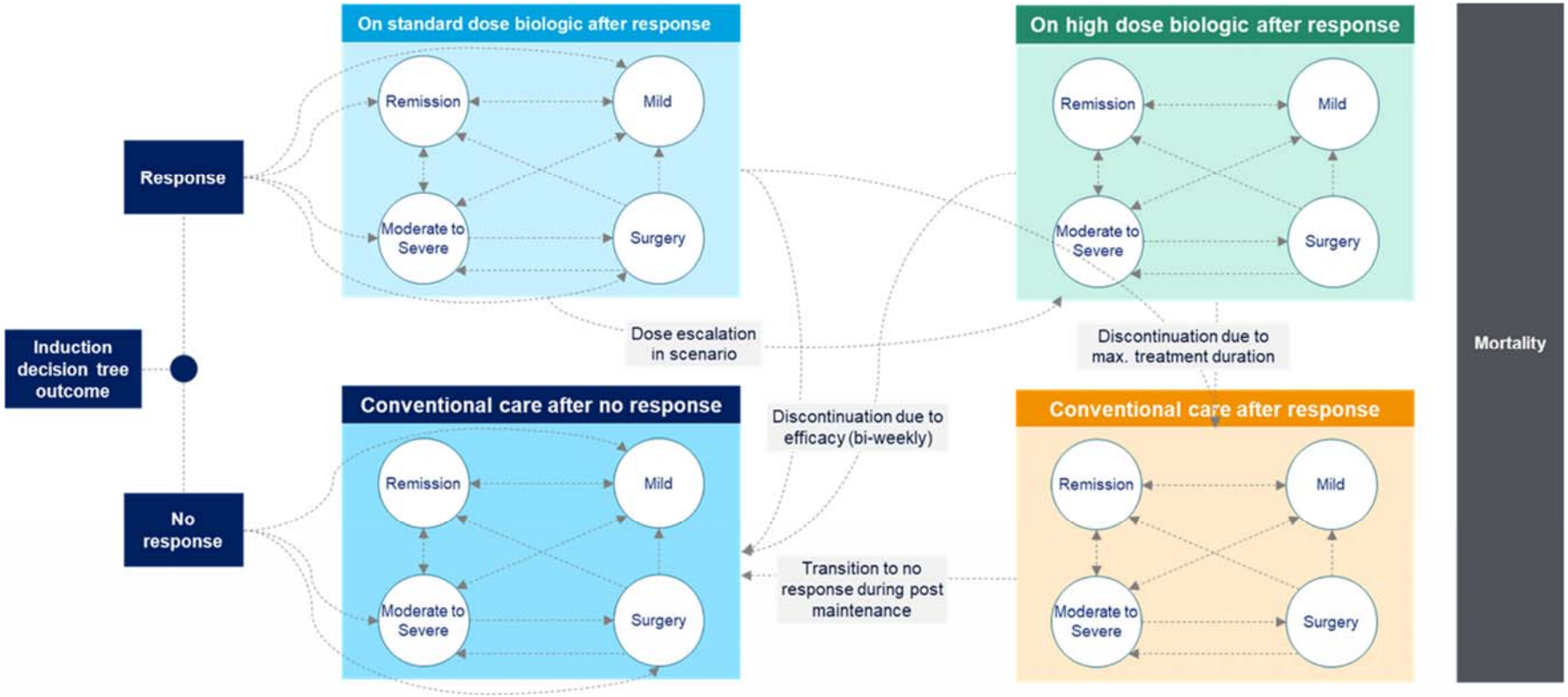
The company's *de novo* economic analysis comprises a cohort-level model developed in Microsoft Excel®, consisting of two distinct phases: i) a decision tree reflecting a short-term induction treatment phase (Figure 5), and ii) a Markov model (as described by the company) representing long-term maintenance treatment and post-maintenance phases.

Figure 5: Company's decision tree model structure diagram (CS Figure 12)



Key: CD, Crohn's disease; CS, company submission; RZB, risankizumab.
Note (CS Figure 12): Squares represent decision nodes, circles are chance nodes, and triangles are termini of the decision tree. The baseline of the induction trials is aligned with the model baseline, which occurs at the first square (decision node) on the left in the figure above.

Figure 6: Company's Markov model structure diagram (CS Figure 13)



Key: CS, company submission.
Note (CS Figure 13): Patients may remain in the health state in which they began a cycle. Surgery includes one surgical (2 weeks) and three post-surgical tunnel (6 weeks) states, such that a surgical episode lasts 8 weeks. Patients may transition to death at any time. Dose escalation in the base case only affects patient biologic costs; patients do not transition to the high-dose matrix as they have failed standard-dose treatment and therefore escalate to achieve standard-dose efficacy.

Patients with moderately to severely active CD enter model via the decision tree, where they receive treatment with risankizumab or comparator biologic therapy (described in Section 4.2.4). The length of the decision-tree differs by treatment arm, depending on the duration of induction treatment and response assessment for each biologic therapy. Efficacy outcomes are assessed at the end of the induction period; at the end of the decision tree, patients enter the Markov model either as responders on biologic treatment or as non-responders on conventional care.

Response at the end of the induction phase is defined in the company's economic analysis as a ≥100-point drop in CDAI score from baseline to end of induction (CR-100). The proportion assumed to achieve induction response is based on selected results from the company's NMA (described in Section 3.4, and discussed further in Section 4.2.6). The EAG notes that the abbreviations "CDAI-100" and "CR-100" appear to be used interchangeably throughout the CS; the EAG understand both CDAI-100 and CR-100 to refer to response determined by a ≥100-point drop in CDAI score from baseline to end of induction.

The company note that different definitions of response were used across trials in the network but justify their use of the CDAI-100 criterium as "a similar approach" (CS, B.3.2.2.1) was taken in the two most recent NICE appraisals in moderately to severely active CD, TA456 (ustekinumab) and TA352 (vedolizumab). The company present a scenario analysis (company scenario #7) in which a ≥70-point drop in CDAI score from baseline (CDAI-70) is used to define response, though no rationale or explanation of the relative merits of CDAI-70 versus CDAI-100 are provided. Importantly, as noted in 3.2.2.5, the EAG's clinical adviser has highlighted that CDAI score is not used in NHS clinical practice for the management of CD, owing to its overcomplicated nature and poor correlation with endoscopy. Instead, the Harvey Bradshaw Index and endoscopic response are used. The company justifies the use of CDAI-100 as a key outcome in their analysis based on its common use as an outcome across CD trials. The company acknowledges that "an NMA performed using endoscopic outcomes would potentially be more relevant to UK clinical practice" (CS, B.3.7.4), but explain their approach in the context of limited endoscopic data, which the company state was only available for risankizumab and ustekinumab overall populations.

At the end of the induction phase, all patients move to the long-term Markov model, which is characterized by CDAI-based health states and the need for surgery. The model structure adopted by the company is based on that presented by Bodger et al. (2009) [30], variants of which were used in TA456 and TA352. The long-term model health states are defined as follows:

- Remission (CDAI <150)
- Mild CD (150 ≤ CDAI <220)
- Moderate to severe CD (220 ≤ CDAI <600)
- Surgery (comprising one surgery model cycle and three post-surgery model cycles)
- Death

The company selected a 2-week cycle length for the long-term model in their analysis. The choice of cycle length was not justified in the company submission; however, the EAG consider a 2-week cycle length short enough to adequately capture the available data.

Each model cycle, patients can remain in their current health state, transition to another CDAI-based health state or experience death (which is an absorbing state). The company's economic model assumes that only patients in the 'moderate to severe CD' health state can experience surgery. Patients who experience surgery remain in the 'surgery' health state for one model cycle (2 weeks), and post-surgery tunnel states for three model cycles (6 weeks), after which patients return to a CDAI-based health state.

The company's economic analysis assumes that the mortality rate of patients with CD is equivalent to that of the age- and sex-matched general population (based on Office for National Statistics [ONS] 2018-20 national life table data for the UK). Consequently, the company's analysis assumes that mortality is not dependent on CDAI score, nor affected by treatment. Clinical advice to the EAG suggests that CD is not generally considered a life-shortening disease, and that it is reasonable to assume that patients with CD have equivalent survival to the general population. However, published evidence identified by the EAG is indicative of a heightened mortality risk for CD patients versus the general population, including risk related to higher rates of colorectal-cancer, pulmonary disease, and nonalcoholic liver disease.[52]

The company describe the long-term model as consisting of "four Markov model matrices that estimated the long-term course of CD including maintenance therapy and post-maintenance phases using clinical trial data" (CS, B.3.2.2). The four sets of transition matrices informing the long-term model are summarised in Table 21; the approach for modelling treatment effectiveness is more fully described and critiqued in Section 4.2.6.

Table 21: Summary of maintenance and post-maintenance transition matrices

Transition matrix	Application	Data informing transitions
Standard-dose biologic after response	Health state occupancy is determined using this transition matrix for patients who experience a CR-100 response at the end of induction and receive standard-dose biologic therapy in the maintenance phase. In the company base case, this matrix is also used for patients who start the maintenance phase on high-dose biologic therapy, as the target remission rate used to inform the calibrated transition matrix is based on weighted standard-dose and high-dose data.	Maintenance NMAs (standard dose and high dose), ordered probit models and 'calibration' (discussed further in Section 4.2.6)
High-dose biologic after response	Health state occupancy is not determined using this transition matrix in the company's base case analysis, as it is assumed the efficacy of those who dose escalate is equivalent to those who receive standard-dose maintenance therapy. This approach assumes that patients who dose escalate have lost response to standard-dose biologic treatment, and therefore the benefit from the increased dose is to match standard-dose efficacy. As such, dose escalation increases comparator costs without changing effectiveness estimates	Maintenance NMA (high dose), ordered probit models and 'calibration' (discussed further in Section 4.2.6)
Conventional care after response	Health state occupancy is determined using this transition matrix when responders discontinue biologic therapy at the point of a maximum treatment duration. The maximum treatment duration for biologics used in the company's analysis (52 weeks) is discussed further Section 4.2.6. This transition matrix assumes a residual treatment effect for patients who discontinue biologic therapy. The residual treatment effect period for biologics used in the company's analysis (52 weeks) is discussed further Section 4.2.6	Maintenance NMA (conventional care after response), ordered probit models, and 'calibration' (discussed further in Section 4.2.6) Ordered probit based on re-randomized placebo SC [withdrawal] arm in FORTIFY (n = 164); patients who received risankizumab IV for induction, had a response at the end of the initial 12-week induction period, and were subsequently randomized to the placebo SC arm in maintenance
Conventional care after no response	Health state occupancy is determined using this transition matrix for: i) non-responders who subsequently receive conventional care in the maintenance phase, and ii) patients for whom the residual treatment effect period has ended	True placebo group from FORTIFY. Namely, IV placebo responders at end of the initial 12-week induction period in ADVANCE and MOTIVATE, who were assigned to receive maintenance placebo SC in FORTIFY. The true placebo group consisted of n = 24 patients

Abbreviations: IV, intravenous; n, number; NMA, network meta-analysis; SC, subcutaneous.

In the company's model structure diagram (CS Figure 13), and as described in Table 21 above, it is assumed that dose escalation in the base case only affects patient biologic costs; patients do not transition to the high-dose matrix as they have failed standard-dose treatment and therefore escalate to achieve standard-dose efficacy. It is also stated in CS Figure 13 that a consistent assumption is applied to patients who initiate maintenance with high dose ustekinumab, as the higher dose is administered where a patient is expected to not respond adequately to the standard dose. However, the EAG interpret from the company's cost-effectiveness model that the 'standard dose' transition matrix for ustekinumab is calibrated using weighted standard dose and high dose NMA data. The EAG prefer the assumption whereby the 'standard dose' transition matrix calibration target is weighted the proportion of patients starting on standard and high dose therapy (in line with the EAG's interpretation of the company's model). Nevertheless, the EAG are concerned that the company's assumption of dose escalation affecting costs but not patient outcomes biases comparative cost-effectiveness estimates in favour of risankizumab, as dose escalation applies only to comparator biologics.

The EAG are concerned with the choice of data used to inform the conventional care after no response transitions. As described in Table 21, health state occupancy for i) non-responders who subsequently receive conventional care in the maintenance phase, and ii) patients for whom the residual treatment effect period has ended is informed using data from the 'true placebo' group from FORTIFY. Firstly, the EAG has concerns with the relatively small sample size of the true placebo group (n = 24), which is used to estimate transitions over a lifetime horizon. Secondly, the EAG has concerns as to whether placebo responders from the pivotal trial are representative of patients in practice who are non-responders or have discontinued biologic therapy. This is particularly important when applying the company's maximum treatment duration and residual treatment effect assumptions (described in further detail in Section 4.2.6), whereby all patients experience 'conventional care after no response' transitions from a maximum of 2 years (despite conventional care not being reflective of the treatment pathway as described by both the company and the EAG's clinical expert). Nonetheless, in the absence of alternative data, the EAG use the company's conventional care after no response transitions in the EAG preferred base case.

4.2.3. Population

The company's economic analysis considers a population in line with the anticipated license for risankizumab; that is, [redacted]

[redacted] The company notes that the patient population considered within the economic analysis is also aligned with the eligibility criteria for the pivotal risankizumab CD induction (ADVANCE and MOTIVATE) and maintenance (FORTIFY) trials.

The final scope issued by NICE specified that the subgroups by location of CD (ileal, colonic and perianal) may be considered, subject to data availability. However, the company did not present subgroups by location of CD, stating that the analysis was untenable due to low subject numbers. Clinical advice to the EAG indicated that location of CD is a key prognostic factor in CD.

The company instead presented the following subgroups in their economic analyses:

- Conventional care failure (CCF) population
- Biological failure (BF) population

As described in Section 2.3, clinical advice to the EAG indicated that the flowchart of current treatment practices presented by the company (Figure 1) was broadly reflective of a national standard of practice (while acknowledging potential differences between centres at the local level). Thus, the EAG considers the two populations presented in the company's economic analysis (CCF and BF) appropriate for addressing the decision problem outlined in the final scope issued by NICE.

Clinical data informing the CCF subgroup in the economic model is sourced from the ADVANCE and FORTIFY studies, while clinical data informing the BF population is taken from the ADVANCE, MOTIVATE and FORTIFY studies.

The company report that ADVANCE included both patients with inadequate response/intolerance to prior biologic therapy (described as the 'Bio-IR' population) and patients with inadequate response/intolerance to conventional therapy (described as the 'non-Bio-IR' population) for CD, whereas MOTIVATE was solely in a Bio-IR population.

The company state that the non-Bio-IR population is analogous to the CCF population; however, the EAG notes the non-Bio-IR population includes patients "who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response". The company report that [redacted] of patients in the non-Bio-IR population had not received a prior biologic therapy, implying that up to [redacted] of patients informing the CCF population had received prior biologic therapy.

The company describe the Bio-IR population, which includes patients “with documented intolerance or inadequate response (either failure to respond to induction treatment, or loss of response to maintenance therapy) to one or more biologics for CD”, as analogous to the BF population.

As ADVANCE, MOTIVATE and FORTIFY were international multicentre studies, it is unclear whether the trial populations can be considered generalizable to patients with moderately-to-severely active CD in NHS England practice. This is particularly in the context of prior treatments and concomitant conventional care received in the clinical trials compared with NHS England practice (discussed further in Section 4.2.8).

4.2.4. Interventions and comparators

The intervention considered in the company’s economic analysis is risankizumab 600 mg administered intravenously as induction therapy in Weeks 0, 4, and 8, followed by a maintenance period of risankizumab 360 mg administered subcutaneously Q8W, up to a maximum treatment duration of 52 weeks.

As described in Section 2.3, in clinical practice, the company anticipates that risankizumab SC will be delivered using an on-body device. Clinical advice to the EAG indicated a low level of clinical familiarity with on-body injectors but identified both potential advantages and disadvantages of this approach. As the company capture the cost implication of this administration difference, but assume no impact on clinical effectiveness parameters, the EAG have significant concerns with regards to the clinical effectiveness estimates informing the risankizumab arm of the economic model. More specifically, it is uncertain whether it is reasonable to assume there are no effectiveness implications from the different administration methods between the trials informing the analysis and expected clinical practice.

The comparators considered in the company’s economic analysis are dependent on the subgroup evaluated. In the CCF population, risankizumab is compared with infliximab, adalimumab and ustekinumab. In the BF population, risankizumab is compared with ustekinumab and vedolizumab. Dosing information for the intervention and comparators (including induction dose, induction duration, response assessment, maintenance dose, and escalated maintenance dose) are presented in Table 22 (adapted from Table 58 of the CS).

The final scope issued by NICE indicated that the availability and cost of biosimilars should be taken into consideration; and as such, the company compares risankizumab with infliximab and

adalimumab biosimilars in the CCF population. The company's economic analysis also considers both IV and SC forms of infliximab, adalimumab and vedolizumab. Furthermore, the company considers two alternative adalimumab induction dosing regimens (referred to in the CS as ADA 160/80 and ADA 80/40). In the company's economic analysis, treatments with biosimilars, IV and SC formulations and alternative induction doses are treated as standalone comparators (as summarized in Table 22).

Table 22: Intervention and comparator dosing information (adapted from CS Table 58)

Treatment	Induction				Maintenance	
	Induction dosing		Induction duration (weeks)	Response assessed (weeks)	Maintenance dosing	Maintenance dose escalation
RZB	600 mg IV at weeks 0, 4 and 8		12	12	360 mg SC Q8W from week 12	N/A
UST	Weight based IV dosing at week 0	<55 kg: 260 mg	8	6 and 8†	90 mg SC Q12W from week 8	90 mg SC Q8W
		>55 kg and <85 kg: 390 mg				
		>85kg: 520 mg				
VDZ IV	300 mg IV at weeks 0, 2 and 6		10	6 and 10‡	300 mg IV Q8W from week 14	300 mg IV Q4W
VDZ SC	300 mg IV at weeks 0, 2 and 6		10	6 and 10‡	108 mg SC Q2W from week 14	N/A
ADA 160/80 biosimilar	160 mg SC at week 0; 80 mg SC at week 2		4	4	40 mg SC Q2W from week 4	40 mg SC QW
ADA 160/80	160 mg SC at week 0; 80 mg SC at week 2		4	4	40 mg SC Q2W from week 4	40 mg SC QW
ADA 80/40	80 mg SC at week 0; 40mg SC at week 2		4	4	40 mg SC Q2W from week 4	40 mg SC QW
IFX IV	5 mg/kg IV at weeks 0 and 2		6	2	5 mg/kg IV Q8W from week 14	10 mg/kg IV Q8W
IFX IV biosimilar	5 mg/kg IV at weeks 0 and 2		6	2	5 mg/kg IV Q8W from week 14	10 mg/kg IV Q8W
IFX SC§	5 mg/kg IV at weeks 0 and 2		6	2	120 mg SC Q2W from Week 6	N/A

Key: ADA, adalimumab; INF, infliximab; IV, intravenous; N/A, not applicable; QxW, every x weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.
Note (CS Table 58): † Manufacturer indicates response assessed at weeks 6 and 8, in the model week 8 is used; ‡ Manufacturer indicates response assessed at weeks 6 and 10, in the model week 10 is used. The biologic labels allow for continued biologic therapy to patients after induction therapy, even for non-responders, for a specified period of time. § For infliximab subcutaneous, only a biosimilar formulation is available, but is referred to as IFX SC throughout the CS.

In the final scope issued by NICE, BSC was specified as a relevant comparator, for people in whom TNF-alpha inhibitors, vedolizumab and ustekinumab have been ineffective, are contraindicated or are not tolerated. However, the company's economic analysis does not include a comparison of risankizumab with BSC. The company argue that BSC is not considered an appropriate comparator as, in clinical practice, if a biologic therapy has failed or are contraindicated, patients would be offered an alternative biologic therapy. The EAG notes that the anticipated license for risankizumab includes "[redacted]". Considering both the anticipated risankizumab license and final scope, the EAG requested the company provide further rationale for excluding BSC as a comparator from the economic analysis (clarification question B4). At the clarification questions stage, the company did not provide further justification but reiterated that BSC is not deemed an appropriate comparator based on clinical feedback and patients who are intolerant or unsuitable for biologic therapy would be considered for a different class of biologic in practice.

Although this is the case, the EAG notes that, while all other comparators in the company's submitted cost-effectiveness model may be included or excluded by the user, conventional care is a mandatory comparator in both the CCF and BF populations.

Nevertheless, clinical advice to the EAG suggested that, in practice, BSC is unlikely to be a relevant comparator to risankizumab for patients with CD for whom TNF-alpha inhibitors, vedolizumab and ustekinumab have failed, are contraindicated or not tolerated. Clinical advice to the EAG suggested that treating clinicians would instead explore every available and suitable biologic option sequentially.

The EAG is satisfied to an extent with the exclusion of BSC as a comparator for patients with moderately to severely active CD in NHS England practice, but notes an issue in the scope of this CD evidence submission and those that have come before (TA456 and TA352).[53, 54] The addition of risankizumab to the treatment options currently available would extend the plausible options available to treat each patient. For example, in the BF population, the EAG understands it would be plausible for a patient to sequentially receive risankizumab, ustekinumab and vedolizumab. In this instance, the availability of risankizumab would increase NHS/PSS treatment acquisition and administration costs while hopefully increasing the HRQL of the affected patient. Yet, the company's submission does not address this decision problem; instead, it assumes that after the initial therapy, patients move to conventional care, on every

treatment arm. In light of the company's argument that BSC is not a relevant comparator as patients would be offered an alternative biologic therapy, this simplistic approach to modelling the treatment pathway appears even more problematic. In the company's analysis, patients are not offered an alternative biologic therapy.

In the company's updated cost-effectiveness model submitted at the clarification question stage (6a. ID3986_Risankizumab CD_NICE_CEM v0.2 040822 v1.2 [ACIC]), when the BF population is selected on the 'Model Setup' worksheet, it is suggested via checkboxes that ustekinumab, vedolizumab IV, and vedolizumab SC are included as comparators. However, vedolizumab IV and vedolizumab SC are excluded from the incremental analysis (see worksheet 'List', range 'list_regimen_active_inc_all'). In EAG correction #1, summarised alongside other EAG corrections in 6.1, vedolizumab IV and SC are included as comparators in the model's incremental analysis.

4.2.5. Perspective, time horizon and discounting

In line with the NICE reference case, the perspective of the company's base case economic analysis is that of the NHS and PSS on costs (as reported Section B.3.2 of the CS), and direct health effects for patients (the perspective on outcomes is not explicitly stated in the CS).

The company present a non-reference case scenario analysis (company scenario #6), which is described in the CS as including "societal (indirect) costs". The company's justification for including indirect costs in a non-reference case scenario is to assess the burden of CD onto society; however, none of the inputs or methods for estimating indirect costs are described in the company submission. In Section B.3.5.4 of the CS, it is stated that "no additional miscellaneous costs are considered in the cost-effectiveness model".

A time horizon of 60 years is used in the company's economic analysis, which the company describe as a lifetime horizon based on a mean age at baseline of 38.83 and 38.22 years in the CCF and BF populations, respectively. Therefore, the company's analysis tracks the cohort of patients to a maximum average age of 98.83 and 98.22 years in the CCF and BF populations, respectively. The EAG consider a lifetime horizon appropriate for decision making, due to the chronic nature of CD and plausibly lifetime implications of treatment. The company assumes no excess mortality due to CD compared with the age- and sex-matched general population; and consequently, the company's economic model estimates that >97.7% and >97.1% of patients will have entered the death state in the CCF and BF arms after 60 years, respectively. In

scenario analysis, the company explore several alternative time horizons between 1 and 10 years in (company scenario #1a-d).

In Section B.3.2.2.2 of the CS, it is stated that a half-cycle correction is applied in the cost-effectiveness model to "account for the fact that events and transitions could occur at any point during the cycle". Typically, in a discrete-time, cohort-level model, a half cycle correction is applied by averaging rows of the 'Markov trace' (i.e., for each health state, the average of the proportion of patients at time T and time T+1 is taken, consequently assuming transitions occur at the mid-point of a cycle, instead of the beginning or end).

In the company's cost-effectiveness model, rather than adjusting the proportion of patients in each health state to half-cycle correct, the company include an additional row of the Markov trace beyond the time horizon in the model calculations and half the 'number of years per cycle' in the first and final row of the long-term model. As the model cycle length is 2 weeks, the 'number of years per cycle' (which is combined with health state occupancy to determine LYs and QALYs) in the long-term model is 0.04 years (to 2 decimal places, calculated as 2/52 weeks). However, when the half-cycle correction switch in the company's model is set to 'yes', the years per cycle in the first and last long-term model cycle are equal to 0.02 years (to 2 decimal places, calculated as (2/52) * 0.5).

The EAG believe the company's half-cycle correction application (i.e., capturing an extra cycle and assuming the first and last cycle of the Markov trace is equivalent to a 1-week duration) is inaccurate when considering time-preference discounted results.

Furthermore, the company apply a half-cycle correction to drug acquisition and administration costs, despite the 1-year dosing schedules for biologic therapies being known and outlined in the "Calc - Dosing" sheet of the company's economic model. The EAG do not consider a half-cycle correction appropriate for costs or outcomes known to occur at the start of a model cycle. In the company's analysis, biologic acquisition and administration costs are marginally underestimated using in the base case.

In Section 6.1 of this report, the modification of the half-cycle correction application is referred to as EAG correction #2.

4.2.6. Treatment effectiveness and extrapolation

The clinical parameters and data sources informing treatment effectiveness estimates in the company's cost-effectiveness model are summarized in Table 23, and described in further detail throughout this section of the report.

Table 23: Summary of treatment effectiveness parameters

Parameter	Source	Assumptions
CDAI response and remission rates at the end of induction	Induction NMA	Observed data (CDAI-100 response definition in the base case)
Percentage of responders and non-responders with CDAI moderate-to-severe CD at the end of induction	Risankizumab CD trials (ADVANCE and MOTIVATE)	Observed data for risankizumab, and assumed equivalence for comparator biologics
CDAI remission rates at the end of maintenance	Maintenance NMA	Observed data, with assumptions regarding the formation of the network
Transition probabilities in the maintenance phase	Ordered probit models and calibration	Derived using the distribution of patients across health states at the end of the induction phase and the end of the maintenance phase (52 weeks), estimated using ordered probit models with calibration of the remission | mild cut-point parameter
Proportion of patients starting standard-dose maintenance therapy and dose escalation	Clinical expert opinion	Assumed dose escalation only increases comparator biologic costs, without increasing efficacy
Biologic discontinuation rates	Risankizumab and comparator CD trials	Observed data and assumed constant discontinuation rate up to assumed maximum treatment duration
Maximum treatment duration and residual treatment effect	Assumption	Assumed maximum treatment duration of 52 weeks for all biologic therapies. Assumed residual treatment effect of 52 weeks following discontinuation of biologic therapy
Surgery	NHS Hospital Episode Statistics	Assumed only patients with moderate-to-severe CD experience surgery. Equivalent rates of surgery assumed across treatments. Assumed constant rate of experiencing surgery
Mortality	Life tables	Assumed the same as the age- and sex-matched general population

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; NMA, network meta-analysis.

4.2.6.1. CDAI response and remission rates (induction NMA)

As described in Section 4.2.2, patients enter the model with moderately-to-severely active CD and efficacy outcomes are assessed at the end of the induction treatment period. The distribution of patients across health states at the end of the induction decision tree is estimated using the following parameters, as set out in Table 24.

- CDAI-remission rate (α)
- CDAI-response rate (β)
- Proportion of responders with moderate-to-severe CD (γ)
- Proportion of non-responders with moderate-to-severe CD (δ)

Table 24: Distribution of patients across health states at the end of induction

Responders			Non-responders		
Remission	**Mild CD**	**Moderate-to-severe CD**	**Remission**	**Mild CD**	**Moderate-to-severe CD**
α	β - α - (β * γ)	β * γ	0	(1 - β) – ([1 - β] * δ)	(1 - β) * δ

Abbreviations: α, CDAI-remission rate; β, CDAI-response rate; γ, proportion of responders with moderate to severe CD; δ, proportion of non-responders with moderate-to-severe CD; CD, Crohn's disease.

4.2.6.2. CDAI-remission (α) and CDAI-response (β) rates

The CDAI-remission and -response rates at the end of the induction period, which are derived from the induction NMA, are presented in Table 25.

As noted in Section 3.4.1, NMA results are provided using a risk difference method, rather than the more usual logit scale. While the rationale for this is not entirely clear this is not, in itself, expected to have a notable impact on the cost-effectiveness impact. The conversion of relative treatment effects to absolute levels of CDAI-response and CDAI-remission are likely to be more susceptible to modelling assumptions, although these will affect all treatments similarly.

As described in Section 4.2.2, given that clinical advice to the EAG indicated that CDAI-scores are not used in clinical practice, and the absence of commentary or explanation from the company on the relative merits of CDAI-70 versus CDAI-100 as a measure of response, the EAG feel unable to comment on relative suitability of CR-100 versus CR-70 response data.

Table 25: CDAI-remission and CDAI-response rates from the induction NMA

Treatment	Remission (CDAI <150)	CDAI-response (CDAI-100, company base case)	CDAI-response (CDAI-70, company scenario analysis)
CCF population			
RZB	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]
ADA 160/80 & biosimilar	[redacted]	[redacted]	[redacted]
ADA 80/40	[redacted]	[redacted]	[redacted]
INF IV & biosimilar	[redacted]	[redacted]	[redacted]
IFX SC	[redacted]	[redacted]	[redacted]
BF population			
RZB	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]
VDZ IV	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BF, biological failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

4.2.6.3. Proportion of responders (γ) and non-responders (δ) with moderate-to-severe CD

In the company's analysis, patients who are not in remission at the end of the induction phase are distributed between the mild CD and moderate-to-severe CD health states.

The company use a post-hoc analysis of ADVANCE and MOTIVATE risankizumab trial data to estimate the proportion of responders who remain in the moderate-to-severe CD state in the CCF population (8.4%) and BF population (7.8%), and similarly the proportion of non-responders who remain in the moderate-to-severe state in the CCF population (71.8%) and BF population (73.5%). In the absence of equivalent reported data from the relevant comparator studies, these proportions are assumed to also apply to all comparators in the company's model.

In NICE TA456, a similar approach was taken, using the proportion of moderate-to-severe responders from the IM-UNITI study. These parameters are commercial-in-confidence and not publicly available, although the Evidence Review Group in TA456 did note that the percentage of moderate-to-severe responders was reported in the NICE appraisal of vedolizumab (TA352).

The proportion of moderate-to-severe responders on vedolizumab, as reported in TA352, is 17.8% and 24.3% in the CCF and TNF-failure populations, respectively.

Nevertheless, in the absence of available data for all relevant comparators for both moderate-to-severe responders and non-responders, the EAG consider the company's approach, assuming the proportions from the risankizumab trials are applicable to all biologics, to be reasonable.

4.2.6.4. CDAI remission rates (maintenance NMA)

Within the maintenance phase, the company splits the evidence network into two separate sets of treatments/doses. A part of the rationale given for this is heterogeneity which it is suggested is seen in the wide range of placebo remission rates. Arguably, this heterogeneity could be modelled, at least in part, which may negate the purported need to split the network, and yield more relevant absolute estimates of CDAI-remission. It would also remove the presence of two different CDAI-remission parameters for conventional care after response, according to the estimates arising from these separate networks. As noted in Section 3.6, the EAG prefer the use of a single maintenance network; and as is noted in Section 3.4.3, modelling placebo CDAI-remission rates by trial date appears a suitable candidate to explain between-trial heterogeneity, and may be justifiable in terms of improvements in available concomitant treatments over time. Modelling placebo CDAI-remission in this way would uplift all treatments CDAI-remission by a similar amount using the risk difference approach.

4.2.6.5. Maintenance phase transition matrix estimation

The company use an ordered probit model to estimate state transition probabilities based on data from the FORTIFY trial for three separate subgroups: those randomised to risankizumab 360 mg SC ('biologic', n = 141); those who were randomised to risankizumab 360 mg SC for induction and placebo SC for maintenance ('placebo withdrawal', n = 164); and those randomised to placebo SC for both induction and maintenance ('true placebo', n = 24). The ordered probit model the company specified has main effects for lagged health state (factor with levels: remission, mild, and moderate-severe), and a linear term for the number of days since the previous (lagged) health state assessment. The ordered probit model then estimates cutpoints for the linear predictor to indicate the boundary between remission and mild, and between mild and moderate-severe health states. The company do not provide detailed justification for choosing an ordered probit, rather than an ordered logit model, although it is likely that the differences would be minimal, and quite likely trivial. However, this is not demonstrated.

The company justify the ordered probit model selection on the basis of its simplicity, rather than any formal model selection. A linear term for the number of days since the previous health state assessment may be reasonable if this variable shows little variability, as might be expected in the absence of missing data with health states recorded at 0, 24 and 52 weeks. However, in cases with only observations at 0 and 52 weeks, this linear term may be inappropriate. Appropriate imputation of missing observations (e.g., multiple imputation, potentially involving CDAI scores) may mitigate this problem. Furthermore, the use of a lagged health state term is potentially more problematic, as it makes certain assumptions, including regarding the absence of any interaction with the other terms (days since previous assessment, and the two cutpoints) relating to the lagged health state. An alternative that could have been investigated would be to fit three separate models according to the previous health state.

In addition to the limitations noted above, it should also be noted that the 'true placebo' ordered probit model is estimated on a particularly small sample (n = 24) and so the estimates may be unreliable, as is suggested by the associated standard errors and the fact that none of the estimated parameters approach statistical significance.

The results of the ordered probit model are used by the company to estimate (uncalibrated) 26-week transition matrices for each of the three subject subgroups. For the 'biologic' group, the linear predictors generated for a 182-day period are -0.00669 x 182 = -1.21758 (from remission); 1.07098 – 0.00669 x 182 = -0.14660 (from mild); 1.68745 – 0.00669 x 182 = 0.46987 (from moderate-severe). With regard to the remission | mild and mild | moderate-severe cutpoints of -0.33324 and 0.47878, respectively, by reference to the standard normal cumulative distribution function (the 'probit' link) we obtain an estimated transition matrix as presented immediately below, where the rows correspond to originator health states (remission, mild, moderate-severe from top to bottom) and columns correspond to destination health states (remission, mild, moderate-severe from left to right)

$$\begin{pmatrix} 0.81174 & 0.14335 & 0.04491 \\ 0.42597 & 0.30817 & 0.26586 \\ 0.21096 & 0.29260 & 0.49645 \end{pmatrix}$$

According to company responses to clarification questions, each 182-day transition matrix is then converted to a 14-day transition matrix using an exponential assumption. For example, the 182-day probability of transition from a remission health state to a mild health state is calculated as $1 - (1 - 0.14335)^{14/182} = 0.01183$. Other transitions are calculated similarly with the

probability of remaining in each state being calculated such that each row sums to one. Applying this method to the above 182-day transition matrix we obtain an estimated 14-day transition matrix of

$$\begin{pmatrix} 0.98464 & 0.01183 & 0.00353 \\ 0.04180 & 0.93471 & 0.02349 \\ 0.01806 & 0.02628 & 0.95566 \end{pmatrix}$$

It is known that this method of changing cycle durations introduces error (Chhatwal et al, 2016);[55] for example, it fails to account for subjects passing through one health state to reach another. The company acknowledges that alternative solutions are possible, for example eigen-decomposition. The exponential assumption method was stated to be used in the interests of convenience. However, in this case if we multiply up the 14-day transition matrix back to 182-days we obtain the following

$$\begin{pmatrix} 0.85082 & 0.10248 & 0.04670 \\ 0.36691 & 0.46527 & 0.16782 \\ 0.22284 & 0.19017 & 0.58699 \end{pmatrix}$$

Quite large discrepancies have been introduced. For example, the probability of transitioning from a mild to a moderate-severe health state over a 182-day period is reduced from 0.26586 to 0.16782 as a result of this approximation.

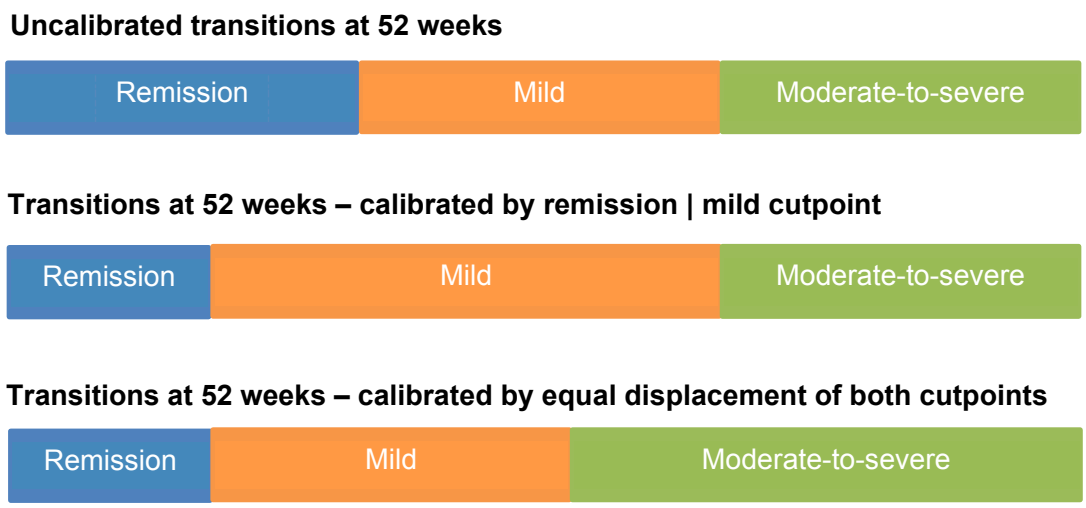
The EAG note that the subsequent calibration process (described below) will adjust the proportion of patients in a remission health state to hit a target level at 52 weeks. However, there is no rationale that this calibration process will adequately correct for the above source of error, and there are no grounds to assume that the individual transition probabilities will not retain significant levels of error, especially for transitions to mild or moderate-to-severe disease, where such adjustment is not made or for different durations of follow up other than 52 weeks.

In the absence of patient-level data for comparators, the company have used a calibration process to adjust the risankizumab transition probabilities for each comparator treatment in order that the proportion of patients in remission at 52 weeks matches the estimates obtained from the maintenance NMA. This calibration process adjusts the remission | mild cutpoint estimated from the biologic ordered probit model and then applies the exponential assumption cycle length change method to obtain 14-day transition probabilities.

Similar calibrations are performed on the 'placebo withdrawal' and 'true placebo' subgroups. The EAG note that the split maintenance network results in different target remission levels according to the placebo estimates resulting from these two sub-networks.

The adjustment of the remission | mild cutpoint is apparently arbitrary, and is illustrated below in Figure 7. Alternative parameter estimates in the ordered probit model could be adjusted to achieve the same 52-week remission proportion calibration. The company justify their approach on the basis of simplicity, as only one value needs to be adjusted, and consequently this is computationally convenient. The EAG note that this adjustment only directly rebalances the 182-day transitions to the remission and mild health states. There is no rationale for why this might adequately reflect the differences in state transitions between different comparators. Indeed, it seems implausible that only the balance between remission and mild health states would be rebalanced.

Figure 7: Methods for calibration of ordered probit estimates



In response to clarification questions, the company provided a comparison with three alternative calibration methods. The first made an equal adjustment to both cutpoints, the second adjusted the probability of remaining in remission only (rather than transitioning to mild or moderate-severe), and the third method rescaled the transitions to/remaining in remission and then scaled the probabilities of transition to/remaining in other health states accordingly for each row. No rationale for preferring any of these approaches is provided. As the ordered probit model

assumes a latent variable with cutpoints, and the health states are defined based on CDAI with thresholds, the first scenario (equal adjustment to both cutpoints) may be more justifiable, albeit not without further simplifying assumptions regarding the relationship between CDAI and the latent variable. The EAG consider that the first of these methods, which is also illustrated in Figure 7 provides a more plausible adjustment than the company's base case.

4.2.6.6. Standard-dose maintenance therapy and dose escalation

The company report that ustekinumab, vedolizumab, infliximab and adalimumab have both standard- and high-dose maintenance regimens. The company note that clinical expert opinion suggested only a small proportion of patients start on high-dose maintenance therapy, with the exception of ustekinumab.

Therefore, based on clinical expert opinion, the company assume that 92.5% of ustekinumab patients begin the maintenance phase on high-dose therapy. For all other biologics, the company assume that all patients start on standard-dose maintenance therapy.

In the company's economic model, the NMA-derived 52-week remission rate, which is used to estimate the calibrated transition matrices, is weighted by the proportion of patients who start on standard-dose and high-dose therapy. As such, for ustekinumab, the transition matrix described as 'response - standard dose maintenance' in the company's economic model incorporates both the standard- and high-dose maintenance NMA.

The company's economic analysis also considers dose escalation throughout the maintenance period, which is applicable to all biologics other than risankizumab. Dose escalation rates are based on clinical expert opinion for infliximab, adalimumab, ustekinumab and vedolizumab. For ustekinumab, the annual probability of dose escalation is the equivalent to the probability of starting on high dose ustekinumab (92.5%). Based on the information reported in CS, it is unclear to the EAG whether clinical advice to the company indicated that both 92.5% of patients start on high-dose maintenance ustekinumab *and* the annual probability of dose escalation is 92.5%, or whether the company assume equivalence to inform these parameters. The EAG is concerned that the company's approach of assuming 92.5% of patients start on high-dose ustekinumab and assuming an annual ustekinumab dose escalation rate of 92.5%, may overestimate the proportion of patients receiving high-dose ustekinumab.

In the company's base case, it is assumed that the treatment effectiveness estimates for those patients who dose escalate are equivalent to those who receive standard-dose maintenance

therapy. This approach assumes that patients who dose escalate have lost response to standard-dose biologic treatment, and therefore the only benefit from the increased dose is to match standard-dose efficacy. As such, dose escalation increases comparator costs without changing effectiveness estimates. As described in Key Issue 6, the EAG view this as an assumption that very likely biases comparative cost-effectiveness estimates in favour of risankizumab, as dose escalation applies only to comparator biologics.

4.2.6.7. Biologic discontinuation rates, maximum treatment duration and residual treatment effect

The company's analysis assumes treatment-specific, constant rates of biologic treatment discontinuation in the maintenance phase of the model, for the first 52 weeks of maintenance therapy, based on available trial data across treatments. The discontinuation probability assumptions applied in the model and their sources are summarised in Table 75 of the CS, and range from 4.3% in the first year (risankizumab) to 41.3% in the first year (vedolizumab IV or SC). Importantly, the company assumes a maximum biologic maintenance treatment duration of 52 weeks. From this point, patients are assumed to move to conventional care, where as noted in 4.2.2, the company assume there is a further 52-week residual treatment effect.

The EAG have several concerns with the company's approach to treatment discontinuation assumptions. First, the EAG's clinical adviser found it difficult to judge whether assuming different 1-year discontinuation rates across treatments based on observed data across trials was appropriate, given differences in inclusion criteria and study design across trials.

Second, and importantly, clinical advice to the EAG indicated that in practice, discontinuation rates are low, discontinuation becomes less likely as treatment duration increases, and that an assumption that all patients discontinue after 52 weeks of maintenance therapy is false. The EAG's clinical adviser's perspective is that if maintenance therapy is working for a patient, there is every effort and incentive to maintain treatment.

Figure 8 shows FORTIFY time to treatment discontinuation (TTD) data, provided by the company in response to an EAG request. From these data and the expert clinical advice received by the EAG, it is clear to the EAG that assuming a 52-week maximum maintenance treatment duration is inappropriate.

Figure 8: Time to treatment discontinuation due to lack of efficacy (FORTIFY ITT1A population, clarification question B8)

Key: ITT, intent-to-treat; IV, intravenous; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's disease.+ censored observations.
ITT1A population includes randomised subjects in the ITT population who received risankizumab IV for only one period of 12 weeks in ADVANCE or MOTIVATE, and ≥1 dose of the study drug in FORTIFY substudy 1 and had eligible SES-CD of ≥6 (≥4 for isolated ileal disease) at baseline of the induction study.
Note: Subjects who discontinued the study due to lack of efficacy are considered as events.

The company argue that universal discontinuation from biologic therapy at 52 weeks "reflects clinical practice and NICE guidance, which states that patients should be re-assessed at 12 months to determine whether continuing with biologic treatment is appropriate" (CS, B.3.2.2). At the clarification question stage, the company went on to cite two primary reasons to assume maximum treatment duration of 52 weeks. Firstly, the 52-week timepoint reflects the available of trial data and modelling outcomes beyond 1 year would require assumptions regarding clinical effectiveness. Secondly, a consistent approach was used in recent NICE appraisals in CD (TA456 and TA352). The EAG do not consider the need to extrapolate beyond the trial period as sufficient justification for assuming a universal maximum treatment duration across biologic therapies: the company's base case analysis adopts a lifetime horizon - by design, outcomes are extrapolated beyond the trial period. Further, the EAG do not feel precedent is a rationale to use assumptions that lack clinical plausibility in this appraisal.

The 52-week discontinuation period in the company's preferred base case grossly underestimates time on biological treatment in clinical practice, as supported by clinical opinion and evidenced in Figure 8. Consequently, both the costs and efficacy of biologic treatments are misrepresented in the company's analysis. In Section 6.2, the EAG explore several alternative treatment discontinuation scenarios, whereby the maximum duration of biologic treatment is increased to align more closely with clinical practice. Furthermore, the EAG explores assuming equivalent rates of discontinuation for biologic therapies, to remove potential confounding issues due to differences in study design.

The company provide little rationale for the assumed 52-week residual treatment effect post-discontinuation, with clinical advice to the EAG estimating a 6-month time to symptomatic return for ustekinumab. Given the similar half-lives across treatments, the EAG considers a 52-week period likely overestimates the residual treatment effect post-discontinuation, with the modelled patients residing in the conventional care after response matrix for longer than is reflective of clinical practice. In Section 6.2, the EAG explore reducing the residual treatment effect to 26-weeks, to align with clinical opinion and a scenario presented by the company (company scenario #2).

4.2.6.8. Surgery

The company report the following inputs used in TA456, by using a Hospital Episode Statistics (HES)-sourced annual surgery rate estimate of 7%, converted to a 2-week cycle probability of 0.28% using an exponential formula (CS, B.3.3.4.3). In TA456, the 2011-14 HES dataset informed surgery risk assumptions,[54] while the HES data cited in the CS for this appraisal is from 2019-20 (CS, B.3.3.4.3 and B.4). It is unclear to the EAG whether the annual rate of surgery was equivalent in the 2011-14 and 2019-20 Hospital Episode Statistics data sets, or whether the value used by the company was lifted from TA456 materials, or identified by the company in the 2019-20 HES dataset.

As described in Section 4.2.2 and in line with TA456, the company assume a risk or surgery only applies to patients in the moderate-to-severe CDAI-based health state. Patients who experience surgery are routed through post-surgery tunnel states for three model cycles before being re-assigned to a CDAI-based health state in the company's model. Post-surgery transition matrices, which were sourced from TA456 and TA352, used data from Bodger (2009).[30]

4.2.6.9. Mortality

As described in Section 4.2.2, the company assume that there is not a heightened risk of death for patients with CD, compared with the general population. As such, age- and sex-matched general population mortality rates are applied each model cycle, regardless of population, health state or treatment. Literature identified by the EAG indicates a heightened risk of mortality for CD patients, though clinical opinion to the EAG advised CD is often not a life-shortening disease. The EAG consider equivalent mortality to the general population to be a reasonable assumption, though explore the relaxation of this assumption in Section 6.2.7 to align with the literature identified.

While reviewing the company model, the EAG identified an error in the calculation of general population mortality risk. The proportion of males and females alive at each year of age is incorrectly calculated in the company model, resulting in slight errors in the general population mortality risk. Though unlikely to have a large impact on the results, EAG correction #3, summarised alongside other EAG corrections in 6.1, corrects the proportion of males and females alive at each year of age.

4.2.7. Health-related quality of life

4.2.7.1. CDAI-based health state utility values

Patient-reported health-related quality of life (HRQoL) data were collected in the risankizumab CD induction and maintenance studies, including data collected using the EQ-5D-5L descriptive system. In line with the NICE reference case, health state utility values informing the company's economic analysis were calculated by mapping EQ-5D-5L data onto the EQ-5D-3L value set, using the algorithm developed by Hernández Alava et al. (2020).[56] The company assume HRQoL in the economic analysis is determined by CDAI-based health state, and not directly determined by patient population (CCF or BF), treatment arm (biologic therapy) or treatment status (on- or off-biologic therapy).

As the number of EQ-5D-5L observations from the pivotal risankizumab trials by CDAI-based health state was not reported in the CS, it was challenging for the EAG to assess the validity of the predicted health state utility values for informing the economic analysis. However, in response to clarification question B24b, the company report that [redacted], [redacted] and [redacted] EQ-5D-5L observations were recorded by patients in risankizumab trials samples assumed to represent the remission, mild CD and moderate-to-severe CD health states, respectively.

In the CS, it is reported that average health state utility values were estimated using ordinary least squares (OLS) regression; however, no rationale was provided for this approach. In clarification question B24a, the EAG requested the company provide justification for OLS estimation of utility values, particularly in the context of within-patient repeated measures. In clarification question B24c, the EAG specifically requested the company provide utility values estimated using a linear mixed model, including a random effect to account for repeated measures.

In response to clarification question B24, the company report that OLS is "simple, straightforward and commonly used (for estimated health state utilities)" and subsequently state it is believed that "allowing for correlated errors at the patient level would yield similar coefficient estimates and utility predictions". However, the company provided health state utility values estimated using a linear mixed model as requested. Table 26 compares CDAI-based health state utility values estimated using OLS (company base case) and a linear mixed model (clarification question B24c).

Table 26: Estimated health state utility values (OLS versus linear mixed model)

Health state	OLS (CS, Table 83), mean (95% CI)	Linear mixed model (clarification question B24c, Table 39), mean (95% CI)
Remission	[redacted]	[redacted]
Mild CD	[redacted]	[redacted]
Moderate-to-severe CD	[redacted]	[redacted]

Abbreviations: CD, Crohn's disease; CI, confidence interval; CS, company submission; OLS, ordinary least squares.

The company conducted an SLR to identify studies reporting HRQoL data for patients with moderate-to-severe CD, and although results of the included studies are presented in CS Appendix K, neither interpretation of these results nor assessment of suitability for inclusion in the economic model is provided in the CS. As such, the EAG requested further information on the relevance of included studies to this appraisal in clarification question B25. The company's response cited previous NICE appraisals in CD and Bodger et al. (2009) [30] as the most relevant HRQoL sources (beyond the risankizumab pivotal trials), based on their alignment with the company's modelled health states, previous use in NICE appraisals and relevance to a UK population.

In the CS, two scenario analyses are presented using alternative sources of health state utility values from the literature. In Section B.3.4.2 of the CS, the company state that the methods for these alternative scenarios are described in Section B.3.11.3; however, very little information is provided. The alternative sources are described as i) mapped ustekinumab Inflammatory Bowel Disease Questionnaire scores (company scenario #4a), and ii) utility values from Bodger (2009)[30] (company scenario #4b). For each of these scenarios, the utility values themselves were not reported in the CS.

The EAG broadly agrees with the company's approach of using patient reported HRQoL data collected in the risankizumab studies to inform health state utility values in the base case, with utility values from the previous NICE appraisals and the literature tested in scenario analysis. However, the EAG considers the linear mixed model a more robust (and therefore more appropriate) approach than OLS for estimating health state utility values, given the ability to account for differences between observations at the patient level.

The EAG notes a range of non-base-case utility sources are available in the company's submitted economic model, beyond the two described above. In clarification question B26, the EAG requested additional information on the process undertaken for selecting the two alternative sources for scenario analyses. The company note that the two sources were used in previous Health Technology Assessment submissions, but do not provide a descriptive comparison of the relative merits or appropriateness of the two sources compared with the additional sources identified by the EAG in the company's model (summarized in Table 27).

Table 27: Utility values from the literature (company model, worksheet: 'Library - HU')

Label: description (company model)	Health state utility value			Scenario in CS?
	Remission	Mild CD	Moderate-to-severe CD	
IBDQ: Data from IM-UNITI mapped using Buxton et al. (2007)[57]; company scenario #4a	0.800	0.680	0.550	Yes
SF36: Buxton et al. (2007)[57]	0.540	0.480	0.420	No
CDAI: Buxton et al. (2007)[57]	0.820	0.700	0.540	No
GEMINI: NICE TA352 (Table 7.4.3.1)[53]	0.820	0.730	0.570	No
Bodger et al. (2009)[30]; company scenario #4b	0.832	0.700	0.550	Yes

Abbreviations: CD Crohn's disease; CDAI, Crohn's Disease Activity Index; CS, company submission; IBDQ, Inflammatory Bowel Disease Questionnaire; TA, technology appraisal; SF36, Short Form 36.

4.2.7.2. Surgery health state utility

The company's economic analysis assumes the health-related quality of life of a patient with CD who experiences surgery is equivalent to that of a patient with CDAI moderate-to-severe CD for one model cycle (2 weeks), and subsequently equivalent to that of a patient in CDAI remission for three model cycles (6 weeks).

The company's description and justification of this approach is somewhat contradictory and unclear. In B.3.2.2.2 of the CS, it is stated that patients experience "surgery-related disutilities and costs". Conversely, in B.3.4.4 of the CS, it is reported that "surgical complications did not incur health utility decrements in the model but only affected costs". The company's rationale for excluding surgery-related utility decrements was that, as surgery is modelled as a health state, the utility value would include the expected utility loss from complications (CS, B.3.4.4). However, the utility value for the surgery health state is assumed equal to the mild-to-severe CD utility, not derived from surgery-specific data. In B.3.9.2 of the CS, the company report the rationale for assuming surgical complications do not incur health losses as a lack of data (rather than assuming health state utility implicitly capturing the health-related quality of surgery patients).

Overall, the EAG infer that the company's approach very likely underestimates the HRQoL implications of surgery, and explore alternative assumptions in Section 6.2.

4.2.7.3. Adverse event disutility values

The company's economic analysis captures utility decrements associated with experiencing treatment-related AEs. Differential AE rates are assumed across biologic treatment arms, based on observed data. The EAG has concerns with this approach as the observational data collected across studies may be affected by confounding, through differences in eligibility criteria and study design. Assuming differential AE rates across arms introduces a treatment effect into the model, and with no direct evidence to support this assumption, the EAG have concerns around the validity of the company's approach. In Section 6.2, the EAG explore the impact of assuming equivalent AE rates across biologic treatment arms.

The company use an exponential formula to convert 52-week AE probabilities from the relevant clinical trials to 2-week probabilities, in order to apply AE decrements each model cycle. Utility decrements are applied to the proportion of patients experiencing AEs in the standard dose and

high dose remission, mild CD and moderate-to-severe CD health states each model cycle. As such, the EAG interprets that the impact of experiencing any adverse event on a patient's HRQL is assumed to last one full model cycle (2 weeks). In clarification question B27, the company confirm that there is no clinical justification for the 2-week AE duration, beyond the assumption that AEs would be resolved quickly.

The EAG consider sourcing AE-specific durations from the literature a more accurate approach to applying disutility values; however, anticipate that the impact on the cost-effectiveness results is likely to be minimal. Nevertheless, the EAG trials alternative AE durations in Section 6.2 to explore the effect on the results.

4.2.7.4. Age-related utility decrement

Although not explicitly described in the CS, the company's economic analysis incorporates an age-related utility adjustment, to account for an expected natural decline in health-related quality of life over time, based on general population data. In Section B.3.4.1.1 of the CS, age-adjusted utility coefficients of -0.000173 (age) and -0.000034 (age^2) are reported. These age and age^2 coefficients are referenced as "NICE TA456, EAG Report Table 63. Data from Ara and Brazier 2010". However, the EAG were unable to identify the reported values in the primary source (Ara and Brazier 2010)[58]; and as such, requested that the company provide further detail in clarification question B28. At the clarification question stage, the company submitted an updated cost-effectiveness model which included corrected coefficients (age: -0.0002587, age^2: 0.0000332), as cited in Ara (2010).[58]

However, beyond this, the EAG identified additional errors with the company's age-adjustment approach. Firstly, the company report that the "average age of utility research" is 40 years (CS, B.3.4.1.1, Table 81), and consequently assume an age-adjustment multiplier >1 for model cycles in which the age is below 40 years. The EAG are unable to identify the reported average age of utility research in the primary source. Secondly, the company included regression coefficients for age and age^2 in their model but did not include the 'constant' (0.950857) or 'male' (0.021213) coefficients reported in Ara and Brazier 2010[58]. In EAG correction #4 (Section 6.1), the EAG update the company's utility age-adjustment approach by calculating the general population utility at baseline age in the model, and the general population utility each subsequent cycle, using the full regression equation reported in Ara and Brazier 2010.[58]

4.2.8. Resources and costs

The company report that an SLR of cost and resource use data identified 14 studies relating to the management of CD that were relevant to the UK. However, none of the identified studies were used to inform cost and resource use data or assumptions in the company's economic analysis. The company's justification for disregarding the output of the SLR was that, compared with the sources described throughout Section B.3.5 of the CS, none of the systematically identified studies had more recent data available. The sources and data informing the company's cost inputs are critiqued throughout this section of the report.

The company consider the following cost categories in their economic analysis:

- Drug acquisition costs
- Administration costs
- Concomitant medication costs
- Resource use costs
- Adverse event, surgery and surgical complication costs

4.2.8.1. Drug acquisition, administration and concomitant medication costs

Risankizumab unit costs (including a simple PAS discount) are provided by the company, while unit costs for comparator biologics are sourced from the British National Formulary (BNF). Drug acquisition unit costs are presented in Section B.5.1 (Table 85) of the CS.

The EAG notes that, per the BNF website, risankizumab is currently available as a 150 mg/ml pre-filled pen/syringe. In response to clarification question B29, the company confirmed that risankizumab will be available in 600 mg vials for induction, and as a 360 mg solution for maintenance therapy. The company model submitted at clarification included an incorrect price of [redacted] (a difference of [redacted] for risankizumab. EAG correction #5, as described in Section 6.1, aligns the risankizumab price to that reported in the CS.

Drug acquisition costs are calculated in line with the dosing schedules reported in Table 22 of this report. The only treatments subject to weight-based dosing schedules are ustekinumab (induction only) and infliximab (induction and maintenance). For ustekinumab, weight distributions based on the usteknimuab induction dosing schedule were calculated from a post-

hoc analysis of MOTIVATE and ADVANCE data (risankizumab induction trials) and used to calculate the average required induction dose. For infliximab, wastage (with regards to weight-based dosing) was considered by rounding to the nearest number of whole vials required, based on the average weight from the risankizumab CD trials. The EAG assumes the company considers wastage for infliximab only due to the weight-based dosing schedule throughout both induction and maintenance. As a fixed dose is administered for ustekinumab in the maintenance phase, no wastage is assumed. The EAG consider the company's approach to wastage and weight-based dosing to be acceptable. Average induction and 52-week maintenance costs are summarized in CS Table 86.

In the company's analysis, administration costs for treatments administered subcutaneously include an initial training cost on first administration (based on one one-hour of nurse time) and no subsequent costs. However, IV treatments are assumed to incur per administration cost based on the NHS Payment by Results tariff 2020/21 (item code FD02H). Risankizumab will be administered using an OBD, as defined in Section 2.3. As the method of administration differs from that in the clinical trials, the EAG have concerns that the efficacy and discontinuation rate of risankizumab may not be consistent with the observed data. However, in the absence of alternative data, the EAG preferred base case accepts the company's assumption of no efficacy and discontinuation rate implications from a different administration method.

Concomitant medication costs were sourced from the Drugs and pharmaceutical electronic market information tool (eMIT) if possible, else from the BNF. An average concomitant medication cost per 2-week cycle was calculated (£13.76) using per-day doses for individual treatments (sourced from TA352)[53] and usage estimates (sourced from TA456).[54] The company assume 61% of patients on biologic also receive conventional care, based on data from FORTIFY.

The company's economic model calculates treatment costs in the maintenance phase using a per-cycle approach, which the EAG considers inaccurate. In cases where the dosing schedule is known (i.e., X vials administered every Y weeks) and can be aligned with the model cycle length, it is unnecessary to estimate a per-cycle cost. The EAG understands that the company's approach may underestimate biologic acquisition and administration costs, as splitting costs which are known to be applied up-front across several cycles will overestimate treatment discontinuation and time-preference discount factors. The EAG's approach to modelling

treatment acquisition and administration costs, in line with the dosing schedules outlined the company's model, is described as EAG correction #6 in Section 6.1.

4.2.8.2. Health care resource use costs

In Section B.3.5.2 of the CS, there is very little information presented that describes the company's approach to modelling health care resource use costs. The company simply state that health-state costs were taken from TA456 and that costs were inflated to a 2020/21 cost year and adjusted to a 2-week cycle. The company do not report any of the following information:

- Resource use items by CDAI-based health state (i.e., itemised list of healthcare resource use requirements for patients with CD)
- Resource use proportions by CDAI-based health state (i.e., the proportion of patients assumed to experience each healthcare resource use item)
- Resource use frequencies by CDAI-based health state (the frequency at which patients with CD are assumed to require each healthcare resource use item)
- Original aggregate healthcare resource use costs from the reference source (TA456).[54]

The company note that in TA456, health care resource usage was gathered from a modified Delphi panel, in which 12 clinicians estimated resource use for each model health state. In TA456,[54] information was collected via telephone interviews and a face-to-face meeting to determine frequency of usage for all items.

Based on the information reported in the CS, the EAG are unable to verify the suitability of the aggregate health care resource use cost estimates. The EAG consider a more robust approach would be to model resource use costs using a 'bottom-up' approach (i.e., combine individual resource use estimates with the latest available unit costs), rather than uplifting aggregate health state costs. As such, in clarification question B30, the EAG requested an itemised list of resources and frequencies assumed for each health state. Furthermore, the EAG asked the company to confirm whether any clinical input was sought to validate the resources and frequencies sourced from TA456 for current practice in 2022.

In response, the company noted that the individual cost components (reported in TA456 Appendix 13)[54] were not publicly available, and that "UK clinicians were invited to review model

inputs used in the CS, but no clinicians provided comments on them". Overall, the EAG feel the company's approach to costing resource use is somewhat lacking, with the response received at clarification showing little understanding of the resources, frequencies and costs used to inform the cost-effectiveness model. The TA456 health care resources and frequencies have not been validated by either the company or clinical experts, nor has the EAG been able to assess the appropriateness of the resources included. In the absence of itemized resource use, the EAG find the company's approach acceptable, though note the limitations of the inability to perform validation.

4.2.8.3. Adverse event, surgery and surgical complication costs

Unit costs associated with surgery, managing surgical complications, and managing AEs from the company's analysis are presented in Table 28.

The cost of surgery is applied each model cycle to the proportion of patients in the surgery health state. Surgical complication and AE costs are applied each model cycle based on the estimated 2-week probabilities (CS Doc B, Table 79 and Table 80).

Table 28: Surgery, surgical complication and adverse event costs

Item	Cost	Reference
Surgery	£9,947	NICE TA456, EAG Report Table 68.[54] Values inflated to 2020/21
Surgical complications		
Wound infection	£986	NHS reference costs 2019/20 (WH07G)[59]
Prolonged ileus / bowel obstruction	£839	NHS reference costs 2019/20 (FD10M)[59]
Intra-abdominal abscess	£986	NHS reference costs 2019/20 (WH07G)[59]
Anastomotic leak	£986	NHS reference costs 2019/20 (WH07G)[59]
Adverse events		
Serious infections	£1,531	NHS reference costs 2019/20 (WJ06J)[59]
Tuberculosis	£1,894	NHS reference costs 2019/20 (DZ14J)[59]
Lymphoma	£842	NHS reference costs 2019/20 (SA31F)[59]
Hypersensitivity	£412	NHS reference costs 2019/20 (WH05Z)[59]
Skin reactions	£986	NHS reference costs 2019/20 (WH07G)[59]

4.2.8.4. Miscellaneous unit costs and resource use

As described in Section 0, the company present a non-reference case scenario analysis (company scenario #6), which is described in the CS as including “societal (indirect) costs”. However, none of the inputs or methods for estimating such costs are described in the company submission. In Section B.3.5.4 of the CS, it is stated that “no additional miscellaneous costs are considered in the cost-effectiveness model”.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

In this section of the report, the company's cost-effectiveness results are presented for the CCF and BF populations. Clinical advice to the EAG indicated that, in practice, risankizumab would likely be used in the BF population, unless there was a strong contraindication to anti-TNF therapy. However, results for both populations are presented for completeness.

5.1.1.1. Base case results

The results reported by the company for the CCF and BF populations are shown in Table 29 and Table 30, respectively. Where biosimilar products are available, the product with the lowest cost is presented. The company report that probabilistic results are presented in the base case (CS B.3.10), based on the updated NICE methods guide. Deterministic base case results, calculated using the company's submitted economic model, are also presented in Table 29 and Table 30.

As the company's cost-effectiveness analysis compares more than two technologies, the company conduct a fully incremental analysis to identify the most cost-effective treatment option. The company's process for conducting incremental analysis is described as follows:

- Treatments are ordered from least to most expensive
- Check for strong dominance. Treatments are dominated if they are both costlier and less effective than another treatment included in the analysis.
- Check for extended dominance. Treatments are extendedly dominated if an alternative treatment can provide more QALYs for a lower cost per QALY. This is because decision makers prefer a more effective treatment with a lower ICER

When using the risankizumab PAS price, the deterministic and probabilistic results for patients with CD in a CCF population indicate risankizumab is dominated (i.e., less effective, more costly) when compared with adalimumab (80/40, 160/80, 160/80 biosimilar), infliximab (SC, IV, IV biosimilar) and ustekinumab. In the BF population, the results indicate that risankizumab is dominant (i.e., more effective and less costly) when compared with ustekinumab, vedolizumab SC, and vedolizumab IV.

The cost-effectiveness analysis reported in the CS uses list prices for all comparator treatments; however, the company notes that ustekinumab and vedolizumab each have confidential PASs.

Table 29: Company base case results (CCF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Company deterministic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£4,387	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£31,259	£31,259
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£55,406	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£283,020	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£195,929	Dominated
Company probabilistic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£26,314	£26,314
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£53,236	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£155,894	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£208,134	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; IFX, infliximab; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 30: Company base case results (BF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Company deterministic base case						
RZB	[redacted]	[redacted]	[redacted]	[redacted]	-	-
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Company probabilistic base case						
RZB	[redacted]	[redacted]	[redacted]	[redacted]	-	-
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: BF, biological failure; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

5.2. Company's sensitivity analyses

5.2.1. One-way sensitivity analysis

The company note that the parameters varied in their 'deterministic sensitivity analysis (DSA)' included baseline patient characteristics, efficacy and safety parameters, health-state utility values and costs (direct medial costs, AE costs, indirect costs). It is unclear to the EAG why the company varies indirect costs in the DSA, as the economic analysis is conducted from an NHS and PSS perspective on costs in line with the NICE reference case, and such changes have no effect upon results.

The company state that 'efficacy outputs' were varied in DSA using the upper and lower 95% confidence/credible intervals (CI/Cr) where possible, but that other inputs were sampled at ± 20% of their mean. The company do not provide rationale for varying any inputs by ± 20%, as opposed to within an estimated 95% CI. The EAG consider a more suitable approach would be to sample the lower and upper bounds from the 95% CI of an assigned probability distribution for each parameter, using the mean and standard error where available (or an assumed standard error where neccesary). The range of values tested when using ± 20% may be smaller than would typically be expected, though the EAG do not anticipate the company's approach to have a great impact on the DSA results.

The company provide a summary of model parameters and corresponding "DSA (low; high)" values in Table 99 of the CS. The company present tornado diagrams summarizing the top 20 most influential parameters on pairwise incremental net monetary benefit (INMB) for the CCF and BF populations based on a willingess-to-pay threshold of £30,000. Tornado diagrams are presented for risankizumab versus ustekinumab, adalimumab 160/80 biosimilar, infliximab IV

biosimilar and infliximab SC, respectively, for the CCF population, and versus ustekinumab, vedolizumab IV and vedolizumab SC, respectively, for the BF population.

The company report that the most influential parameters, in both the CCF and BF populations, are the efficacy inputs dervied from the NMAs (specifically, risankizumab probability of response and remission).

The company also report that body weight is a key driver of incremental NMB in the comparison of risankizumab and ustekinumab. However, the EAG are concerned with the company's approach to varying body weight. Ustekinumab induction dosing is based on weight-bands (i.e. <55 kg; >55 kg and ≤ 85 kg; >85 kg), and in the base case, the proportion of patients in each band is based on risankizumab trial data. However, for DSA, the company report lower bound values assuming 100% of patients are < 55 kg and upper bound values assuming 100% of patients are > 85 kg. The EAG do not believe that such extreme value testing is truly reflective of parameter uncertianty, and the company's approach is likely to overestimate the influence of weight distribuitions on cost-effectiveness results.

5.2.2. Probabilistic sensitivity analysis

The company undertook probabilistic sensitivity analysis (PSA) to explore parametric uncertainty by assigning various distributions to input parameters and running the model for 1,000 simulations. In the CS, no justification is provided for the chosen number of PSA iterations, nor are PSA convergence diagrams for costs, QALYs or incremental NMB provided in the company's cost-effectiveness model. The EAG believe the company should have performed an assessment of the stability of probabilistic outcomes, to determine whether 1,000 iterations are suitable for decision making.

In B.3.11.1 of the CS, it is reported that the parameters varied in PSA were baseline patient characteristics, health utilities, efficacy rates, and costs. To inform the PSA, the company assign a probability distribution to all included parameters (reported in B.3.9.1 of the CS), except for induction and maintenance treatment efficacy, for which Convergence Diagnostic and Output Analysis (CODA) samples are used to capture uncertainty in the NMA output. The EAG consider the company's approach, drawing CODA samples with replacement, appropriate for capturing uncertainty around NMA outputs in the PSA.

In addition to reporting tabulated, probabilistic results in the base case, the company present cost-effectiveness acceptability curves (CS B.3.11.1). The company report risankizumab (PAS

price) is associated with [redacted] and [redacted] probabilities of being the most cost-effective treatment option at a willingness-to-pay threshold of £30,000 per QALY gained in the CCF and BF populations, respectively. The EAG infer from the company's submitted cost-effectiveness model that risankizumab (PAS price) was the most cost-effective treatment option in [redacted] and [redacted] of simulations in the CCF and BF populations, respectively, at a willingness-to-pay threshold of £20,000 per QALY gained.

5.2.3. Scenario analyses

The company provide a series of deterministic scenario analyses to assess structural and methodological uncertainty in the cost-effectiveness analysis. In CS B.3.11.3, the company describes seven scenario analyses settings, which include: model time horizon, residual treatment effect, NMA, utility values, dose escalated regimens (start of maintenance), indirect costs and CDAI score.

The company presented the results of the scenario analyses in Section B.3.11.3.1 of the CS, and note that, in the CCF population, the TNF-alpha inhibitors remain cost-effective versus risankizumab. In the BF population, the company notes that risankizumab (PAS price) remains either dominant or is the cost-effective treatment option in all scenarios tested.

5.3. Model validation and face validity check

In CS Section B.3.14, the company describe internal validity checks, with regards to verification of the cost-effectiveness model. However, the company do not provide evidence of external validation, with regards to a comparison of modelled outcomes and trial-observed outcomes over time.

To justify approaches and assumptions throughout the CS, advice from a clinical expert advisory board meeting is cited by the company. The EAG notes the report for this meeting is citation 80 in Document B of the CS; however, the report itself is not provided. In clarification question B2, the EAG requested the company provide this meeting report (as commercial-in-confidence material). The company response indicated that the report could not be provided in full, as elements of the report include proprietary and confidential information that is not relevant for the purposes of the appraisal. The company noted that, where referenced in the CS, relevant excerpts of the advisory board report are disclosed within the Document B reference pack. In CS B.2.3.4, it is noted that eight experts (six clinicians and two health economic experts) were approached to join in a virtual advisory board meeting, all of whom participated. The company

report that “the criteria for selecting suitable experts were expertise and experience of treating CD in the UK (clinician) and specialised technical expertise in economic evaluation and health technology assessment (health economic expert)” (CS B.2.3.4).

The company report that their model was prepared according to several best practice guidelines, and is aligned with NICE guidance (CS, B.3.14.1). Furthermore, the company note that the results of the cost-effectiveness model were verified through an independent review of the model for coding errors, inconsistencies and the plausibility of model inputs (CS, B.3.14.1).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and has explored the impact of alternative assumptions which the EAG believes are plausible. The EAG note that addressing all of the identified issues with the company's approach was not possible within the scope of the EAG's review. Specifically, the EAG has not explored key issues around uncertainty around the company's chosen model structure (Key Issue 4), nor around the company's approach to dose escalation (Key Issue 6). The EAG noted, with concern, that this will likely bias results in favour of risankizumab.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of exploratory analyses investigating the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis. The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

- Company's choice of maximum treatment duration for biologics
- Company's choice of residual treatment effect duration following biologics
- Company's approach to treatment discontinuation rates
- Company's choice of network structure in the maintenance NMA
- Company's decision to calibrate transition matrices by adjusting the remission | mild cut-point estimated from the biologic ordered probit model
- Company's approach to adjust transition matrices for a model 2-week cycle length using an exponential assumption
- Company's background mortality assumptions
- Company's approach to capturing AEs costs and consequences
- Company's approach to estimating health state utility values using OLS regression
- Company's assumption regarding patient HRQL in the surgery state

In Section 6.3, the EAG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2. In Section 6.4, additional EAG scenarios are presented around the EAG preferred base case.

6.1. EAG corrections and adjustments to the company's base case model

The company implemented an amendment to general population utility parameters in an updated version of the cost-effectiveness model submitted alongside EAG clarification question responses; however, the EAG made further corrections to the company's utility age-adjustment approach (see EAG correction #4). Beyond this, a small number of additional errors were identified by the EAG in the company's cost-effectiveness model submitted at clarification question stage. The EAG have made corrections for these errors, which are described as EAG correction #1 to #6 throughout Section 4, and summarized below.

- EAG correction #1, as described in Section 4.2.4, includes vedolizumab IV and vedolizumab SC as comparators in the incremental analysis for the BF population
- EAG correction #2, as described in Section 0, corrects the half-cycle correction application
- EAG correction #3, as described in Section 4.2.6.9, corrects the approach to estimating general population mortality
- EAG correction #4, as described in Section 4.2.7.4, corrects the utility age-adjustment application
- EAG correction #5, as described in Section 4.2.8.1, aligns the risankizumab pack price with the cost reported in the CS
- EAG correction #6, as described in Section 4.2.8.1, applies biologic treatment acquisition and administration costs per the reported dosing schedules, without estimating an average per 2-week model cycle cost

EAG-corrected company base case results are presented for the CCF and BF populations in Table 31 and Table 32, respectively. In the CCF population, risankizumab remains dominated (more costly and less effective) when the EAG's corrections are applied. In the BF population, risankizumab remains a dominant (less costly and more effective) treatment option when the EAG's corrections to the company's base case are implemented.

The design of the company's economic model and volume of VBA code is a limiting factor for exploring probabilistic analysis. The economic model includes one 'Markov trace' (calculation) sheet for the selected comparator, and therefore must cycle through the list of included comparators using automated processes to perform incremental analysis, while also drawing recalibrated transition matrices. The above factors and number of included comparators contribute to a PSA run-time of approximately 9 hours when sampling 1,000 iterations; as such, the EAG did not consider it feasible to produce probabilistic results for each EAG preferred assumption or exploratory analysis within the EAG report timeframe. Additionally, the EAG note the company's economic model presents probabilistic results only in graphical form. In clarification question B31, the EAG requested an executable version of the cost-effectiveness model that included fully incremental probabilistic analysis (in line with the company base case); however, such model was not provided by the company. As such, the EAG present incremental analysis results deterministically (except for the EAG preferred base case in Section 6.3, where incremental analysis results are presented deterministically and probabilistically).

Table 31: EAG-corrected company base case results (CCF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG-corrected company deterministic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£4,229	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£32,556	£32,556
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£57,977	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£329,812	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£211,356	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 32: EAG-corrected company base case results (BF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG-corrected company deterministic base case						
RZB	[redacted]	[redacted]	[redacted]	[redacted]	-	-

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-£26,902	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£51,865	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£34,655	Dominated

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

6.2. Exploratory and sensitivity analyses undertaken by the EAG

This section explains and interprets results from the additional analyses conducted by the EAG in turn. Pairwise, deterministic results from each individual exploratory analysis are presented in Table 33 and Table 34 for risankizumab compared to the optimal comparator (as described in Section 1.7) in the CCF (infliximab SC) and BF (vedolizumab SC) populations, respectively.

The volume of VBA code implemented in the company's model is a limiting factor for exploring additional EAG scenarios. When applying alternative assumptions in the model, the VBA code used to calculate the cost-effectiveness results often overwrites changes to settings in favour of the company's base case assumptions. As such, adapting the model to explore alternative scenarios can be a lengthy process, requiring careful checking to ensure the results correspond to the desired settings.

6.2.1. Increased maximum treatment duration

As discussed in Section 4.2.6.7, the EAG considered the maximum treatment duration of 52 weeks to be inappropriate based on the patient-level data observed in the FORTIFY clinical study (Figure 8) and clinical advice provided to the EAG. Clinical opinion indicated that patients would continue to receive treatment while remaining in remission or exhibiting controlled disease, with a high proportion of patients expected to remain on treatment for several years following treatment initiation. Given the lifetime horizon modelled, the EAG considered a maximum treatment duration of 20 years a more realistic estimate of duration, with alternative durations ranging between 5 and 40 years explored in sensitivity analysis.

In the CCF population, increasing the maximum treatment from 1 to 20 years for all biologic therapies results in lower incremental costs and higher incremental QALYs for risankizumab versus infliximab SC. As such, risankizumab moves from the north-west quadrant (dominated,

more costly and less effective) to the north-east quadrant (more costly and more effective) on the incremental cost-effectiveness plane versus infliximab SC, with an ICER of £52,449.

In the BF population, increasing the maximum treatment duration resulting in higher incremental costs and QALYs for risankizumab compared with vedolizumab SC. Therefore, risankizumab moves from the south-east quadrant (less costly and more effective) to the north-east quadrant of the cost effectiveness plane versus vedolizumab SC, with an ICER of £65,837.

6.2.2. Residual treatment effect

As discussed in Section 4.2.6.7, following discontinuation of biologic therapy, the company assumes a residual treatment effect lasting 52 weeks. Clinical advice to the EAG estimated a 6-month time to symptomatic return for ustekinumab. Given the similar half-lives across treatments, the EAG anticipates that a 52-week period likely overestimates the residual treatment effect post-discontinuation, with 26-weeks a more realistic time point in clinical practice. To align with clinical opinion, the EAG reduced the residual treatment effect duration from 52 to 26 weeks (consistent with company scenario #2).

In the CCF population, risankizumab remains dominated by infliximab SC (more costly and less effective) when assuming a 26-week residual treatment effect duration.

In the BF population, risankizumab remains dominant over vedolizumab SC (less costly and more effective); however, incremental costs and QALYs are lower (relative to the EAG-corrected company base case) when assuming a 26-week residual treatment effect for biologics.

6.2.3. Treatment discontinuation

The EAG considered differences in treatment discontinuation rates between biologic treatments could be an artifact of confounding between study designs, rather than a true difference. The EAG's clinical adviser found it difficult to judge whether assuming different 1-year discontinuation rates across treatments based on observed data across trials was appropriate, given differences in inclusion criteria and study design across trials. Consequently, the EAG explored the impact of applying risankizumab discontinuation rates to all biologic treatments considered in the analysis.

Consistent with the EAG-corrected company base case, when assuming equivalent biologic discontinuation rates across treatments, risankizumab was dominated by infliximab SC. In the BF population, risankizumab remained dominant over vedolizumab SC.

6.2.4. Single maintenance network

As discussed in Section 3.4.6, the EAG considered a single network more appropriate than a split network for estimating efficacy in the maintenance phase. The EAG disagreed with the company's approach to splitting the evidence into two networks, and found the rationale to support the approach inconsistent. Aligned with the basis that network formulation should be based on comparator connections, the EAG implements a single maintenance network in the analysis, using data requested at clarification.

In a version of the cost-effectiveness model submitted by the company at clarification stage, a scenario was presented using a single NMA network in the maintenance phase (described as 'Scenario 2: Single NMA network (all biologics)' in the 'Results – Deterministic (Pair)' worksheet of the model. The EAG note that, while the company updated NMA inputs on the 'Model NMA inputs' worksheet for the standard dose NMAs in this scenario, high dose NMA inputs were unchanged. As transition matrices for ustekinumab are estimated using weighted standard-dose and high-dose NMA inputs, the EAG include a scenario described in the cost-effectiveness model as 'Scenario 3: Corrected single NMA network (all biologics)' in which the high-dose single network inputs are also updated, using data provided by the company in response to clarification question A15. Within the timeframe of the EAG's review of the cost-effectiveness analysis and implementation of the additional and exploratory analysis, the EAG were unable to reflect the parametric uncertainty around the single maintenance network inputs.

When using the EAGs corrected single NMA network scenario, risankizumab remains dominated (more costly and less effective) by infliximab SC in the CCF population. When compared with corrected company base case, the single network results in higher incremental costs ([redacted] versus [redacted] and a larger QALY decrement for risankizumab ([redacted] versus [redacted]).

In the equivalent scenario in the BF population, risankizumab remains dominant (less costly and more effective) when compared with vedolizumab SC. However, compared with the corrected company base case, risankizumab cost savings are lower ([redacted]versus [redacted]) and QALY gains are lower ([redacted] versus [redacted]).

6.2.5. Single maintenance network, adjusted for a temporal effect

Beyond the use of a single maintenance network, the EAG notes heterogeneity is a key limitation of the maintenance phase NMA, as discussed in Section 4.2.6. Generally over time, remission outcomes have improved as treatments themselves have improved. As such, an EAG analysis models the placebo remission rate to include a temporal association with the time at which clinical trials were conducted and bases the absolute remission rates in maintenance on this anchor point (described as 'Scenario 4: Temporal trend single NMA network (all biologics)' on the 'Model NMA Inputs' sheet of the cost-effectiveness model). Within the timeframe of the EAG's review of the cost-effectiveness analysis and implementation of the additional and exploratory analysis, the EAG were unable to reflect the parametric uncertainty around the single maintenance network (adjusted for a temporal effect) inputs.

When applying a single network with temporal effect to the maintenance phase, risankizumab remains dominated (more costly and less effective) by infliximab SC in the CCF population. When compared with corrected company base case, the single network results in higher incremental costs ([redacted] versus [redacted] and a larger incremental QALY decrement for risankizumab ([redacted] versus [redacted]).

In the equivalent scenario in the BF population, risankizumab remains dominant (less costly and more effective) when compared with vedolizumab SC, with marginally lower risankizumab cost savings ([redacted] versus [redacted]) and QALY gains ([redacted] versus [redacted]) company with the corrected base case.

6.2.6. Maintenance phase transition matrix estimation

As discussed in Section 4.2.6.5, the company convert 182-day transition matrices to 14-day transition matrices using an exponential assumption. However, as demonstrated by the EAG, this approach is limited as discrepancies are introduced through the methods inability to account for patients passing through health states to reach others. As such, the EAG proposes an alternative approach to changing cycle length, as suggested in Chhatwal et al., (2016)[55], to avoid the use of an approximate exponential assumption. The EAG's alternative approach estimates the 14-day transition probabilities which, when multiplied repeatedly for 13 cycles, more closely approximate the 182-day transition matrix. This approach minimizes the sum of differences between the observed 182-day transition probabilities and that implied by the 14-day transition probabilities.

In the cost-effectiveness model, the EAG estimates transition matrices without the use of exponential assumption for the single network scenario described in Section 6.2.4 and the single maintenance network, adjusted for a temporal effect scenario described in Section 6.2.5.

In the CCF population, risankizumab remains dominated by infliximab SC in i) the single maintenance network, with non-exponential transition matrix estimation and ii) the single maintenance network (adjusted for a temporal effect), and non-exponential transition matrix estimation.

In the BF population risankizumab remains dominant over vedolizumab SC in i) the single maintenance network, with non-exponential transition matrix estimation and ii) the single maintenance network (adjusted for a temporal effect), with non-exponential transition matrix estimation.

As discussed in Section 4.2.6, the company adjust the ordered probit remission | mild cut point for each treatment to calibrate transition probabilities, in order that the proportion of patients in remission at 52-weeks matches the estimates obtained from the maintenance NMA. As a result, changes to the proportion of patients in the remission and mild health states are allowed in each cycle transition, though no impact is assumed upon the proportion in the moderate-to-severe group. The EAG found this approach unrealistic and preferred instead to adjust both the remission | mild and mild | moderate-to-severe cut points by the same amount.

Without an exponential assumption to adjust cycle length, the EAG estimate transition probabilities by adjusting both cut points for the single network scenario described in Section 6.2.4 and the single maintenance network, adjusted for a temporal effect scenario described in Section 6.2.5. Within the timeframe of the EAG's review of the cost-effectiveness analysis and implementation of the additional and exploratory analysis, the EAG were unable to reflect the parametric uncertainty around the EAG-derived transition matrices.

In the CCF population, risankizumab remains dominated by infliximab SC in i) the single maintenance network, with non-exponential transition matrix estimation and adjustment of both ordered probit cut points and ii) the single maintenance network (adjusted for a temporal effect), with non-exponential transition matrix estimation and adjustment of both ordered probit cut points.

In the BF population, when exploring a single maintenance network, with non-exponential transition matrix estimation and adjustment of both ordered probit cut points, risankizumab is

associated with higher incremental costs and lower incremental QALYs compared with vedolizumab SC. Furthermore, on the incremental cost-effectiveness plane versus vedolizumab SC, risankizumab moves from the south-east quadrant (dominant, less costly and more effective) to the north-east quadrant (more costly and more effective), with an ICER of £63,812.

However, in the BF population when assuming a single maintenance network (adjusted for a temporal effect), with non-exponential transition matrix estimation and adjustment of both ordered probit cut points, risankizumab remains dominant versus vedolizumab SC.

6.2.7. Increased mortality for CD

Advice to the EAG concurred with the company assumption that CD is not a life-shortening disease. While the EAG consider it reasonable to assume patients with CD have equivalent survival to the general population, applying an SMR to increase CD mortality was explored in sensitivity analysis. Based on published evidence identified by the EAG, it is possible that patients with CD are at a heightened mortality risk versus the general population thus, the EAG considered the exploration necessary. Bewtra et al. (2013) [52] report all-cause mortality SMRs varying from 0.71 to 3.20 for CD, with a summary SMR of 1.38.

In the CCF population, applying SMRs of 1.38 and 3.20 to general population mortality results in a change in ICERs of -£33 and -£192, respectively (as such, risankizumab remains dominated by infliximab SC).

Similarly, in the BF population, applying SMRs of 1.38 and 3.20 to general population mortality results in increased ICERs by £11 and £63, respectively (as such, risankizumab remains dominant over vedolizumab SC).

6.2.8. Equivalent AEs across biologic treatments

As discussed in Section 4.2.7.3., differential AEs are assumed across biologic treatments in the company analysis. The EAG considered this a limitation given the differential AEs are based on observed data across studies which could be affected by confounding. This limitation was further affirmed by clinical advice to the EAG, indicating that comparing observed data naively may be inappropriate due to differences in study design. To align with clinical opinion, using the risankizumab observed AEs, the EAG explored the impact of assuming equivalent AEs between biologic treatments.

Incorporating equivalent AEs between biologics results in consistent results with the corrected company base case, with risankizumab remaining dominated (more costly and less effective) by infliximab SC in the CCF population and risankizumab remaining dominant (less costly and more effective) over infliximab SC in the BF population.

6.2.9. AE duration

The company indicated at clarification that the 2-week AE duration assumed in the model was arbitrarily chosen (as discussed in Section 4.2.7.3). In absence of AE-specific durations sourced from the literature, the EAG reduced the AE duration to 1 week, and increased the AE duration to 4-weeks and 8-weeks in various scenario analyses to investigate the impact on the cost-effectiveness results. The EAG implemented the AE duration exploratory analysis in the company's cost-effectiveness model by adjusting the per-cycle weight attributed to AEs.

In the CCF population, when comparing risankizumab with infliximab SC, changing the AE duration did not have a large impact on cost-effectiveness results, with risankizumab remaining dominated (more costly and less effective). When compared with the corrected company base case, increasing the assumed AE duration to 8 weeks marginally reduces incremental costs for risankizumab versus infliximab SC ([redacted] versus [redacted]), while also marginally reducing the incremental QALY decrement ([redacted] versus [redacted]).

In the BF population, risankizumab remains dominant (less costly and more effective) over vedolizumab SC when exploring alternative AE durations; increasing the assumed AE duration marginally increases cost savings and QALY gains for risankizumab versus vedolizumab SC.

6.2.10. Utility estimation for CDAI-based health states

As discussed in Section 4.2.7.1, within-patient repeated EQ-5D-5L observations are not adjusted for in the company base case health state utility estimates. At clarification question stage, the company provided rationale for the use of an OLS regression to estimate utility values, but also presented utility values with a linear mixed model including a random effect to account for repeated measures. Although the estimated values are reasonably similar between methods (Table 26), the EAG considers the linear mixed model a more robust (and therefore more appropriate) approach, given the ability to account for differences between observations at the patient level.

In the CCF population, when applying the linear mixed model estimated utility values in the analysis, the predicted incremental lifetime QALY loss associated with risankizumab compared

with infliximab SC marginally decreases relative to the EAG-corrected company base case; however, risankizumab remains dominated by infliximab SC (more costly and less effective).

In the BF population, when applying the linear mixed model estimated utility values in the analysis, the predicted incremental lifetime QALY gain associated with risankizumab versus vedolizumab SC marginal decreases compared with the corrected company base case ([redacted] versus [redacted]). However, risankizumab remains dominant (less costly and more effective) when compared with vedolizumab SC.

6.2.11. Utility assumptions for the surgery health state

As discussed in Section 4.2.7.2, the company's analysis assumes the surgery health state utility value is equivalent to the CDAI moderate-to-severe utility for one model cycle (2 weeks), and subsequently equivalent to that of CDAI remission for three model cycles (6 weeks). Furthermore, the company's rationale for excluding surgery-related utility decrements was that, as surgery is modelled as a health state, the utility value would include the expected utility loss from complications (CS, B.3.4.4).

Overall, the EAG infer that the company's approach very likely underestimates the HRQoL implications of surgery, and explore cost-effectiveness results when the health state utility value for surgery is assumed to be 80% and 90% of the health state utility value for CDAI moderate-to-severe CD.

In the CCF population, incremental QALYs remain generally consistent with the corrected company base, and when applying a surgery utility multiplier of 80% and 90%, the ICER for risankizumab versus infliximab SC changes by +£155 and +£310, respectively (with risankizumab remaining dominated).

Similarly, in the BF population, incremental QALYs remain generally consistent with the corrected company base, and when applying a surgery utility multiplier of 80% and 90%, the ICER for risankizumab versus vedolizumab SC changes by +£23 and +£46, respectively (with risankizumab remaining dominant).

6.2.12. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.11 individually. The effect of each change upon the EAG-corrected company base case for the optimal comparator in each

population (infliximab SC and vedolizumab SC, CCF and BF respectively – as discussed in Section 1.7) are provided in Table 33 and 34.

In the CCF population, risankizumab remains dominated by infliximab SC in most exploratory analyses performed. The greatest difference in incremental costs and QALYs is observed when exploring assumptions regarding the use of a single maintenance network (adjusted for a temporal effect), with non-exponential transition matrix estimation and adjustment of both ordered probit cut points. This scenario is associated with incremental costs for risankizumab versus infliximab SC of [redacted] (compared with [redacted] in the corrected base case), and incremental QALYs of [redacted] (compared with [redacted] in the company base case). Furthermore, compared with the corrected base case, increasing the maximum treatment duration for biologic therapies to 20 years had a large impact on incremental QALYs for risankizumab versus infliximab SC ([redacted]). Relatively small differences in results are observed when changing assumptions around background mortality rates, adverse event rates and durations and the utility value in the surgery health state.

In the BF population, the cost-effectiveness results appear most sensitive to assumptions regarding the maximum treatment duration. Assuming a 20-year maximum treatment duration for biologic therapies results in incremental costs for risankizumab versus vedolizumab SC of [redacted] (compared with [redacted] in the corrected base case) and incremental QALYs of [redacted] (compared with [redacted] in the company base case), with a resulting ICER of £65,837.

Table 33: EAG's exploratory analyses – CCF population (risankizumab versus infliximab SC)

Scenario	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
EAG corrected company base-case	[redacted]	[redacted]	Dominated, -£102,827	N/A
Maximum treatment duration, 5 years	[redacted]	[redacted]	Dominated, -£70,999	+£31,828
Maximum treatment duration, 10 years	[redacted]	[redacted]	£109,669	+£212,496
Maximum treatment duration, 20 years	[redacted]	[redacted]	£52,499	+£155,326
Maximum treatment duration, 40 years	[redacted]	[redacted]	£61,486	+£164,313
Residual treatment effect, 26 weeks	[redacted]	[redacted]	Dominated, -£100,343	+£2,484

Scenario	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
Treatment discontinuation rate equivalent to risankizumab for all biologics	[redacted]	[redacted]	Dominated, -£97,765	+£5,062
Single maintenance network	[redacted]	[redacted]	Dominated, -£81,619	+£21,208
Single maintenance network, with non-exponential transition matrix estimation	[redacted]	[redacted]	Dominated, -£81,870	+£20,957
Single maintenance network, with non-exponential transition matrix estimation and adjustment of both ordered probit cut points	[redacted]	[redacted]	Dominated, -£83,597	+£19,231
Single maintenance network (adjusted for a temporal effect)	[redacted]	[redacted]	Dominated, -£78,107	+£24,720
Single maintenance network (adjusted for a temporal effect), and non-exponential transition matrix estimation	[redacted]	[redacted]	Dominated, -£78,005	+£24,822
Single maintenance network (adjusted for a temporal effect), with non-exponential transition matrix estimation and adjustment of both ordered probit cut points	[redacted]	[redacted]	Dominated, -£76,763	+£26,064
SMR for CD compared with the general population = 1.38	[redacted]	[redacted]	Dominated, -£102,860	-£33
SMR for CD compared with the general population = 3.20	[redacted]	[redacted]	Dominated, -£103,019	-£192
AEs equivalent to risankizumab	[redacted]	[redacted]	Dominated, -£100,355	£2,472
AE duration, 1 week	[redacted]	[redacted]	Dominated, -£98,592	£4,235
AE duration, 4 weeks	[redacted]	[redacted]	Dominated, -£113,414	-£10,587
AE duration, 8 weeks	[redacted]	[redacted]	Dominated, -£149,448	-£46,621
Health state utility values, risankizumab trials, EQ-5D, linear mixed model	[redacted]	[redacted]	Dominated, -£123,458	-£20,630
Surgery versus moderate-to-severe, health state utility multiplier = 0.9	[redacted]	[redacted]	Dominated, -£102,672	+£155
Surgery versus moderate-to-severe, health state utility multiplier = 0.8	[redacted]	[redacted]	Dominated, -£102,517	+£310

Abbreviations: AE, Adverse event; CCF, conventional care failure; CD, Crohn's Disease; EAG, Evidence Assessment Group; EQ-5D, European Quality of Life Five Dimension; ICER, incremental cost-effectiveness ratio; LMM, linear mixed model; N/A, not applicable; QALY, quality adjusted life year; SC, subcutaneous; SMR, standardized mortality ratio.

Table 34: EAG's exploratory analyses – BF population (risankizumab versus vedolizumab SC)

Scenario	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
EAG corrected company base-case	[redacted]	[redacted]	Dominant, -£26,902	N/A
Maximum treatment duration, 5 years	[redacted]	[redacted]	£32,798	+£59,699
Maximum treatment duration, 10 years	[redacted]	[redacted]	£53,111	+£80,013
Maximum treatment duration, 20 years	[redacted]	[redacted]	£65,837	+£92,739
Maximum treatment duration, 40 years	[redacted]	[redacted]	£71,529	+£98,431
Residual treatment effect, 26 weeks	[redacted]	[redacted]	Dominant, -£19,550	+£7,352
Treatment discontinuation rate equivalent to risankizumab for all biologics	[redacted]	[redacted]	Dominant, -£32,609	-£5,707
Single maintenance network	[redacted]	[redacted]	Dominant, -£12,547	+£14,355
Single maintenance network, with non-exponential transition matrix estimation	[redacted]	[redacted]	Dominant, -£9,709	+£17,193
Single maintenance network, with non-exponential transition matrix estimation and adjustment of both ordered probit cut points	[redacted]	[redacted]	£63,812	+£90,714
Single maintenance network (adjusted for a temporal effect)	[redacted]	[redacted]	Dominant, -£22,368	+£4,534
Single maintenance network (adjusted for a temporal effect), and non-exponential transition matrix estimation	[redacted]	[redacted]	Dominant, -£19,745	+£7,157
Single maintenance network (adjusted for a temporal effect), with non-exponential transition matrix estimation and adjustment of both ordered probit cut points	[redacted]	[redacted]	Dominant, -£3,869	+£23,033
SMR for CD compared with the general population = 1.38	[redacted]	[redacted]	Dominant, -£26,891	+£11
SMR for CD compared with the general population = 3.20	[redacted]	[redacted]	Dominant, -£26,839	+£63
AEs equivalent to risankizumab	[redacted]	[redacted]	Dominant, -£29,641	-£2,739
AE duration, 1 week	[redacted]	[redacted]	Dominant, -£27,615	-£713
AE duration, 4 weeks	[redacted]	[redacted]	Dominant, -£25,635	£1,267

Scenario	Incremental costs	Incremental QALYs	ICER £/QALY	+/- corrected company base case
AE duration, 8 weeks	[redacted]	[redacted]	Dominant, -£23,596	+£3,306
Health state utility values, risankizumab trials, EQ-5D, linear mixed model	[redacted]	[redacted]	Dominant, -£31,061	-£4,159
Surgery versus moderate-to-severe, health state utility multiplier = 0.9	[redacted]	[redacted]	Dominant, -£26,879	+£23
Surgery versus moderate-to-severe, health state utility multiplier = 0.8	[redacted]	[redacted]	Dominant, -£26,856	+£46

Abbreviations: AE, Adverse event; BF, biologic failure; CD, Crohn's Disease; EAG, Evidence Assessment Group; EQ-5D, European Quality of Life Five Dimension; ICER, incremental cost-effectiveness ratio; LMM, linear mixed model; N/A, not applicable; QALY, quality adjusted life year; SC, subcutaneous; SMR, standardized mortality ratio.

6.3. EAG's preferred assumptions

The EAG's preferred adaptations to the EAG-corrected company base case draw on several of the exploratory analyses described and presented in Section 6.2. Table 35 and Table 36 demonstrate the deterministic, pairwise, step-by-step impact of the EAG-preferred assumptions, from the EAG-corrected company base case to the EAG preferred base case, against the optimal in the CCF (infliximab SC) and BF (vedolizumab SC) populations (as described in Section 1.7), respectively.

The EAG note that neither the company's base case nor the EAG's preferred base case address issues with the company's chosen model structure (Key Issue 4) and approach to dose escalation (Key Issue 6).

Table 37 and Table 38 summarise incremental deterministic and probabilistic results for the EAG base case in the CCF and BF populations, respectively.

Table 35: EAG's preferred model assumptions – CCF population (risankizumab versus infliximab SC)

Preferred assumption	Section in EAG report	Cumulative ICER, £/QALY (stepwise change)
Company's base case (probabilistic)	Section 5.1.1.1	Dominated, -£81,752
Company's base case (deterministic)	Section 5.1.1.1	Dominated, -£84,028
EAG corrected company base case	Section 6.1	Dominated, -£102,827 (-£18,800)

Preferred assumption	Section in EAG report	Cumulative ICER, £/QALY (stepwise change)
+ Maximum treatment duration of 20 years for all biologic treatments	Section 4.2.6.7 and 6.2.3	£52,499 (+£155,326)
+ Residual treatment effect of 26 weeks for all biologic treatments	Section 4.2.6.7 and 6.2.3	£57,503 (+£5,004)
+ Single maintenance network, with an estimated maintenance placebo remission proportion that is adjusted for a temporal effect	Section 4.2.6 and 6.2.1	Dominated, -£76,611 (-£134,114)
+ Transition matrices estimated by adjusting both the remission | mild and mild | moderate-to-severe cut points, and without an exponential assumption to estimate 2-week transitions	Section 4.2.6 and 6.2.6	Dominated, -£75,237 (+£1,374)
+ Health state utility values estimated using a mixed linear model	Section 4.2.7.1 and 6.2.10	Dominated, -£88,792 (-£13,555)
EAG's preferred base case (deterministic)	Section 6.2 and 6.3	Dominated, -£88,792
EAG's preferred base case (probabilistic)	Section 6.2 and 6.3	Dominated, -£90,018

Abbreviations: CCF, conventional care failure; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

Table 36: EAG's preferred model assumptions – BF population (risankizumab versus vedolizumab SC)

Preferred assumption	Section in EAG report	Cumulative ICER, £/QALY (stepwise change)
Company's base case (probabilistic)	Section 5.1.1.1	Dominant, -£44,642
Company's base case (deterministic)	Section 5.1.1.1	Dominant, -£43,738
EAG corrected company base case	Section 6.1	Dominant, -£26,902 (+£16,836)
+ Maximum treatment duration of 20 years for all biologic treatments	Section 4.2.6.7 and 6.2.3	£65,837 (+£92,739)
+ Residual treatment effect of 26 weeks for all biologic treatments	Section 4.2.6.7 and 6.2.3	£66,781 (-£943)
+ Single maintenance network, with an estimated maintenance placebo remission proportion that is adjusted for a temporal effect	Section 4.2.6 and 6.2.1	£55,959 (-£10,822)
+ Transition matrices estimated by adjusting both the remission | mild and mild | moderate-to-severe cut points, and without an exponential assumption to estimate 2-week transitions	Section 4.2.6 and 6.2.6	£119,509 (+£63,550)
+ Health state utility values estimated using a mixed linear model	Section 4.2.7.1 and 6.2.10	£143,088 (+£23,579)

Preferred assumption	Section in EAG report	Cumulative ICER, £/QALY (stepwise change)
EAG's preferred base case (deterministic)	Section 6.2 and 6.3	£143,088
EAG's preferred base case (probabilistic)	Section 6.2 and 6.3	£142,074

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

Table 37: EAG incremental base case results – CCF population

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG preferred deterministic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£5,536	£5,536
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£56,481	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£52,086	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£1,349,539	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£4,358,832	Dominated
EAG preferred probabilistic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]				
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£6,744	£6,744
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£55,111	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£48,951	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£867,497	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£91,825,236	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 38: EAG incremental base case results – BF population

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG preferred deterministic base case						
VDZ SC	[redacted]	[redacted]	-	-	-	-
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£2,198,195	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£252,156	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£143,088	£143,088
EAG preferred probabilistic base case						
VDZ SC	[redacted]	[redacted]	-	-	-	-
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£1,487,732	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£248,239	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£142,074	£142,074

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; IV, intravenous; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

6.4. EAG scenarios around the EAG preferred base case

In Section 6.1 of this report, EAG corrections to the company's executable cost-effectiveness model are described. In Section 6.2, several exploratory analyses around the EAG-corrected company base case are individually presented using pairwise cost-effectiveness analysis. In Section 6.3, both the step-by-step effect of EAG preferred changes on pairwise cost-effectiveness results, and fully incremental EAG preferred base case results are reported.

Here, in Section 6.4, additional EAG scenario analyses applied to the EAG-preferred base case are presented for the CCF and BF populations, using fully incremental, deterministic analysis.

6.4.1. Maximum treatment duration assumption

As outlined in Key Issue 5, the EAG has significant concerns with the company's treatment discontinuation assumptions; in particular, assuming all patients discontinue biologic therapy at 52 weeks. As such, the EAG's preferred base case assumes a 20-year maximum treatment duration rate for all biologic therapies.

However, Table 39 (CCF population) and Table 40 (BF population) present full incremental analysis results from a scenario around the EAG's preferred base case, in which the EAG's preferred 20-year maximum treatment duration assumption is relaxed to both 1 and 5 years.

In the CCF population, consistent with the EAG preferred base case, risankizumab is dominated by TNF-alpha inhibitors when the maximum treatment duration is assumed to be 1 or 5 years. In the BF population, when reducing the maximum treatment duration from 20 years to 5 years the ICER for risankizumab versus vedolizumab SC falls from £143,088 (EAG base case) to £103,081. Moreover, lowering the maximum treatment duration to 1 year leads to a further reduction in the ICER for risankizumab versus vedolizumab SC (£568).

Table 39: Maximum treatment duration scenarios around EAG preferred base case (CCF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Maximum treatment duration of 1 year						
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-	-
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£3,825	£3,825
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£19,503	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£23,242	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	-£358,121	Dominated
UST6	[redacted]	[redacted]	[redacted]	[redacted]	-£868,516	Dominated
Maximum treatment duration of 5 years						
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£49,495	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£8,824	£8,824
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£42,057	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	-£560,218	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£6,699,647	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 40: Maximum treatment duration scenarios around EAG preferred base case (BF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Maximum treatment duration of 1 year						
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£568	£568
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£1,332,202	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£65,355	Dominated
Maximum treatment duration of 5 years						
VDZ SC	[redacted]	[redacted]	-	-	-	-
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£2,018,541	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£215,997	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£103,081	£103,081

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

6.4.2. Estimation and application of maintenance treatment effectiveness assumptions

As outlined in Key Issue 6, the EAG has significant concerns with the company's maintenance treatment effectiveness estimates and assumptions. The EAG recommends the use of a single network for the maintenance NMA and a placebo remission model allowing for plausible causes of heterogeneity (in particular, a temporal association with the time at which individual clinical trials were conducted). Furthermore, the EAG prefers transition matrices that are calibrated by adjusting both the remission | mild and mild | moderate-to-severe ordered probit cut points, and a transition matrix cycle length adjustment approach that does not rely on an exponential assumption.

However, a scenario analysis is presented around the EAG-preferred base case in Table 41 (CCF) and Table 42 (BF), which relaxes the EAG's preferred assumptions around the single maintenance network, placebo remission temporal adjustment, transition matrix calibration method and transition matrix cycle length adjustment approach.

In the CCF population, when the majority of EAG preferred assumptions are combined with the company's base case NMA and transition matrix calibration and adjustment approach, risankizumab is associated with an ICER of £62,821 versus infliximab SC. In the equivalent BF population scenario, risankizumab is associated with an ICER of £79,559 versus vedolizumab SC.

Table 41: NMA and transition matrix calibration scenario around EAG preferred base case (CCF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
ADA 80/40	[redacted]	[redacted]	-	-	-	-
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£46,941	Extendedly dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£34,456	£34,456
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£41,283	£62,821
UST	[redacted]	[redacted]	[redacted]	[redacted]	£72,392	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£230,961	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 42: NMA and transition matrix calibration scenario around EAG preferred base case (BF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Maximum treatment duration of 5 years						
VDZ SC	[redacted]	[redacted]				
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£3,190,924	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£208,011	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£79,559	£79,559

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; IV, intravenous; NMA, network meta-analysis; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

6.4.3. Health state utility estimation

As described in Key Issue 7, the company use OLS regression to estimate CDAI-based health state utility values from patient-reported risankizumab trial data in their base case. In the context of within-patient repeated measures, the EAG prefer to use health state utility values based on the same data but estimated using a (linear) mixed model that includes a random effect to account for repeated measures.

However, a scenario is presented in Table 43 (CCF) and Table 44 (BF) around the EAG-preferred base case, which combines the majority of EAG preferred assumptions with the company preferred OLS-estimated health state utility values. In this scenario, consistent with the EAG preferred base case, risankizumab is dominated in the CCF population incremental analysis. In the equivalent scenario in the BF population, the risankizumab ICER versus vedolizumab SC is £119,509 (compared with £143,088 in the EAG preferred base case).

Table 43: Health state utility estimation scenario (OLS estimation) around EAG preferred base case (CCF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£4,947	£4,947
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£45,377	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£46,553	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£5,472,524	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£13,855,370	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; OLS, ordinary least squares; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 44: Health state utility estimation scenario (OLS estimation) around EAG preferred base case (BF population)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Maximum treatment duration of 5 years						
VDZ SC	[redacted]	[redacted]	-	-	-	-

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£1,876,962	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£193,271	Extended dominance
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£119,509	£119,509

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; IV, intravenous; OLS, ordinary least squares; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

6.5. Conclusions of the cost-effectiveness section

The company's cost-effectiveness analysis estimates that risankizumab is dominated by (more costly and less effective than) relevant comparator treatment options in NHS England and, as such, is not a cost-effective treatment option for patients with moderately-to-severely active CD in a CCF population. However, the company's cost-effectiveness analysis estimates that risankizumab is dominant (generates more QALYs at a lower cost), when compared with relevant NHS England treatment options, for patients with moderately-to-severely active CD in a BF population.

The EAG was not satisfied that the cost-effectiveness evidence submitted by the company fully addressed the decision problem at hand. Although the company's cost-effectiveness analysis provides an estimate of the lifetime cost and QALY implications of introducing risankizumab to NHS England practice for moderately-to-severely active CD (from an NHS and PSS cost perspective and a direct health effect perspective for patients), the EAG has significant concerns with the cost-effectiveness evidence that neither the company's base case nor the EAG's preferred base case can address. Primarily, as outlined in Key Issue 4, the EAG are concerned that company's CDAI-based model structure is not reflective of relevant patient outcomes. Furthermore, adding risankizumab to the list of currently available treatment options currently available would extend the plausible biologic options available to treat each patient, yet the company assumes that after the initial therapy (up to 52 weeks in the company's base case), all patients move to conventional care. The EAG are concerned that this assumption does not reflect the treatment pathway as described by both the company and the EAG's clinical expert.

The EAG was not satisfied that the company's cost-effectiveness results provide an unbiased estimate of the likely cost-effectiveness of moderately-to-severely active CD. The company's

cost-effectiveness analysis is largely driven by assumptions regarding the estimation and application of treatment effectiveness, and the assumed maximum treatment duration for biologic therapies.

The EAG was unable to provide alternative solutions for all identified issues; namely, the chosen model structure as described above, the company's dose escalation assumptions which the EAG worry bias in favour of risankizumab (Key Issue 6) and the method of administration for risankizumab (Key Issue 8). However, the EAG was able to carry out several exploratory analyses (as described throughout Section 6.2); some of which were preferred adaptations which were used to form the EAG preferred base case (as described in Section 6.3). The EAG's preferred analysis increases the maximum treatment duration for all biologic therapies to 20 years, reduces the residual treatment effect following biologic therapy to 26 weeks, uses a single maintenance network that is combined with an estimated maintenance placebo remission proportion that is adjusted for a temporal effect, estimates transition matrices by adjusting both the remission | mild and mild | moderate-to-severe cut points in the ordered probit model, adjusts transition matrices for a 2-week cycle length without using an exponential assumption, and estimates health state utility values estimated using a mixed linear model.

In line with the company's cost-effectiveness estimate, in the CCF population, risankizumab is dominated by (more costly and less effective than) relevant NHS England treatment options in the EAG's preferred base case. In the BF population, vedolizumab IV is dominated by vedolizumab SC, and ustenkinumab extendedly dominated risankizumab. The ICER for risankizumab versus vedolizumab SC (the optimal comparator in the BF population incremental analysis), in the EAG's preferred base case, falls above the typical NICE willingness-to-pay threshold of £20,000 to £30,000 per QALY gained.

References

1. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380(9853):1590-605.

2. Petagna L, Antonelli A, Ganini C, Bellato V, Campanelli M, Divizia A, et al. Pathophysiology of Crohn's disease inflammation and recurrence. Biol Direct. 2020;15(1):23.

3. NHS Inform. Crohn's Disease – Illness & Conditions 2020 [Available from: https://www.nhsinform.scot/illnesses-and-conditions/stomach-liver-and-gastrointestinal-tract/crohns-disease (last accessed: August 2022.)

4. Perler BK, Ungaro R, Baird G, Mallette M, Bright R, Shah S, et al. Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. BMC Gastroenterol. 2019;19(1):47.

5. Crohn's, Colitis UK. Mental health and wellbeing. 2021. Available from: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/mental-wellbeing (Accessed June 2022).

6. Floyd DN, Langham S, Séverac HC, Levesque BG. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. Dig Dis Sci. 2015;60(2):299-312.

7. Gay M, Barrison I, Bean K, Bevan S, Carroll R, Clark S. Crohn's, Colitis and Employment-from career aspirations to reality. Hertfordshire: Crohn's and Colitis UK. 2011.

8. Irving P, Barrett K, Nijher M, de Lusignan S. Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. Evid Based Ment Health. 2021;24(3):102-9.

9. Lönnfors S, Vermeire S, Greco M, Hommes D, Bell C, Avedano L. IBD and health-related quality of life -- discovering the true impact. J Crohns Colitis. 2014;8(10):1281-6.

10. Norton BA, Thomas R, Lomax KG, Dudley-Brown S. Patient perspectives on the impact of Crohn's disease: results from group interviews. Patient Prefer Adherence. 2012;6:509-20.

11. NHS Digital. Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20 2022 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 (last accessed: August 2022.)

12. King D, Reulen RC, Thomas T, Chandan JS, Thayakaran R, Subramanian A, et al. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. Aliment Pharmacol Ther. 2020;51(10):922-34.

13. Office for National Statistics. Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland 2021 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland (last accessed: August 2022.)

14. National Institute for Health and Care Excellence. Crohn's disease: management (NG129) Manchester: NICE; 2019 [Available from: https://www.nice.org.uk/guidance/ng129/resources/crohns-disease-management-pdf-66141667282885 (last accessed: August 2022.)

15. Kashani A, Schwartz DA. The Expanding Role of Anti-IL-12 and/or Anti-IL-23 Antibodies in the Treatment of Inflammatory Bowel Disease. Gastroenterol Hepatol (N Y). 2019;15(5):255-65.

16. Ma C, Panaccione R, Khanna R, Feagan BG, Jairath V. IL12/23 or selective IL23 inhibition for the management of moderate-to-severe Crohn's disease? Best Pract Res Clin Gastroenterol. 2019;38-39:101604.

17. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj. 2017;358:j4008.

18. National Institute for Health and Care Excellence. Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24) 2022 [Available from: https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#qualityassessment-of-the-relevant-clinical-effectiveness-evidence.)

19. 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. Bmj. 2019;366:l4898.

20. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease (ADVANCE [M16-006]). Clinical Study Report. Risankizumab. 2021.

21. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment (MOTIVATE [M15-991]). Clinical Study Report. Risankizumab. 2021.

22. D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel J-F, Danese S, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. The Lancet. 2022;399(10340):2015-30.

23. AbbVie. Multicenter, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Crohn's Disease (FORTIFY [M16-000]). Clinical Study Report. Risankizumab. 2021.

24. Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease:

results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet. 2022;399(10340):2031-46.

25. AbbVie. Crohn’s disease HTA advisory board report. Data on file. 2021. (MAP ID: 2021-GB-MNP-00091).

26. Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohns Colitis. 2012;6(2):160-73.

27. Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T, Suzuki Y, et al. Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. J Gastroenterol. 2020;55(3):291-306.

28. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-analysis for decision-making: John Wiley & Sons; 2018.

29. Glanville J, Kaunelis D, Mensinkai S. How well do search filters perform in identifying economic evaluations in MEDLINE and EMBASE. International Journal of Technology Assessment in Health Care. 2009;25(4):522-9.

30. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Aliment Pharmacol Ther. 2009;30(3):265-74.

31. Catt H, Bodger K, Kirkham JJ, Hughes DA. Value Assessment and Quantitative Benefit-Risk Modelling of Biosimilar Infliximab for Crohn's Disease. Pharmacoeconomics. 2019;37(12):1509-23.

32. Lindsay J, Punekar YS, Morris J, Chung-Faye G. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease--modelling outcomes in active luminal and fistulizing disease in adults. Aliment Pharmacol Ther. 2008;28(1):76-87.

33. Loftus EV, Jr., Johnson SJ, Yu AP, Wu EQ, Chao J, Mulani PM. Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease. Eur J Gastroenterol Hepatol. 2009;21(11):1302-9.

34. Robson RE, Vanoli A, Tolley K. Cost-effectiveness of vedolizumab compared with conventional therapy in patients with Crohn's disease in the United Kingdom (UK). Value Health. 2018;21(Supplement 3):S455-S6.

35. Saito S, Shimizu U, Nan Z, Mandai N, Yokoyama J, Terajima K, et al. Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: a cost-effectiveness analysis. J Crohns Colitis. 2013;7(2):167-74.

36. Wilson M, Lucas A. Cost-effectiveness of vedolizumab versus ustekinumab in United Kingdom Crohn's disease patients who previously failed TNF inhibitor therapy. Value Health. 2018;21(Supplement 3):S145.

37. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.

38. Efficace F, Bottomley A, Osoba D, Gotay C, Flechtner H, D'Haese S, et al. Beyond the development of health-related quality-of-life (HRQOL) measures: a checklist for evaluating HRQOL outcomes in cancer clinical trials--does HRQOL evaluation in prostate cancer research inform clinical decision making? J Clin Oncol. 2003;21(18):3502-11.

39. Bassi A, Dodd S, Williamson P, Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut. 2004;53(10):1471-8.

40. Buchanan J, Wordsworth S, Ahmad T, Perrin A, Vermeire S, Sans M, et al. Managing the long term care of inflammatory bowel disease patients: The cost to European health care providers. J Crohns Colitis. 2011;5(4):301-16.

41. Burisch J, Vardi H, Pedersen N, Brinar M, Cukovic-Cavka S, Kaimakliotis I, et al. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom Study. Inflamm Bowel Dis. 2015;21(1):121-31.

42. Ding Z, Muser E, Hoops T, Izanec JL, Ma T, Gao L-L, et al. S723 Improvements in Work Productivity Loss and Associated Cost Reductions with Ustekinumab and Adalimumab in Biologic-Naïve Patients with Moderately-to-Severely Active Crohn's Disease: Results From the SEAVUE Study. Official journal of the American College of Gastroenterology| ACG. 2021;116:S330.

43. Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. Frontline Gastroenterol. 2015;6(3):169-74.

44. Jin R, Nduka C, Courmier D, Knight H, Meadows R, Piercy J, et al. REAL-WORLD UTILIZATION OF ADALIMUMAB BIOSIMILAR (ABP 501) IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE IN EUROPE. Gastroenterology. 2022;162(3):S109-S10.

45. Lim S, Gros Alcade B, Lehmann A, Lindsay J, Gaya D, Caulfield L, et al. P554 Vedolizumab Associated quality of Life and inflammatory bowel disease control Upon Entering a subcutaneous switching program (VALUE) – Results from a multi-centre UK study. Journal of Crohn's and Colitis. 2022;16(Supplement_1):i499-i500.

46. Louis E, Löfberg R, Reinisch W, Camez A, Yang M, Pollack PF, et al. Adalimumab improves patient-reported outcomes and reduces indirect costs in patients with moderate to severe Crohn's disease: Results from the CARE trial ☆. Journal of Crohn's and Colitis. 2013;7(1):34-43.

47. Moore AC, Russell D, Dart R, Dias S, Ghuman S, Petri B, et al. P411 Stable pharmacokinetics and biochemical markers of inflammatory bowel disease activity: Results from a real-world adalimumab biosimilar switching program. Journal of Crohn's and Colitis. 2022;16(Supplement_1):i401-i2.

48. Obando C, Ding Z, Gao L, Pires A, Muser E, Gasink C. Reduced Healthcare Costs of Crohn's Disease-Related Hospitalizations and Surgeries in Patients Initiated with Ustekinumab

in the IM-UNITI LTE Study. 2018. Presented at Academy of Managed Care Pharmacy Nexus 2018 (abstract #K4). Available at: https://www.jmcp.org/doi/pdf/10.18553/jmcp.2018.24.10-a.s1 (Accessed June 2022).

49. Peyrin-Biroulet L, Vermeire S, D'Haens GR, Panés J, Dignass A, Magro F, et al. DOP90 Efficacy of the treat-to-target approach in modifying disease course with ustekinumab in patients with moderate-to-severe Crohn's Disease: Results from the STARDUST trial. Journal of Crohn's and Colitis. 2022;16(Supplement_1):i132-i4.

50. Ponsioen CY, de Groof EJ, Eshuis EJ, Gardenbroek TJ, Bossuyt PMM, Hart A, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol Hepatol. 2017;2(11):785-92.

51. Teeple A, Muser E, Naessens D, Lueza B, Kamal Z, Colonier AF, et al. S0464 Cost Reduction Associated With Improvement in Work Productivity Loss From Ustekinumab Treatment by Disease Severity States in Crohn's Disease Patients: Results From the IM-UNITI Clinical Trial. Official journal of the American College of Gastroenterology| ACG. 2020;115:S233.

52. Bewtra M, Kaiser LM, TenHave T, Lewis JD. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. Inflamm Bowel Dis. 2013;19(3):599-613.

53. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [TA352]. Manchester: NICE; 2014 [Available from: https://www.nice.org.uk/guidance/ta352/documents/crohns-disease-moderate-to-severe-vedolizumab-committee-papers2 (last accessed: August 2022.)

54. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy STA (TA456). Manchester: NICE; 2017 [Available from: https://www.nice.org.uk/guidance/ta456/documents/committee-papers (Accessed June 2022) (last accessed: August 2022.)

55. Chhatwal J, Jayasuriya S, Elbasha EH. Changing Cycle Lengths in State-Transition Models: Challenges and Solutions. Med Decis Making. 2016;36(8):952-64.

56. Hernández Alava M, Wailoo A, Pudney S, Gray L, Manca A. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. 2020;24:34.

57. Buxton MJ, Lacey LA, Feagan BG, Niecko T, Miller DW, Townsend RJ. Mapping from disease-specific measures to utility: an analysis of the relationships between the Inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index in Crohn's disease and measures of utility. Value Health. 2007;10(3):214-20.

58. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.

59. National Health Service. National Schedule of NHS Costs 2019/20 2022 [Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ (last accessed: August 2022.)

Single Technology Appraisal

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

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 **13 September 2022** 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 separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Subgroup analysis per Crohn's disease (CD) location, incorrect statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Statement from the EAG that the company submission (CS) excluded subgroup analysis (by CD location) from their decision problem. Section 1.3, Page 13, Key Issue 1.	The company suggest that the EAG amend this part to state that the CS highlighted that 'due to low subject numbers the analysis of outcomes by CD location was deemed untenable' (CS Section B.1.1, Table 1).	The final scope by NICE stated that the subgroup analyses by CD location should be considered if evidence allows. As the company stated, evidence does not allow for this analysis to be conducted.	This is not a factual error.
The EAG stated that 'the company should as a minimum have retained the CD location subgroup analysis in the decision problem and stated that it was unable to provide data to conduct this analysis'. Section 1.3, Page 13, Key Issue 1.	The company suggest that the EAG amend this part to: 'Due to the clinical significance of this subgroup analysis, the EAG considered that the company should as a minimum have retained the CD location subgroup analysis.'	The company did mention that they were unable to provide data to conduct the subgroup analysis; therefore, this statement is inaccurate. More precisely, in the CS Section B.1.1, Table 1 (decision problem), the company specify that 'Due to low subject numbers the analysis of outcomes by CD location was deemed untenable.'	This is not a factual error.
The EAG report states that 'Table 12 in the CS showed 155 patients with ileocolic	The company suggest that the EAG amend this part to:	To clarify that these are the total patient numbers by CD location across both arms of	This is not a factual error. However, in the interest of clarity, the

CS, 76 patients with colonic CD and 55 patients with ileal CD in FORTIFY. Section 2.4, Page 30, Table 7.	'Table 12 in the CS showed 155 patients with ileocolic CS, 76 patients with colonic CD and 55 patients with ileal CD in FORTIFY across both intervention and placebo arms.'	the FORTIFY trial, as this statement may be misinterpreted.	EAG has made the suggested amendment.

Issue 2 Risankizumab administration methods incorrectly described

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states 'Risankizumab SC was delivered using IV or SC injections in the risankizumab CD studies included in the CS'. Section 2.3, Page 26, second paragraph.	The company suggest the EAG amend this sentence to the following: 'Risankizumab was delivered IV in the induction trials (ADVANCE, MOTIVATE) and SC in the maintenance trial (FORTIFY).' Alternatively, the EAG can remove the sentence all together since the sentence before states the routes of administration already (and correctly).	To correctly report risankizumab's route of administration in the EAG report. The original text specifies risankizumab SC (subcutaneous) was delivered with IV (intravenous) in the clinical trials which is factually incorrect.	Amended to "Risankizumab was delivered IV in the risankizumab induction trials (ADVANCE and MOTIVATE) and SC in the risankizumab maintenance trial (FORTIFY) included in the CS."

Issue 3 Clinical trial data, incorrect statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG refers to FORTIFY (maintenance trial of risankizumab in CD) as a 'supplementary trial', which is incorrect. FORTIFY, ADVANCE and MOTIVATE are all pivotal trials. Section 3.2.2.3, Page 43, second paragraph.	The company suggest that the EAG amend the statement 'Dosing and method of administration differed between the pivotal trials and the supplementary trial' to the following: 'Dosing and method of administration differed between the pivotal induction (IV administration in ADVANCE and MOTIVATE) and maintenance trial (SC administration in FORTIFY).'	FORTIFY is a pivotal trial, not supplementary to the induction trials (ADVANCE, MOTIVATE).	Amended to "Dosing and method of administration differed between the pivotal induction trials (IV administration in ADVANCE and MOTIVATE) and the maintenance trial (SC administration in FORTIFY)."
The EAG report states that 'In the FORTIFY sub-study 1, which is included in the company submission, the intervention is a maintenance dose of risankizumab; administered subcutaneously to	The company suggest that the EAG amend the text to correctly describe the FORTIFY maintenance study: '…the intervention is a maintenance dose of risankizumab, or placebo; administered subcutaneously to participants randomised thereto	The description of patient flow through the pivotal trials of risankizumab in CD (ADVANCE, MOTIVATE, FORTIFY) were incorrectly captured by the EAG.	Amended to state "…the intervention is a maintenance dose of risankizumab; administered subcutaneously to participants randomised thereto as either 360 mg Q8W (licensed dose) or 180 mg Q8W risankizumab for 52 weeks following response to induction treatment with risankizumab in the ADVANCE or MOTIVATE induction trials. Non-randomised intervention arms in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
participants randomised thereto as either 360 mg Q8W (licensed dose) or 180 mg Q8W for 52 weeks. Non-randomised participants with response to non-licensed induction doses of risankizumab (360 mg Q8W or 180 mg Q8W) during ADVANCE or MOTIVATE continued to receive this dose.' This statement has a few errors in it. Section 3.2.2.3, Page 43, third paragraph.	as either 360mg Q8W (licenced dose), 180mg Q8W, or SC placebo, following response to induction treatment with risankizumab in ADVANCE or MOTIVATE. Non-randomised arms in FORTIFY included participants who responded to non-licenced induction doses of risankizumab in ADVANCE or MOTIVATE and included 360mg Q8W (following 12 weeks of 600mg risankizumab IV induction plus 12 weeks of 360mg SC risankizumab), 180mg Q8W risankizumab and responders to induction placebo.'		FORTIFY included participants who responded to non-licensed induction doses of risankizumab in ADVANCE or MOTIVATE, i.e. 360 mg Q8W (following 12 weeks of 600 mg risankizumab IV induction plus 12 weeks of 360 mg SC risankizumab) or 180 mg Q8W risankizumab." The EAG have not included suggested details on the placebo treatment under Section 3.2.2.3 as it details the intervention. Further amendments to Section 3.2.2.4, describing comparators, are as follows: "In participants randomised thereto in FORTIFY SS1 **following response to induction treatment with risankizumab in ADVANCE or MOTIVATE**, placebo was administered as subcutaneous injection Q8W. Non-randomised participants with response to intravenously administered placebo during ADVANCE or MOTIVATE received subcutaneous placebo Q8W during FORTIFY SS1."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The sentence reporting the Crohn's Disease Activity Index (CDAI) clinical response at Week 4 for the MOTIVATE trial is incomplete. Section 3.2.3.1, Page 51, first paragraph.	The company suggest that the EAG add the following information (in bold): 'At week 4, significantly more participants in the risankizumab arm achieved CDAI clinical response than those in the **placebo arm (36.6% vs 20.9%, respectively; p=0.001)**.'	To correctly report the CDAI clinical response in the EAG report.	Thank you, the EAG has amended the text to include the suggested information.

Issue 4 SLRs, incorrect statement

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that 'The EAG noted that where trials presented findings for both CCF and BF, but did not stratify by these groups, they were reportedly excluded from analyses; however, it is not clear how many trials were excluded on this basis. A number of other exclusions are worth mentioning.' Section 3.3, Page 57, third paragraph.	The company suggest that the EAG amend the part that says 'however, it is not clear how many trials were excluded on this basis. A number of other exclusions are worth mentioning' and mention that a complete reference list for the excluded studies and the reason of their exclusion has been provided in CS Appendix Section D.1.2.2, Table 5.	The company have provided a complete reference list for the excluded studies and the reason of exclusion in CS Appendix Section D.1.2.2, Table 5.	This is not a factual error. Furthermore, it is not clear from Table 5 how many trials were excluded on the basis of their failure to stratify results by CCF and BF subgroups.

Issue 5 Network meta-analysis (NMA), missing data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Infliximab is missing as comparator in the CCF population. Section 3.4.2.2, page 63, Table 13.	The company suggest that the EAG add a row to present the NMA CDAI-100 outcomes of infliximab in the CCF population, as presented in the CS Section B.2.9.2.2.2, Table 39. CCF: IFX5 [redacted]	Adding data for completeness.	These data are not presented in Section B.2.9.2.2.2., Table 39 of the CS. The EAG also could not find this information anywhere else in the CS.

Issue 6 Cost-effectiveness section, incorrect statement/results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that the cost-effectiveness model has 'an untenable PSA run-time when sampling 1,000 iterations'. Section 1.7, Page 21, first paragraph & Section 6.1, Page 122, first paragraph.	The company would disagree with this as the probabilistic sensitivity analysis (PSA) run-time when sampling 1,000 iterations is approximately 9 hours. The company suggest that the EAG amend this statement since the PSA can run within reasonable times (change from the word 'untenable' to be more exact, i.e., approximately 9 hours).	To list a more factual rather than subjective description of the PSA run-time. The company does not consider the PSA as having an untenable run-time, especially considering the PSA provides results for	Text amended to "…contribute to a PSA run-time of approximately 9 hours when sampling 1,000 iterations; as such, the EAG did not consider it feasible to produce probabilistic results for each EAG preferred assumption or

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		both CCF and BF populations in one run.	exploratory analysis within the EAG report timeframe."
The EAG report states that 'In clarification question B31, the EAG requested an executable version of the cost-effectiveness model that included fully incremental probabilistic analysis (in line with the company base case presented in CS B.3.10.1); however, such model was not provided by the company. Thus, the EAG present full incremental analysis results probabilistically for the EAG preferred base case only'. Section 1.7, Page 21, first paragraph & Section 6.1, Page 122, first paragraph.	The response of the company to clarification question B31 was that 'The probabilistic cost-effectiveness results (CS Section B.3.10) can be sourced from the "Calc – Prob (Multi) CCF" and "Calc – Prob (Multi) BF" worksheets of the Microsoft® Excel economic model that has been provided by the company.' Therefore, the company suggest that the EAG amend these two sentences.	This is factually inaccurate since the company suggested that the full incremental results of the probabilistic analysis can be found in the 'Calc – Prob (Multi) CCF' and 'Calc – Prob (Multi) BF' worksheets of the Microsoft® Excel economic model.	This is not a factual error. Mean total costs and total QALYs from the probabilistic analysis are presented in the 'Calc – Prob (Multi) CCF' and 'Calc – Prob (Multi) BF'. However, full incremental analyses calculations based on probabilistic results (including dominance and extended dominance) cannot be found in these worksheets, nor elsewhere in the model.
The EAG report states that 'No data are provided for surgery or colectomy in the CS or other supplied documents. The EAG noted that the CS stated that	The company suggest that the EAG mention that surgery is included as a health state within the cost-effectiveness model, and both surgery data and its	The EAG's statement negates the data included within the CS relating to surgery as a treatment of CD.	Amended to state "No clinical data from the risankizumab trials are provided for surgery or colectomy in the CS or

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
trial outcomes were reported according to the NICE scope, and its decision problem (Document B, Table 1) included surgery as an outcome' which is incorrect as the model includes surgery as an outcome and data pertaining to both costs and HRQoL is included. Section 3.2.3.1, Page 53, first paragraph.	associated health-related quality of life (HRQoL) are included within the CS.		other supplied documents. The EAG noted that the CS stated that trial outcomes were reported according to the NICE scope, and its decision problem (Document B, Table 1) included surgery as an outcome. HRQoL and cost-effectiveness implications of surgery were factored into the economic model, though the EAG noted these values were based on Hospital Episode Statistics data, reported in a prior appraisal, as well as various assumptions."
The EAG report states that '…vedolizumab IV and vedolizumab SC are excluded from the incremental analysis (see worksheet 'List', range	The company suggest that EAG remove this part since vedolizumab IV and SC are included in the incremental analysis of the BF population (e.g., see CS Section B.3.10.1.2, Table 103: Base case	Vedolizumab IV and SC have been included as comparators in the BF population in the	This is not a factual error. In the company's model ('6a. ID3986_Risankizumab CD_NICE_CEM v0.2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'list_regimen_active_inc_all')'. Section 4.2.4, Page 91, second paragraph & Section 6.1, Page 121, Correction #1.	results: BF population (fully incremental CE results) and the 'List' worksheet of the cost-effectiveness model provided (vedolizumab IV and SC are labelled as 'VDZ300' and 'VDZ300-SC', respectively).	incremental analysis submitted by the company.	040822 v1.2 [ACIC]'), in the BF population, 'VDZ300' and 'VDZ300-SC' are not included in the range 'list_regimen_active_inc_all' (on the 'List' worksheet).
The EAG report states that 'The company do not provide detailed justification for choosing an ordered probit, rather than an ordered logit model, although it is likely that the differences would be minimal, and quite likely trivial'. Section 4.2.6.5, Page 96, fourth paragraph.	The company suggest that the EAG amend this part since they have mentioned in clarification question B15 that 'The probit distribution was chosen given that it is one of the most commonly used distributions in multinomial, ordered models – the logit and probit form the majority of these models. The company chose the ordered probit model as it is based on the (cumulative) normal or Gaussian distribution.' as well as that '…the logit and probit functions are nearly identical, the company is confident that an ordered logit would not produce different model results.'	The company have provided justification for using the ordered probit instead of the ordered logit model to estimate transition probabilities in the economic model.	This is not a factual error.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>Deterministic base-case results for risankizumab in the conventional care failure (CCF) population are reported incorrectly. Section 5.1.1.1, Page 115, Table 29 (Row 7).</td><td>The company suggest that the EAG amend these to the following values in the table (semi-colon indicates columns):
RZB; [redacted]; [redacted]; [redacted]; [redacted]; £313,414; Dominated</td><td>To correctly report the deterministic base-case results for risankizumab in the CCF population in the EAG report.</td><td>This is not a factual error.
The company-proposed results to the left are produced when erroneously increasing the risankizumab pack price (see EAG correction #5 as described in Section 4.2.8.1 and 6.1 of the EAG report).</td></tr>
<tr><td>Deterministic base-case results for the biologic failure (BF) population are reported incorrectly. Section 5.1.1.1, Page 115, Table 30 (Rows 3–6).</td><td>The company suggest that the EAG amend these to the following values (in bold):<table><tr><th></th><th>Discounted Costs</th><th>Discounted QALYs</th><th>Incremental discounted Costs</th><th>Incremental discounted QALYs</th><th>ICER vs Baseline</th><th>ICER Incremental</th></tr><tr><td colspan="7">Company deterministic base case</td></tr><tr><td>RZB</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td></tr><tr><td>UST</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td><u>-£51,214</u></td><td><u>Dominated</u></td></tr></table></td><td>To correctly report the deterministic base-case results for the BF population in the EAG report.</td><td>This is not a factual error.
The company-proposed results to the left are produced when erroneously increasing the risankizumab pack price (see EAG correction #5 as described in Section 4.2.8.1 and 6.1 of the EAG report).</td></tr>
</table>

Description of problem	Description of proposed amendment							Justification for amendment	EAG response
	VDZSC	[redacted]	[redacted]	[redacted]	[redacted]	-£36,048	Dominated		
	VDZIV	[redacted]	[redacted]	[redacted]	[redacted]	-£42,643	Dominated		

Issue 7 Text statements that may lead to misinterpretation / AbbVie suggested additions for clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The description of IV or SC administration of risankizumab (and other relevant biologics) is referred to as the method of administration. This may lead to unnecessary confusion as the route and method of administration are muddled together.	The company would prefer the description of 'route of administration' when referring to the IV vs SC administration (applies to all biologic treatments). Only referring to 'method of administration' when discussing the 'device' used for SC administration (i.e., injectable pen, syringe or on-body device).	Method of administration and route of administration have a different perception; to make it clearer that the route of administration for risankizumab maintenance treatment (i.e., SC) is no different to the route of administration for maintenance with ustekinumab, vedolizumab (SC option) or adalimumab. The 'device' (i.e., the method used to administer the SC dose) differs between all treatments (e.g., adalimumab offers both a pen device and a syringe option to patients), suggesting this impacts user experience/preference rather than drug efficacy (since the 'route' is the same).	This is not a factual error.
The EAG report states that the analyses 'Assume all patients discontinue biologic therapy at 52 weeks. From this point, assume patients move to conventional care'.	The company suggest that the EAG amend this using the following sentence: 'Assume all patients discontinue biologic therapy by 52 weeks.	The sentence is misleading as it appears as if patients cannot discontinue treatment (due to loss of response or adverse events) until the end of the 52 weeks (i.e., end of maintenance	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1, Page 11, Table 2 (row 2).	After discontinuation, assume patients move to conventional care.'	phase). This is not the case since patients can discontinue treatment at any point during the maintenance phase.	
The EAG report states that a single maintenance NMA is preferred as 'the EAG believes this is likely to produce more stable estimates'. Section 1.4, Page 14, Key Issue 3.	The company suggest that the EAG acknowledge that a single maintenance NMA network provides implausible results as demonstrated by the company in clarification question A15.	The company consider it misleading to categorise single maintenance NMA network results as 'stable' without acknowledging the methodological and outcome concerns that come with it.	This is not a factual error.
The EAG report states that the company defended their approach of using CDAI outcomes in the evidence submission 'in the context of limited endoscopic outcome data, which the company describes as only available from risankizumab and ustekinumab overall populations'. Section 1.5, Page 15, Key Issue 4.	The company suggest the EAG reword this to include that the company also listed precedence as a fundamental reason for selecting CDAI outcomes as CDAI-based outcomes have been used in all previous NICE submissions in CD, and therefore this allows for most comparability. In addition, the company suggests adding that all CD trials to date report CDAI as their primary outcome.	Precluding the full rationale for the use of CDAI outcomes as the primary outcomes introduces bias.	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that 'In the company's and EAG's CCF population base case, adalimumab biosimilar is the 'reference' (lowest cost) treatment, and infliximab SC is the optimal comparator in the incremental analysis at a willingness-to-pay threshold of £20,000 to £30,000 per QALY gained.' The EAG also used IFX SC as an optimal comparator in their analysis. Section 1.7, Page 21, second paragraph & Section 6.2, Page 123, first paragraph.	The company suggest that the EAG amend this in their report and use ustekinumab as the most appropriate comparator in the CCF population.	The mechanism of action, cost and health benefits of ustekinumab makes it the most appropriate comparator.	This is not a factual error. The EAG disagree, including based on clinical advice, that ustekinumab is the most appropriate comparator.
Risankizumab induction dosing (used in the ADVANCE and MOTIVATE clinical trials). Section 3.2.2.1, Page 36, Table 9 (rows 2-3, 'intervention' column).	The company suggest that the statement 'Risankizumab, 600 mg or 1200 mg IV Q4W' needs to be stated as 'Risankizumab doses (600 mg or 1200 mg IV) were given at Weeks 0, 4 and 8' in both induction trials (ADVANCE, MOTIVATE).	Induction dosing is quoted as 'Q4W' for induction studies; however, no duration of study is given. Therefore, this could be misleading.	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Population. Section 3.2.2.2, Page 37, last two paragraphs.	The company suggest that the EAG amend text to be clear that the 'risankizumab' patient numbers quoted are only from the 600mg groups.	Clinical evidence included in CS mentions both 600 and 1200mg groups. In the population section, the patient numbers included under 'risankizumab' is only the 600mg patients in both induction trials (ADVANCE, MOTIVATE).	Amended to indicate that these participants received risankizumab 600 mg IV.
Duplication of paragraph. Section 3.3, Pages 57-58, third paragraph	The company suggest that the EAG remove the third paragraph of this Section (starting with 'The company included 16 trials…') since it duplicates the first paragraph of the Section.	Duplicate paragraph.	Thank you, the EAG has removed this paragraph.
The EAG report states that 'Specifically, the overall population implied by NMAs for the BF population would not strictly be at risk of every treatment of the network. This is because by definition, experiencing the failure of one biologic treatment suggests that not all subsequent treatments are appropriate treatment	The company suggest that the EAG amend this part since given that the clinical trials of the different comparators were conducted at different timepoints, where not all comparators were always available for use in clinical practice, it is expected that the BF population is defined slightly differently in the NMA of each submission. The company has provided a data on file reference	The company have provided evidence from an expert advisory board that addresses the issue of the different BF populations in the clinical trials of the different comparators.	This is not a factual error. The EAG's response is based on a consideration of the epidemiological issues present in this NMA.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
choices. The implication of this for NMA estimates is unclear, and the specific provenance of the BF subgroups in the analysis is unclear; that is, whether all trials contributing to the BF NMA defined the subgroup similarly.' Section 3.3.2.2, Page 59, second paragraph.	(expert advisory board report [reference #80]) where clinicians agreed that the BF populations of the different trials can be considered analogous.		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that with the single maintenance NMA network 'All comparators perform better than placebo, though the difference is not always significant'. Section 3.4.2.2, Page 64, first paragraph.	The company suggest that the EAG amend this sentence based on its response to clarification question A15: '…the single maintenance NMA network does not stand up to basic face validity as the outputs suggest that in some cases placebo is more effective than ustekinumab, vedolizumab and risankizumab; this observation goes against the results presented in the Phase 3 clinical trials of the respective biologic therapies…'	When a single maintenance NMA network is used, several comparators (e.g., ustekinumab) appear to be less effective than placebo, which contradicts what is reported in their clinical trials and diminishes their clinical value as treatments in CD.	This is not a factual error.
The EAG report states that 'On top of this the EAG noted in clarification question A15 the similarity in the half-life and induction period between vedolizumab and ustekinumab, and that they are seen as similar therapy options'. Section 3.4.6, Page 72, last paragraph.	The company suggest that EAG amend the part that describes vedolizumab and ustekinumab as similar therapy options since as mentioned in the CS (e.g., Section B.1.3.3), the two drugs have different mechanism of actions (i.e., vedolizumab is an integrin α4β7 inhibitor, whereas ustekinumab is an interleukin 12/23 inhibitor).	The term 'similar therapy options' for vedolizumab and ustekinumab is inaccurate since their mechanisms of action are different and this is one of the reasons why they are used differently by clinicians in clinical practice.	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that 'Three clinical trials were included in the CS.' Section 3.6, Page 74, second paragraph.	The company suggest that the EAG update the sentence to the following to make it clearer that they discuss the clinical trials of risankizumab in CD: 'Three risankizumab CD clinical trials were included in the CS.'	Minor change for clarification purposes.	This is not a factual error.
CDAI outcomes used in the NMA and cost-effectiveness model. Section 4.2.2, Page 82, third paragraph.	The company suggest that the EAG amend this paragraph to mention that several times within the CS, the company has also acknowledged the use of the Harvey Bradshaw Index as being a more commonly used measure of clinical effectiveness in UK clinical practice; however, the company has provided the reasoning for using the CDAI measure in both NMA and economic model (e.g., CS Section B.3.7.4).	The company acknowledged all the clinical measures used in UK clinical practice and justified the use of CDAI scores in the NMA and economic model.	This is not a factual error.
The EAG report states that '…to assume that patients with CD have equivalent survival to the general	The company suggest that the EAG amend this part in the EAG report to mention that the company did also acknowledge	Minor amendment to clarify that the company has also acknowledged conflicting	This is not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
population. However, published evidence identified by the EAG is indicative of a heightened mortality risk for CD patients versus the general population, including risk related to higher rates of colorectal-cancer, pulmonary disease, and nonalcoholic liver disease'. Section 4.2.2, Page 83, fourth paragraph.	that there is evidence that shows small increase in mortality in people with CD based on clinical feedback received (data on file reference – expert advisory board report [reference #80]). However, the clinicians recommended that 'it was not required to model this in the cost-effectiveness model'.	evidence on the impact of CD on mortality.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that 'Based on the information reported in CS, it is unclear to the EAG whether clinical advice to the company indicated that both 92.5% of patients start on high-dose maintenance ustekinumab and the annual probability of dose escalation is 92.5%, or whether the company assume equivalence to inform these parameters'. Section 4.2.6.6, Page 100, fifth paragraph.	The company suggest that the EAG amend this part since they have provided clinical feedback (data on file reference – expert advisory board report [reference #80]) that says that the median probability of patients starting on high-dose maintenance ustekinumab and escalating to high-dose ustekinumab annually is 92.5%.	The company have provided clinical feedback on the probability of starting on high-dose and escalating to high-dose for all comparators.	This is not a factual error.

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Typographical errors in the number of tables cross-	The company suggest that the EAG make the following changes:	Wrong cross-references within the text (most likely the in-	Cross-references amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
referenced throughout the EAG report.	• Section 3.2.2.1, Page 36, second paragraph: Reference to Table 7 should be amended to Table 9 • Section 3.2.2.2, Page 39, first paragraph: Reference to Table 8 should be amended to Table 10 • Section 3.2.2.5, Page 44, second paragraph: Reference to Table 9 should be amended to Table 11 • Section 3.4.3, Page 65, third paragraph: Reference to Table 14 should be Table 16 • Section 4.1, Page 77, Table 19 (row 2): Reference to Table 15 should be Table 17 • Section 5.2.2, Page 117, last paragraph: Reference to CS B.11.1 should be CS Section B.3.11.1 • Section 5.2.3, Page 118, third paragraph: Reference to CS B.11.3.1 should be CS Section B.3.11.3.1 • Section 6.1, Page 121, last paragraph: Reference to Tables 29 and 30 should be Tables 31 and 32	text links were not updated).	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	• Section 6.4.2, Page 139, last paragraph: Reference to Tables 42 and 43 should be Tables 41 and 42 • Section 6.4.3, Page 141, second paragraph: Reference to Table 43 should be Table 44 for the BF population		
The EAG report states that 'The company estimated the effect of CDAI category upon patient HRQL in FORTIFY patient-reported data using ordinary least squares estimation, in order to inform cost-effectiveness model health state utility assumptions'. Section 1.5, Page 18, Key Issue 7.	As stated in CS Section B.3.4.1.1, Pages 159–160, EQ-5D data from both the induction (ADVANCE, MOTIVATE) and maintenance (FORTIFY) clinical trials were used in this analysis. The company suggest that the EAG amend this part in the report.	Inaccurate data reference.	Text amended to "The company estimated the effect of CDAI category upon patient HRQL in ADVANCE, MOTIVATE and FORTIFY patient-reported data…"
Typographical error. Section 3.2.2.2, Page 38, third paragraph.	In the third paragraph 'ITTC' is mentioned; this should be 'ITT1C'.	Typographical error.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states that 'Data and control parameters were not supplied initially, resulting in the EAG requesting complete code in clarification question A6.' Section 3.4.1, Page 60, second paragraph.	The company provide the additional parts of the NMA code as a response to clarification question A7 (not A6).	Wrong reference.	Amended.
Microsoft® Excel cost-effectiveness model reference (file name). Section 4.2.4, page 91, second paragraph.	The file name of the economic model is incorrect. The correct file name is: 6a. ID3986_Risankizumab CD_NICE_CEM_Final_ACIC_v1.2	Incorrect file name.	This is not a factual error. The file name of the cost-effectiveness model submitted at the clarification question stage was: '6a. ID3986_Risankizumab CD_NICE_CEM v0.2 040822 v1.2 [ACIC])'
The estimated health state utility value for the moderate-to-severe health state estimated using the	The mean value should be [redacted] and not [redacted].	Minor error in calculation.	This is not a factual error. The mean (95% CI) health state utility

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
linear mixed model is slightly wrong. Section 4.2.7.1, Page 105, Table 26 (last row).			value for the moderate-to-severe health state using the linear mixed model reported by the company in clarification question B24c, Table 39 was "[redacted] Although, the corresponding health state utility value estimated by the EAG when using the linear mixed model coefficients (provided by the company to 3 decimal places in clarification question B24c) is [redacted] to 3 decimal places.

Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
CS Document B Appendices: Value of [redacted] in CS Appendix Section M.5.3.3, Table 92.	Redactions can be removed from this value.	Redactions removed.	Removed.
The confidence intervals for the subgroup analysis by Bio-IR and Non-Bio-IR in Tables 15, 16, 18, 19, 21, 22, 27, and 28 in the original CS Document B.	Redactions can be removed from the confidence intervals of the different outcomes presented in the subgroup analysis.	Redactions removed.	Removed.
Risankizumab method of administration: Pages 19, 20, 26, 27, 57, 74, 87, and 110.	The term 'on-body device' or 'OBD' can be unredacted on these pages. From the redacted paragraph on Pages 20, 21 and Page 28, the first sentence can have its CIC marking removed as shown in the amended marking.	''Risankizumab 600mg intravenous (IV) induction will be administered in a hospital setting whilst risankizumab 360mg subcutaneous (SC) maintenance will be administered through the on-body device (OBD) either at home or in clinic. The OBD is a self-injection device which takes up to five minutes to administer from when the OBD is placed on the body at the injection site. The OBD allows for at-home treatment	Amended.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		(where agreed with the healthcare team). The device can be placed to the abdomen or thigh and then upon pressing the button the OBD delivers a steady injection. In terms of administration the OBD should be stored in the refrigerator (at 2–8°C) and just before injecting the medication should be left to come up to room temperature. Upon activating the OBD a beeping sound will be heard, and a flashing blue status light will appear. The OBD can be secured on the injection site and the grey injection button should then be firmly pressed and released to deliver the medication. The OBD will beep, and the status light will flash green as the injection is delivered. The patient may do moderate physical activities, such as walking, reaching and bending, during the injection. The status light will change from flashing green to solid green and the device will beep once the medication has been	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		delivered, at this stage and then the OBD can be removed by peeling the adhesive OBD off the skin. The OBD and cartridge can then be disposed by placing them into a special disposal container'.	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is the end of **21st October 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

About you

Table 1 About you

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

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Company response

AbbVie would like to thank NICE for the opportunity to respond to the key issues raised by the EAG during technical engagement. Ahead of addressing these key issues (**Table 2**), the company would like to highlight that the base-case cost-effectiveness results have been updated to reflect a revised lower cost of the risankizumab 600mg induction dose as further detailed in the letter to NICE below (pages 4-5). Furthermore, the company's model base case has also been updated for the six amends that the EAG have identified in Section 6.1 of the EAG report factual accuracy check. The changes have been implemented in the revised company model (as detailed in **Table 4**) submitted as part of the company's technical engagement response.

NICE National Institute for Health and Care Excellence

To: National Institute for Health and Care Excellence
2nd Floor, 2 Redman Place
London
E20 1JQ

Attn: [redacted]
CC: [redacted]

Date: 11th November 2022

RE: NICE appraisal of Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986] ("Appraisal")

Dear [redacted],

We are writing in response to your email dated November 3rd, 2022 and we also refer to a separate email we received from [redacted] (in CC) on October 26th, 2022. We understand there may be some shared concerns within NICE and PASLU in relation to our Appraisal submission and we would like to use this opportunity to address them in a consistent and constructive manner.

We are also attaching to this letter the information you requested with respect to the base-case cost-effectiveness results. For completeness, we have included a version reflecting the currently agreed Patient Access Scheme for Risankizumab (**Appendix F**), as well as a version including the Risankizumab 600mg induction dose at a lower cost (**Appendix G**), which is reflective of the intended price across England and Wales. AbbVie take the view that the latter version should be considered by the Appraisal Committee at the upcoming meeting, for the reasons set out below.

As a preliminary point, AbbVie are focused on securing timely access to Risankizumab for patients with Crohn's disease. As you may be aware, Risankizumab is included in an Early Access Medicine Scheme (EAMS) for Crohn's Disease patients, which emphasises the significant added value that Risankizumab brings to an area of high unmet clinical need.

For this reason, we are keen to avoid delays to Risankizumab access that would prevent new patients from accessing Risankizumab, following EAMS closure at marketing authorisation, thereby adversely impacting patients. We have, therefore, endeavoured to put forward a proposal that can deliver significant value to the NHS and support efficient decision-making at Committee level.

We would point out that the Appraisal concerns a complex technology comprising of two components:

- An induction dose (600mg) administered intravenously, anticipated to be delivered mainly in a hospital setting.
- A maintenance dose (360mg) administered using an on-body injector device, anticipated to be delivered mainly in an outpatient setting.

The mode of administration and intended usage of these two presentations are very different than the existing Risankizumab 150mg self-injecting pre-filled syringe and the Risankizumab Technical engagement response form

Crohn's Disease therapy as a whole is more complex than a higher or lower concentration or dose of the same product. This type of scenario is not explicitly reflected in the terms and conditions of Patient Access Schemes or in the NICE Manual.

Our approach has been to (i) align the price for the 360mg maintenance dose to the current Patient Access Scheme, and (ii) offer a lower price for the 600mg induction dose through listing on a Commercial Medicines Unit (CMU) tender framework covering the settings for which this presentation is expected to be used at national level.

We believe this is consistent with the NICE Manual, which does not include any provisions suggesting that, where technologies comprising of two or more components are appraised, the source of prices for all components must be the same. The fundamental principle reflected in the NICE Manual is that reference case analyses **'should be based on prices that reflect as closely as possible the prices that are paid in the NHS**'. Both Patient Access Schemes and CMU contracts are listed in Section 4.4.4 of the Manual as equally viable sources of prices, in line with this principle of 'close reflection of real cost'.

We would also point out that, even though the relevant CMU tender has not yet been formally awarded as of the date of this letter, this is anticipated in early January 2023, very soon after the Committee meeting. Based on the tender design, we do not anticipate the CMU would have grounds to reject AbbVie's price proposal. Of course, AbbVie remain firmly committed to maintain the relevant presentation of Risankizumab on the tender framework at the proposed price and will ensure all administrative steps are executed to this effect.

Considering the above, we respectfully ask that Risankizumab is appraised holistically and pragmatically to ensure our commitment to deliver value for the NHS is given due consideration in the context of Risankizumab's specific situation.

We trust the clarifications above provide helpful context and we remain grateful for your support of the efficient and timely appraisal of Risankizumab that would enable accelerated patient access to this innovative therapy. We also encourage you to consider including this letter in the committee papers pack, allowing stakeholders contributing to the Appraisal to do so with a better understanding of the context and rationale supporting AbbVie's submission.

Kind regards,

[redacted]

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Feasibility of exploratory subgroup analysis by CD location	Yes	The company validated the impact of an analysis by location of Crohn's disease (CD) with UK clinical experts (n=6; gastroenterologists), who advised that disease location does not drive treatment choice for individuals with moderate-to-severe CD. One gastroenterologist stated that 'In clinical practice location of disease is not a clinically relevant distinction and patients are not stratified by this subgroup for developing treatment plans'. The only distinction that is seen as clinically relevant in adjusting treatment choice is penetrating perianal disease, which is not relevant to the decision problem. The company included percentages of subjects with colonic, ileal, or ileal-colonic disease in Section B.2.3.3 of the company submission (CS) highlighting the low subject numbers with isolated ileal disease. Gastroenterologists stated that there is limited ability to draw inferences from an exploratory analysis on CD by location. Additionally and consistent with the approach taken in previous submissions in CD (i.e., ustekinumab [TA456] and vedolizumab [TA352] (1, 2), a descriptive analysis of outcomes by disease location were included in CS Section B.2.7, while the CS also comprised the full clinical study reports (CSRs) with the requested subgroup outcomes. Correspondingly, in addition to the low subject numbers per subgroup location in the risankizumab CD clinical trials, there has also been a lack of reporting of outcomes by disease location across all relevant comparator treatment studies identified in the systematic literature review. Consequently, a comparison of the relative efficacy of risankizumab versus relevant comparator therapies in a network meta-analysis (NMA) by subgroup location was not feasible. Nevertheless, in light of the EAG's request, a summary of results from each trial by disease location for co-primary efficacy outcomes i.e., the proportion of subjects with Crohn's Disease Activity Index (CDAI) clinical remission or endoscopic response are presented in Appendix A (Table 5 and Table 6 for ADVANCE; Table 7 and Table 8 for MOTIVATE; Table 9 and Table 10 for FORTIFY).

Key issue	Does this response contain new evidence, data or analyses?	Response
2. Unexplored heterogeneity in network meta-analyses in relation to baseline risk	Yes	The company decided to retain the original CS NMA, i.e., the split-network risk difference (RD) fixed effects (FE) maintenance NMA (without use of priors) without adjustment for the temporal effect, and maintain that this is the most appropriate method to present the relative efficacy of each biologic therapy for CD for the following reasons: • The results of the split-network RD FE maintenance NMA are most representative of those seen in the relevant clinical trials and produce the most plausible credible intervals (CrIs). • FE models do not require a prior; there is no informative prior that has specifically been used in previous NMAs in CD, while it is also challenging to identify the most appropriate prior to use on a RD scale for the random effects (RE) model. • The temporal effect addresses one of the issues concerning placebo heterogeneity (i.e., the years in which the relevant clinical trials where conducted), but not other factors contributing to the heterogeneity, such as trial design, duration of induction phase and drug half-life. • Baseline risk adjustment cannot be used since the sparseness of network data results in models that do not converge, have non-significant regression coefficients and/or produce unrealistically wide CrIs (i.e., lack face validity). The company acknowledge the EAGs suggestions to further explore the heterogeneity in the maintenance NMA and have assessed/conducted the following NMAs, noting an absence of any tangible impact across the different methodologies assessed: • Adjustment for the temporal effect • Use of informative priors • Baseline risk adjustment

Key issue	Does this response contain new evidence, data or analyses?	Response
		Adjustment for the temporal effect The EAG-suggested approach to incorporate an adjustment for the temporal effect in a single-network maintenance NMA (see Key Issue 6) was assessed by the company. The EAG raised an assumption that the temporal effect (i.e., temporal association of the placebo remission rates [dependent variable] with the time/year at which the clinical trials of the different biologics were conducted [independent variable]) could create heterogeneity in placebo rates across the comparator trials. As set out in the CS, the company consider the heterogeneity across the relevant comparator trials a complex combination of the differences (e.g., in study designs, duration of induction phase, drug mechanisms of action, drug half-lives etc.) and not just limited to the time at which the different trials were conducted. However, the company conducted an analysis aimed to replicate the EAG methodology with the information provided during the technical engagement phase and based on the methods outlined in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2 and 5 (3, 4). Results from the single-network RD maintenance NMAs (with adjustment for the temporal effect) conducted by the company are shown in Appendix B. Table 11 and Table 12 present the RD FE and RE results (with informative priors) with the adjustment for the temporal effect, for the conventional care failure (CCF) and biologic failure (BF) populations, respectively. The results are compared with those from the single-network RD FE maintenance NMA corresponding to the results from the company's response to clarification question A15. In summary, the point estimates of the temporal adjusted maintenance NMA are similar to those presented in the EAG cost-effectiveness (CE) model 'Scenario 4: Temporal trend single NMA network (all biologics)'. However, the 95% CrIs are unfeasibly wide regardless of whether a FE or RE model is used (0% to 100% in most cases for treatments in the BF population).

Key issue	Does this response contain new evidence, data or analyses?	Response
		These NMA results lack face validity when compared against the clinical trial data that are available for each biologic therapy. More precisely, the results indicate no difference in efficacy across treatments and placebo, whereas in all clinical trials, the respective active treatment is significantly more effective compared with placebo on both clinical response and remission. In addition, the results show efficacy values that are not representative of the outcomes collected from the comparator trials and expected to be seen in clinical practice (e.g., [redacted] efficacy for adalimumab). The results highlight that the suggested EAG approaches are associated with too much heterogeneity to produce plausible CrIs. This is substantiated by the reasons described within the CS and during the clarification questions phase where it was explained that as well as the single-network maintenance NMA contradicting comparator trial results, the lack of a true common comparator due to variations in the withdrawal placebo effect between the studies violates a core NMA assumption. For example, at Week 52 in FORTIFY (patients re-randomised at Week 12), 40.9% of withdrawal placebo subjects were responders, in comparison with the CHARM study (patients re-randomised at Week 4) where 12% of withdrawal placebo subjects were responders at Week 56. **Use of informative prior** As per the CS, in the cost-effectiveness analysis, the company decided to present a scenario analysis that uses RD RE results (with use of a vague/non-informative prior) (see Appendix F.3) (5, 6). The EAG highlighted that the use of an informative prior might help address between-study heterogeneity, assist with any model convergence problems encountered, and produce more plausible/narrower CrIs that would not lack face validity when an RE NMA model is used. To investigate if the application of an informative prior for the RE model would indeed produce more

Key issue	Does this response contain new evidence, data or analyses?	Response
		plausible/narrower CrIs, the company explored the options and impact of using an informative instead of a vague/non-informative prior in a single-network RD RE maintenance NMA. However, the company are of the opinion that the non-informative prior is the best option when a split-network RD RE maintenance NMA is selected (used as scenario in CS), due to the following reasons: • Choice of an informed prior distribution over a vague prior distribution needs to be rigorously defended (indeed, NICE DSU TSD 3 cautions that even the explicitly discussed half-normal prior 'should not be used unthinkingly') (7). • The company could not identify a prior that has specifically been used in CD or the general gastroenterology disease area. • Generic informative priors (as an example suggested by the EAG – Turner et al. (2015) (8)) do offer an informative prior, but this approach is only to be used for pairwise meta-analyses, while current evidence mainly applies to binary outcomes estimated on an odds scale (no evidence on the RD scale). The authors state, in the only mention of NMA in the paper: 'In a network meta-analysis including multiple intervention comparisons, it is common to assume equal heterogeneity variances across comparisons. Provided all intervention comparisons are within one category presented in this paper, the priors here can also be applied in this setting.' Considering the complicating factors of placebo arms in the CD clinical trials, particularly the withdrawal-of-treatment placebo utilised in the maintenance phase of the trials, it is debatable which category/prior distribution would be most applicable to the risankizumab CD NMA. The company note that Turner et al. (2015) (8), is not cited in any of the NICE DSU TSDs. The company tested the EAG suggested methods and decided to use the commonly used half-normal prior for the RE model. No tangible impact was observed, other than the unfeasibly wide CrIs, which lack face validity; Table 13 and Table 14 (Appendix B) present the single-network RD RE maintenance

Key issue	Does this response contain new evidence, data or analyses?	Response
		NMA results with vague/non-informative (see clarification question A15) and informative priors (without adjustment for the temporal effect), for the CCF and BF populations, respectively. It is important to contextualise potential impacts of different prior distributions for the between-study heterogeneity parameter on the results of the NMA. In short, tangible impacts to NMA estimates are unlikely. Indeed, Dias et al. (2018) (5) conducted multiple NMAs to illustrate the application of priors from Turner et al. (2015) (8). In the context of these examples, Dias et al. (2018) conclude that '[…] although three very different prior distributions for the between-study heterogeneity were used, the main conclusions are unchanged'. In the risankizumab CD NMA, the vast majority of treatments in the maintenance phase lack multiple studies. Short of using an extremely narrow prior on the between-study heterogeneity parameter (akin to utilising an FE model), estimates will produce wide/implausible 95% CrIs. On the contrary, FE models showed appropriate fit across both induction and maintenance phase NMAs in the risankizumab CD case and produce more representative results of those seen in the relevant clinical trials. **Baseline risk adjustment** As highlighted previously, the company maintain that the split-network RD maintenance NMA is the most appropriate method to be used to indicate the relative efficacy of the different biologic treatments for CD. The EAG recommended that baseline risk adjustment be explored for RD meta-analyses. The company explored this option during the feasibility assessment stage and considered the use of the RD-link methodology more appropriate. As discussed in the CS (Appendix D) and during the clarification questions phase (Questions A4 and A10), the sparse data from the networks prohibit the use of baseline-risk adjustment (i.e., formal meta-regression) since the models do not converge, have non-significant regression coefficients and/or produce unrealistically wide 95% CrIs (i.e., lack face

Key issue	Does this response contain new evidence, data or analyses?	Response
		validity). This is potentially problematic given the observed heterogeneity in placebo outcomes; however, as mentioned by the company, the impact of this observed heterogeneity is reduced by leveraging the RD NMA framework. RD models constitute a valid analytical method when conducting NMAs (as discussed in NICE DSU TSD2 (3)). RD results approximate those of baseline risk adjustment, meaning that they can represent an alternative approach to dealing with the presence of variations in baseline risk between studies (9). For these reasons, baseline risk adjustment was not applied.
3. Network structure in maintenance network meta-analyses should be connected	Yes (as part of Key Issue 2)	The company believe that the CS approach of a split-network maintenance NMA is most appropriate due to the deficiencies of the single-network maintenance NMA and methodological challenges in accounting for the heterogeneity by means other than splitting the network. This is further elaborated upon in the response to Key Issue 2. Accordingly, the split-network RD FE maintenance NMA is maintained in the company's base case. The company concluded that the split-network RD FE maintenance NMA was most appropriate after testing and evaluating several methods attempting to address the EAG concerns. The incorporation of suggestions from the EAG into the company's maintenance NMA methodology were attempted by the company with methodological changes (as described in Key Issue 2) aimed to address the heterogeneity in the baseline risk that is seen across the comparator trials (i.e., single-network maintenance NMA using RD RE models with informative priors, with and without adjustment for the temporal effect) as well as the two NMAs presented as a response to clarification question A15 (i.e., split-network maintenance RD FE NMA that includes ustekinumab, risankizumab and vedolizumab in the same network; single-network maintenance RD FE NMA that includes all biologic treatments for CD in one network).

Key issue	Does this response contain new evidence, data or analyses?	Response
		No tangible impact was observed across the different methodologies that attempted to further address the heterogeneity issue across comparator trials, other than the unfeasibly wide CrIs, which lack face validity for the reasons mentioned in the response to clarification question A15 and Key Issue 2 above.
4. Appropriateness of the model structure	No	The company believe that the cost-effectiveness model (CEM) submitted alongside the technical engagement response reflects the best approach for addressing the decision problem. The submitted CEM aims to address the decision problem by reflecting UK clinical practice as closely as possible whilst recognising that a model is a simplification of reality and is limited by data availability. The current model structure is based on the models used in previous NICE technology appraisals (TAs) for CD (TA352 and TA456 (1, 2)) and published literature (e.g., Bodger et al. (2009) (10); however, the model is augmented to address some of the limitations brought forward in previous appraisals (e.g., use of the ordered probit model to estimate transition probabilities in the maintenance phase of the model instead of using the 'goal-seek' approach). The structure is reflective of the risankizumab CD Phase 3 clinical trials and makes best use of the available clinical and economic evidence in CD. The company recognise the limitations of the current model structure in terms of accurately reflecting the real-world clinical pathway; however, an alternative model structure would still experience many of the same issues, if not more, given the lack of data on treatment sequencing and long-term outcomes for individuals with CD. Key elements of the CEM are discussed below with further details and company considerations during CEM development, including: • Use of CDAI and the relevance to UK clinical practice • Transition to conventional care after biologic failure • Data used to populate conventional care after discontinuation of biologic treatment • Dose escalation and the appropriateness of using standard-dose efficacy

Key issue	Does this response contain new evidence, data or analyses?	Response
		Use of CDAI The EAG expressed concern around the relevance of the CDAI scoring measure to UK clinical practice. However, the EAG concluded in their report that they '…saw no alternative to the use of CDAI outcomes within the cost-effectiveness model to address the decision problem, given the data limitations described by the company'. As stated in the CS, the CDAI outcome measure was used to define disease severity and progression as it is the most frequently used clinical endpoint in CD trials and therefore facilitates indirect treatment comparisons (ITCs) with other treatments for CD (11, 12). Furthermore, the CEM presented in the CS utilises CDAI outcomes to define CD health states in alignment with previous CD NICE submissions (1, 2) and published literature (e.g., Bodger et al. (2009) (10). While the Harvey Bradshaw Index (HBI) and endoscopic assessments (i.e., Simple Endoscopic Score for Crohn's Disease [SES-CD]) (13-17) are measures of relevance in UK clinical practice, they limit the applicability of ITCs due to the limited data availability for comparators and, for endoscopic outcomes, differences in outcome definitions across trials. Several assumptions would be required to estimate HBI scores based on CDAI values which would introduce more uncertainty in the model, would lack credibility and would not give confidence in the results produced. Given that the CDAI shares several common items with the HBI and studies have shown that results from HBI highly correlate with CDAI results (≈0.93 correlation coefficient between the two measures) (17, 18), the company consider the use of CDAI outcomes in the model to be aligned with those from the HBI measure. With respect to endoscopic outcomes, endoscopy is a procedure that takes place infrequently in clinical practice (perhaps 1-2 times per year, if not less), and therefore it is not an appropriate measure that clinicians can use to assess disease progression and determine transition

Key issue	Does this response contain new evidence, data or analyses?	Response
		between different health states. For these reasons, a model structure designed based on endoscopic outcomes is considered infeasible. **Transition to conventional care after biologic failure** The EAG expressed concern with the assumption of transition to conventional care (CC) after biologic failure. In the company model, all non-responders to biologic therapy after induction or maintenance treatment transition to CC, meaning that all patients would experience the same outcomes following discontinuation of initial biologic therapy regardless of which treatment they were receiving. Whilst the company acknowledges that transition onto alternative therapies after biologic failure is expected in UK clinical practice, treatment sequencing in the CEM was not considered appropriate due to a lack of available data. Furthermore, transition to CC after biologic failure is consistent with the approach taken in previous NICE TAs in CD (TA352 and TA456 (1, 2)) and published literature (10). The choice of biologic, particularly after a loss of response/failure of a prior biologic therapy, is a complex clinical decision with a range of factors to be taken into consideration for each individual patient (including patients characteristics, response to prior treatment and reason for discontinuation). The British Society of Gastroenterology (BSG) guidance states that when switching to a different class of biologic is required, factors to be considered in decision making include patient preference, cost, likely adherence, safety data and speed of response to the drug (16). Additionally, new biologic treatments entering the market change the dynamics and change the potential order in which biologics are used. As such, there is no typical treatment sequence for individuals who have discontinued a biologic therapy. Furthermore, response rates are typically lower in those who have proven to be refractory to other biologic therapies and for individuals with a longer disease duration (16), making estimations of how individuals would respond to subsequent therapies beyond the limit of available clinical trial data highly uncertain. As evidence with increasing and unknown uncertainty is introduced

Key issue	Does this response contain new evidence, data or analyses?	Response
		into the analysis with each additional line of treatment considered, the relevance for decision making becomes more uncertain. Such an approach is not aligned to face validity of the clinical trial results, the NMA results presented by the company and statements from clinical experts. As the purpose of the CEM is to compare the cost effectiveness of individual biologic therapies and not of treatment sequences, the use of CC after biologic failure is considered to be the most appropriate approach. **Defining conventional care after no response** The EAG raised concerns around the use of 'true placebo' data from the FORTIFY maintenance trial to inform the 'CC after no response' transition matrix. However, they acknowledged that they used these data in their preferred base-case analysis as no other appropriate data were available. Although the company understand the EAG's concerns around the relatively small number of subjects included in this trial cohort (n=24 subjects), the response of this group to treatment was not affected by previous biologic therapy use (as was the case for the 'withdrawal placebo' cohort). In addition, standard CC (e.g., steroids, immunomodulators etc.) was allowed for the 'true placebo' cohort, and these subjects can therefore be considered to best reflect individuals with moderate-to-severe CD who are not receiving biologic therapy in clinical practice. Furthermore, these data were applied equally across all comparators to reflect what happens after a loss of response/failure to prior biologic treatment, meaning that any limitations with these data apply to all comparators. **Dose escalation and use of standard-dose efficacy** The EAG expressed concern with the company's assumption that dose escalation for comparator treatments only affects costs and not patient outcomes (see also Key Issue 6). As stated in the CS and the EAG report factual accuracy form, clinicians (n=6 during an advisory board and n=5 in follow-up discussions) have stated that dose escalation is used to achieve the same level of response as those patients who do not need to dose escalate. In clinical practice, experts stated that the majority

Key issue	Does this response contain new evidence, data or analyses?	Response
		of patients are started on higher dose therapies with the aim of achieving the expected level of response, rather than to achieve greater levels of efficacy. This is done with the aim of giving patients the greatest opportunity to respond to the respective biologic before moving onto the next therapy; this is considered especially important in CD where only a small number of biologic treatments are available. Therefore, using different effectiveness outcomes for those patients who dose-escalate would lead to an overestimation of the actual effectiveness of the escalated doses therapies, over and above what is seen in clinical practice.
5. Treatment duration and residual treatment effect assumptions	Yes	**Biologic treatment duration** The company believe that 1 year is the most appropriate biologic treatment duration to use in the CEM to assess the cost-effectiveness of risankizumab given the available trial data for risankizumab CD (52 weeks) and the general lack of long-term outcomes for individuals with CD. The 1-year biologic treatment duration is consistent with previous NICE TAs (e.g., TA352 and TA456 (1, 2)) and published literature in CD (10) as well as with the EAG's preferred base case in TA456 (1). Whilst in clinical practice patients who respond to treatment may continue to receive that treatment beyond 1 year, there is no data (from trials or observational studies) to support long-term effectiveness after this timepoint, as acknowledged by clinical experts during TA456 (19) and reconfirmed by clinical experts over the course of the current submission. Extrapolation of treatment response beyond the clinical trial period duration would require some substantial assumptions on the hazard of discontinuation over time. Based on discussions with clinical experts to inform the CS, efficacy and discontinuation rates over time are hard to predict making estimations of these outcomes beyond the limit of available clinical trial data highly uncertain. The longer the assumed treatment duration, the greater the uncertainly around the model outcomes would be as the impact of any assumptions made on post-trial treatment efficacy would be amplified over the duration of the model. As highlighted in the discussion of Key Issue 4, the transition of patients to CC after biologic failure is a limitation of the

Key issue	Does this response contain new evidence, data or analyses?	Response
		model necessitated by the lack of treatment sequencing data for all biologic therapies. As a result, assuming a lengthy treatment duration would disproportionately reward less-effective treatments, where patients discontinue sooner due to lack of efficacy and therefore incur fewer treatment costs for the remainder of the model. Although in clinical practice patients may continue biologic treatment beyond 1 year, in line with the argumentation against treatment sequencing, an assumption of efficacy beyond the trial period lacks clinical validity. **Residual treatment effect duration** The company have considered the EAG's concerns around the use of a 1-year residual treatment effect duration and have amended the base-case analysis to include a residual treatment effect from previous biologic exposure after biologic discontinuation to last 6 months, with a 1-year duration explored in scenario analysis. A 1-year residual treatment effect duration was used as base case in the CS based on evidence for risankizumab from FORTIFY, which showed that C-reactive protein, faecal calprotectin and IL-22 levels had not returned to baseline levels (i.e., start of induction) in the withdrawal placebo arm at the end of 52 weeks. As such, the risankizumab residual treatment effect is likely to last at least 52 weeks (20). However, there is currently limited clinical evidence from trials and observational studies demonstrating the length of residual treatment effect for other licensed biologic therapies in CD. Therefore, the company acknowledge the uncertainty underpinning this assumption and assume a 6-month residual treatment effect duration in their updated base case for all biologic treatments in the model (i.e., intervention and comparators).
6. Estimation and application of maintenance	Yes	**Between-study heterogeneity in placebo remission rates** The EAG suggested that placebo remission rates be modelled to include a temporal effect (i.e., relationship between placebo remission rates [dependent variable] and the time/year that the

Key issue	Does this response contain new evidence, data or analyses?	Response
treatment effectiveness assumptions		respective clinical trial was conducted [independent variable]), and that absolute remission rates in maintenance be then based on this anchor point. As mentioned in Key Issues 2 and 3, the company considered the EAG's request and conducted a new maintenance NMA which adjusted for the temporal effect. However, the results included 95% CrIs which were unfeasibly wide regardless of whether a FE or RE RD model was used (0% to 100% in most cases for treatments in the BF population; Appendix B Table 12) and lacked face validity versus the original clinical trials of the different biologic therapies. Therefore, the outcomes were not considered appropriate to be utilised in the company's updated base-case analysis. **Calibration approach (ordered probit model)** The EAG highlighted that they consider a calibration approach which adjusts both of the estimated ordered probit cutpoints (i.e., remission|mild and mild|moderate-to-severe) by the same amount to derive the 2-week transition probabilities for the maintenance-phase Markov matrices to be less arbitrary than using a single remission|mild cutpoint. The company have added this option to the CEM to be used as a scenario analysis but maintained the adjustment of only one cutpoint as the base case. Results after adjusting both cutpoints are presented in Table 44 and Table 45 for the CCF and BF populations, respectively. The company believe that the EAG's preferred approach for approximating and calibrating maintenance-phase Markov matrices generates inaccurate initial 26-week matrices (and subsequently 2-week matrices) in the sense that the predicted Week 52 proportion of patients in remission does not match with the corresponding maintenance NMA-specified remission proportion. The goal of calibration is to align the Markov dynamics used by the model engine with the NMA estimates for the Week 52 outcomes. The company's base case model meets this objective, whereas the EAG-suggested methodology does not. As shown in Appendix C Table 15 and Table 16, the

Key issue	Does this response contain new evidence, data or analyses?	Response
		EAG's 2-week maintenance-phase Markov matrices fail to yield Week 52 remission proportions consistent with (the EAG's) specified maintenance NMA estimates, leading to relative differences of more than 10%. From a clinical perspective, the trials were not designed to measure the impact of treatment on disease severity and rather were designed to measure the impact of treatment on individual patients relative to their own baseline disease scores. 'Moderate to Severe' CD was a requirement for inclusion into the risankizumab CD clinical studies, but after that point there was no measure of severity in terms of whether patients had mild, moderate, or severe disease. All efficacy outcomes are a numeric or percentage improvement from baseline and are therefore either achieved or not achieved. The argument for movement between disease states lacks validity as a patient who was at the severe end of the disease scale at baseline could technically respond to treatment but still have moderate to severe disease. Similarly, an eligible patient who was not classified as a responder and who was at the lower end of the inclusion criteria could move into the moderate disease category. As noted during the clarification questions phase (Question B20), multiple calibration methods could be used to alter transition probabilities in the maintenance-phase of the CEM. Nevertheless, adjusting only the remission|mild cutpoint to achieve the desired calibration constrains the problem to the adjustment of a single parameter, reducing the computational overhead in modelling calibration. Additionally, when this method is applied, the Week 52 outcomes meet the values of the maintenance NMA results. **Cycle length and transition matrix estimation** The EAG also recommended an alternative approach to changing cycle length which avoids the use of the approximate exponential assumption (Chhatwal et al. (2016) (21)). The company evaluated the

Key issue	Does this response contain new evidence, data or analyses?	Response
		feasibility of the suggested approach and, for the reasons set out below, decided not to implement any changes with regard to the method for cycle-length conversion in the CEM. Chhatwal et al. (2016) (21) do not provide a Microsoft Excel-based implementation for matrix conversion, and instead provide Matlab code and a Mathematica-based tool. To the company's knowledge, such an approach has not been implemented in any economic models submitted to NICE. Srivastava et al. (2021) (22) reviewed NICE TAs from January 1st, 2019 to May 27th, 2020 and reported that the 'generalisability and applicability of [the methods proposed in Chhatwal et al. (2016)] is still unexplored and their recommendations have not been implemented yet'. In the context of the CS CEM, the lack of an Excel-based implementation makes use of the Chhatwal et al. (2016) algorithm difficult, as the matrix cycle-length conversion is endogenous to the calibration process. Specifically, to obtain a calibrated 2-week maintenance-phase Markov matrix, one must: 1. Choose a cutpoint value (or values) in the ordered probit model 2. Derive the 26-week Markov matrix from the ordered probit model 3. Find the 2-week transition matrix from the given 26-week matrix using the Chhatwal et al. (2016) (21) algorithm 4. Repeat (that is, continue to vary the cutpoint value) until the week 52 remission proportion predicted using the 2-week matrix derived in Step 3 is equal to the target value (i.e., NMA estimate) This procedure is highly challenging to implement in Microsoft Excel as the conversion from 26-week to 2-week cycles must be completed for each cutpoint value considered, and the process itself must be carried out dynamically if the user alters the NMA target value. The company rejected this approach when developing the CEM because: 1) NICE recommend keeping models self-contained in Microsoft Excel; 2) a Microsoft Excel implementation of Chhatwal et al. (2016) would significantly increase the

Key issue	Does this response contain new evidence, data or analyses?	Response
		complexity and computational overhead in model calibration; and 3) the calibration of Markov matrices to NMA target values is the primary driver of comparative results and necessarily entails significant changes to the baseline estimated 2-week matrix. **Dose escalation assumptions** The EAG expressed concern regarding the company's assumption that dose escalation for comparator treatments only affects costs and not patient outcomes. A response to this point raised by the EAG has been discussed in Key Issue 4 ('Dose escalation and use of standard-dose efficacy').
7. Health state utility value estimation	No	The company understand the EAG's concerns around the use of the ordinary least squares (OLS) model to estimate health-state utilities and have used the linear mixed model health-state utility values estimated using patient health-related quality of life data from the risankizumab CD trials in their updated base-case cost-effectiveness analysis, with OLS model values considered in a scenario analysis. As discussed in EAG clarification question B24, the company decided to use OLS to estimate health-state utilities (based on the EQ-5D data collected from the risankizumab CD trials) as it is a simple, straightforward, and commonly used regression method for this purpose. However, as requested by the EAG, the company provided the values produced when using a linear mixed model, showing only negligible differences from the OLS model values. In the EAG report, it is stated that the EAG-preferred health-state utility scores would be those from the linear mixed model since it includes a random effect to account for repeated measures. The slight difference in the outcomes of each of the two regression methods has only a minor impact on the cost-effectiveness results produced. This is because, these values are applied equally for all comparators (utilities depend on the patient's health state and not the biologic treatment used). This also aligns with what is shown in the different

Key issue	Does this response contain new evidence, data or analyses?	Response
		scenarios tested in the CS (Section B.3.11.3), where the use of different utility value leads to cost-effectiveness outcomes that are similar to those produced in the base-case analysis.
8. Method of administration for risankizumab	Yes	Evidence for the on-body device (OBD) (also known as the 'on body injector [OBI]') was included in the regulatory submissions to the EMA and MHRA for the assessment of safety and efficacy of risankizumab. M19-128 sub study 1 [SS1] was a Phase 1 pharmacokinetic study which compared administration of risankizumab using the OBD with the pre-filled syringe (PFS) that was used in the clinical trial programme (23). An overview of methods and key results are presented in Appendix D. Both the MHRA and EMA highlighted that the [redacted] with a range of [redacted] to [redacted] and a point estimate of [redacted] (24, 25). This difference in [redacted] based upon safety/tolerability and efficacy results from Phase 1 through Phase 3 studies in healthy subjects and subjects with CD. The EMA also stated that there was no trend of increased adverse events with increasing exposure and there were no clinical consequences of treatment-emergent anti-drug antibodies (25). This was considered sufficient to rule out potential safety implications of the slightly higher C_{max} with the OBD during the maintenance phase. No efficacy concerns were raised by the EMA (25), and the MHRA stated that efficacy was mainly driven by average risankizumab concentration linked to the overall exposure AUC, which successfully met the bioequivalence (24). Additional evidence on the OBD is provided from M16-000 SS4, which was an open-label (OL) OBD administration and long-term extension study. The objective of the OBD period was to evaluate the usability of the OBD (the ability of the subjects to successfully self-administer risankizumab using the OBD) and also to assess patient-reported outcomes, efficacy, safety, tolerability, PK, and

Key issue	Does this response contain new evidence, data or analyses?	Response
		immunogenicity of risankizumab administered by the OBD in subjects who were receiving maintenance treatment with risankizumab. An overview of the methods and results are presented in Appendix D. Overall, the results do not reveal any unanticipated clinical concerns or harms associated with the use of the OBD. With regards to the concerns of confidentiality marking, the company propose to remove the commercial in confidence redactions from the paragraph in Key Issue 8 (p.19 of EAG report). Instructions for use for the OBD are now available to download at rxabbvie.com.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Incorrect comparator	Section 6.2.8. Last Paragraph, Page 129	No	At the end of the paragraph, it is stated that risankizumab remains dominant over infliximab SC in the BF population. The comparator here should be ‘vedolizumab SC’.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4: Summary of changes to the company's cost-effectiveness estimates

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Corrections applied to the original base case	The original submission (only listing elements that have been amended) • 12-month residual treatment effect duration • OLS model to estimate health-state utilities • Half-cycle correction (company implemented approach) • All-cause mortality (company implemented approach)	Correction #1: Include comparator in incremental analysis Correction #2: Half-cycle correction (EAG suggested approach) Correction #3: All-cause mortality (EAG suggested approach) Correction #4: Corrected utility age-adjustment (EAG correction) Correction #5: Risankizumab CD pack price Correction #6: Biologic treatment acquisition and administration costs per dosing schedule (EAG suggested approach)	See Appendix F.1 for the revised base-case results See Appendix G.1 for the revised base-case results with the 600mg induction dose at a lower cost.
Key Issues 1, 2, 3, 4, 6 and 8		No changes required following technical engagement as discussed in the responses to Key Issues (Table 2) above	
Key Issues 5 and 7		The revised base-case analysis applies the following changes in the CEM from the original company submission (only listing amendments) • 6-month residual treatment effect duration • Linear mixed model to estimate utilities	

Abbreviations: CD, Crohn's disease; CEM, cost-effectiveness model; EAG, External Assessment Group; EAR, External Assessment report; ICER, incremental cost-effectiveness ratio; OLS, ordinary least squares.

Sensitivity analyses around revised base case

The company have run several scenario analyses, as presented in Sections F2 to F5. Scenario analyses included the consideration of a 12-month residual effect duration (Section F.2), RD RE NMA results (Section F.3), utility data modelled as per the CS (OLS model) (Section F.4), and a scenario with a 2-cutpoint calibration of the ordered probit model (Section F.5). All scenarios were run using the deterministic model.

Appendix A: Subgroup analyses by CD location

Table 5: CDAI clinical remission at Week 12 (NRI-C) – CD location at baseline subgroup analysis (ADVANCE ITT1A population)

Disease location Treatment	Responder (NRI-C)				Response rate diff vs PBO		
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	[95% CI]§	P-value§
Colonic only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal-colonic							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; Diff, difference; ITT, intention-to-treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (RZB– PBO); § 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
Source: ADVANCE CSR (26)

Table 6: Endoscopic response at Week 12 (NRI-C) – CD location at baseline subgroup analysis (ADVANCE ITT1A population)

Disease location Treatment	Responder (NRI-C)				Response rate diff vs PBO		
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	[95% CI]§	P-value§
Colonic only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal-colonic							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CD, Crohn's disease; CI, confidence interval; Diff, difference; ITT, intention-to-treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (risankizumab – placebo); § 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
Source: ADVANCE CSR (26)

Table 7: CDAI clinical remission at Week 12 (NRI-C) – CD location at baseline subgroup analysis (MOTIVATE ITT1A population)

Disease location Treatment	Responder (NRI-C)				Response rate diff vs PBO		
	N	n (%)	[95% CI]†	Missing due to COVID-19, n	Diff (%)‡	[95% CI]§	P-value§
Colonic only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal-colonic							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; Diff, difference; ITT, intention-to-treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (RZB – PBO); § 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
Source: MOTIVATE CSR (27)

Table 8: Endoscopic response at Week 12 (NRI-C) – CD location at baseline subgroup analysis (MOTIVATE ITT1A population)

Disease location Treatment	Responder (NRI-C)				Response rate diff vs PBO		
	N	n (%)	[95% CI][†]	Missing due to COVID-19, n	Diff (%)[‡]	[95% CI][§]	P-value[§]
Colonic only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal only							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal-colonic							
RZB 600 mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CD, Crohn's disease; CI, confidence interval; Diff, difference; ITT, intention-to-treat; IV, intravenous; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (RZB – PBO); § 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.
Source: MOTIVATE CSR (27)

Table 9: CDAI clinical remission at Week 52 (NRI-C) – CD location at baseline subgroup analysis (FORTIFY ITT1A population)

Disease location Treatment	Responder (NRI-C)				Response rate diff vs PBO		
	N	n (%)	[95% CI][†]	Missing due to COVID-19, n	Diff (%)[‡]	[95% CI][§]	P-value[§]
Colonic only							
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO SC[¶]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal only							
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO SC[¶]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal-colonic							
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO SC[¶]	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; Diff, difference; ITT, intention-to-treat; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab; SC, subcutaneous.
† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (RZB – PBO); § 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV RZB induction therapy and were randomised to receive PBO in the maintenance study.
Source: FORTIFY CSR (28)

Table 10: Endoscopic response at Week 52 (NRI-C) – CD location at baseline subgroup analysis (FORTIFY ITT1A population)

Disease location Treatment	Responder (NRI-C)				Response rate diff vs PBO		
	N	n (%)	[95% CI][†]	Missing due to COVID-19, n	Diff (%)[‡]	[95% CI][§]	P-value[§]
Colonic only							
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO SC[¶]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal only							
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO SC[¶]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ileal-colonic							
RZB 360 mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO SC[¶]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CD, Crohn's disease; Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; Diff, difference; ITT, intention-to-treat; NRI-C, Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab; SC, subcutaneous; TNF-alpha, tumour necrosis factor alpha.

† 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 COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19; ‡ Risk difference = (RZB – PBO); § 95% CI for difference 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 COVID-19 or non-responder imputation only if there are no missing data due to COVID-19; ¶ The withdrawal (placebo SC) arm consisted of subjects who achieved SF/APS clinical response to IV RZB induction therapy and were randomised to receive PBO in the maintenance study.

Source: FORTIFY CSR (28)

Appendix B: Additional maintenance NMA results

Given that the exact methodology undertaken by the EAG was unclear even after the information provided during the technical engagement phase, to conduct the updated maintenance NMA, the company also followed the recommendations outlined in NICE DSU TSD 2 and TSD 5 (3, 4). Namely, mean and precision of the baseline-risk model results contained within comments of the EAG Stan and R code for maintenance baseline-risk temporal adjustment regression were incorporated into the current single-network RD RE maintenance NMA framework.

Results of the estimated remission rates using the EAG's FE and RE models' derived predicted baseline (placebo) clinical remission probabilities and the current single-network RD RE maintenance NMA framework are displayed in Table 11 and Table 12.

Table 13 and Table 14 present the RD RE results with vague/non-informative and informative priors (without adjustment for the temporal effect), for the CCF and BF populations, respectively.

Table 11: Estimated absolute CDAI remission rate using the EAG estimated baseline remission with temporal effect mean and precision, CCF population

Treatment	Single network from CQ, median (95% CrI)	NMA estimated AR with temporal effect – EAG FE model, median (95% CrI)	NMA estimated AR with temporal effect – EAG RE model, median (95% CrI)
ADA Q2W	[redacted]	[redacted]	[redacted]
ADA QW	[redacted]	[redacted]	[redacted]
IFX5/10 Q8W	[redacted]	[redacted]	[redacted]
IFX5 Q8W	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; AR, absolute remission; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CQ, clarification questions; CrI, credible interval; EAG, External Assessment Group; FE, fixed effects; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; RE, random effects; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

Table 12: Estimated absolute CDAI remission rate using the EAG estimated baseline remission with temporal effect mean and precision, BF population

Treatment	Single network from CQ, median (95% CrI)	NMA estimated AR with temporal effect – EAG FE model, median (95% CrI)	NMA estimated AR with temporal effect – EAG RE model, median (95% CrI)
ADA Q2W	[redacted]	[redacted]	[redacted]
ADA QW	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; AR, absolute remission; BF, biologic failure; CDAI, Crohn's Disease Activity Index; CQ, clarification questions; CrI, credible interval; EAG, External Assessment Group; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; RE, random effects; RZB, risankizumab; UST, ustekinumab; VDZ, vedolizumab.

Table 13: Single-network maintenance NMA results for CDAI remission, CCF population

Treatment	RD, FE (single network from CQ)		RD, RE, vague prior		RD, RE, half-normal prior	
	Median	95% CrI	Median	95% CrI	Median	95% CrI
ADA QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 5/10 Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX5 Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 14: Single-network maintenance NMA results for CDAI remission, BF population

Treatment	RD, FE (single network from CQ)		RD, RE, vague prior		RD, RE, half-normal prior	
	Median	95% CrI	Median	95% CrI	Median	95% CrI
ADA QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RZB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Appendix C: Approach to model calibration

Table 15: EAG NMA targets (single network) versus 52-week remission predictions using EAG-calibrated matrices: RZB vs VDZ-SC

	NMA Target	EAG 52-week prediction	Absolute difference	Relative difference
Intervention on biologic (RZB)	[redacted]	[redacted]	[redacted]	[redacted]
Comparator on biologic (VDZ-SC)	[redacted]	[redacted]	[redacted]	[redacted]
Intervention CC after response (RZB)	[redacted]	[redacted]	[redacted]	[redacted]
Comparator CC after response (VDZ-SC)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CC, conventional care; EAG, External Assessment Group; NMA, network meta-analysis; RZB, risankizumab; SC, subcutaneous; VDZ, vedolizumab.

Table 16: EAG NMA targets (single network with temporal adjustment) versus 52-week remission predictions using EAG-calibrated matrices: RZB vs VDZ-SC

	Target from NMA after correct calibration	EAG 52-week value after incorrect calibration	Absolute difference	Relative difference
Intervention on biologic (RZB)	[redacted]	[redacted]	[redacted]	[redacted]
Comparator on biologic (VDZ-SC)	[redacted]	[redacted]	[redacted]	[redacted]
Intervention CC after response (RZB)	[redacted]	[redacted]	[redacted]	[redacted]
Comparator CC after response (VDZ-SC)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CC, conventional care; EAG, External Assessment Group; NMA, network meta-analysis; RZB, risankizumab; SC, subcutaneous; VDZ, vedolizumab.

Appendix D: Study M19-128 (23)

Objective

Study M19-128 was a Phase 1, single-dose, randomised, open-label, multi-centre study, conducted in healthy volunteers and comprised of two sub-studies. Sub-study 1 (SS1) was designed to assess the relative bioavailability of risankizumab in the to-be-marketed 360 mg OBD system (single SC administration of 2.4 mL) versus the 90 mg prefilled syringe (PFS; 4 × SC administrations of 1 mL) used in the Phase 3 CD studies (ADVANCE, MOTIVATE and FORTIFY). SS1 also assessed the pharmacokinetics of risankizumab in a 180 mg OBD system following a single SC administration of 1.2 mL at the dose of 180 mg.

Methods

In SS1, non-Japanese subjects were randomised in a 4:4:1 ratio into Groups 1, 2 and 3, respectively. The first 16 Japanese subjects who were enrolled were randomised in a 1:1 ratio to Groups 1 and 2. The additional Japanese subjects who were enrolled were randomised in a 4:4:1 ratio to the three groups. Subjects received a single dose of risankizumab as follows:

- Group 1: 360 mg SC (90 mg PFS × 4, Reference) (N = 127, including N = 8 Japanese)
- Group 2: 360 mg SC (OBD, 2.4 mL of 150 mg/mL, Test) (N = 129, including N = 8 Japanese)
- Group 3: 180 mg SC (OBD, 1.2 mL of 150 mg/mL) (N = 30)

Results

Following administration of a single 360 mg SC dose, risankizumab concentrations in Group 2 (360 mg OBD × 1 SC injection) [redacted] when compared to Group 1 (90 mg PFS × 4 SC injections), [redacted]. Thus, the pharmacokinetic parameters between the 90 mg PFS (4 × 90 mg/mL) and 360 mg OBD groups [redacted] (Table 17). The relative bioavailability of the risankizumab 360 mg OBD compared to the risankizumab 90 mg PFS is presented in Table 18.

Table 17: Geometric mean (arithmetic mean, % CV) pharmacokinetic parameters of risankizumab following a single SC dose administration in healthy subjects (Study M19-128, SS1)

Pharmacokinetic parameters (units)	Group 1 90 mg PFS × 4 N = 116	Group 2 360 mg OBD N = 114	Group 3 180 mg OBD N = 28	Japanese	
				Group 1 90 mg PFS × 4 N = 7	Group 2 360 mg OBD N = 8
C_{max} (µg/mL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T_{max}† (day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AUC_t (µg•day/mL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AUC_{inf} (µg•day/mL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$t_{1/2}$‡ (day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AUC, area under the curve; OBD, on-body device; PFS, pre-filled syringe; SC, subcutaneous; SS, sub-study.
AUCinf, area under the serum concentration-time curve from time 0 to infinite time; AUCt, area under the serum concentration-time curve from time 0 to the last measurable concentration; Cmax, maximum observed serum concentration; Tmax, time to maximum observed serum concentration.
† Median (minimum through maximum); ‡ Harmonic mean (pseudo-standard deviation); evaluations of t1/2 were based on statistical tests for β.

Table 18: Relative bioavailability and 90% CIs for the bioavailability assessment (Study M19-128, SS1)

		Central value		Relative bioavailability	
Group (risankizumab dose) Test vs reference	Pharmacokinetic parameter	Test	Reference	Point estimate	90% CI
Group 2: 360 mg OBD vs Group 1 90 mg x 4 SC Injections	C_{max} (µg/mL)	[redacted]	[redacted]	[redacted]	[redacted]
	AUC_t (µg•day/mL)	[redacted]	[redacted]	[redacted]	[redacted]
	AUC_{inf} (µg•day/mL)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AUC, area under the curve; OBD, on-body device; PFS, pre-filled syringe; SC, subcutaneous; SS, sub-study.
Note: 28 subjects from SS1 are excluded from analysis (11 subjects for OBD-dosing failures or related issues; 8 subjects for incomplete pharmacokinetic profiles without terminal phase; 8 subjects for violating eligibility criterion #23 from the protocol by enrolling in both sub-studies; 1 subject for violating eligibility criterion #23 from the protocol by enrolling in two treatment groups of SS1).

Appendix E: M16-000 sub-study 4 (29)

Objective

M16-000 SS4 was an open-label (OL) OBD administration and long-term extension study. The objective of the OBD period was to evaluate the usability of the OBD (i.e., the ability of the subjects to successfully self-administer risankizumab using the OBD and assess patient-reported outcomes, efficacy, safety, tolerability, PK, and immunogenicity of risankizumab administered by the OBD in subjects who are receiving maintenance treatment with risankizumab.

Methods

M16-000 SS4 consisted of two periods: 1) the RLHS evaluation period of OBD self-administration (OBD period), including use at home, and 2) an open label extension (OLE) period (PFS period; not reported here). SS4 enrolled subjects from the OLE portion of M16-000 SS3. Subjects received the same dose of risankizumab in SS4 as they received in SS3. Main eligibility criteria were as follows: subjects were receiving maintenance treatment in SS3 and were willing to comply with the requirements of SS4, including self-administration with the OBD, and were on stable doses of risankizumab (i.e., in SS 3 for at least 16 weeks and no risankizumab rescue within 16 weeks).

The RLHS evaluation period of SS4 (OBD period) evaluated subjects' ability to self-administer risankizumab 180 mg or 360 mg SC via one OBD at Weeks 0 and 16 in the office under direct site supervision, and at Week 8 at home. At Week 24 (the first visit of the PFS period), subjects were to return to the site and transition back to 180 mg SC Q8w or 360 mg SC Q8w PFS. At the Week 0 visit, subjects were trained (pre-injection) by the site staff on how to inject risankizumab via an OBD using the instructions for use and video. Subjects were to follow the IFU and administer the OBD on the abdomen or thigh. After training, the site staff observed the subject self-administer their dose using the OBD. Site staff were instructed not to intervene with any self-administration unless the subject was going to harm themself. The subject was then sent home with an OBD kit and the instructions for use and were instructed to self-administer risankizumab via the OBD at home at Week 8. Additional training was not provided unless requested by the subject.

Results

A total of [redacted] subjects enrolled in Sub-Study 4: [redacted] in the risankizumab 180 mg OBD arm and [redacted] subjects in the risankizumab 360 mg OBD arm. Results are presented for the licensed 360 mg SC dose only.

Efficacy: The proportion of patients with CDAI clinical remission (CDAI score <150) at Visit 0 and Visit 16 are presented in Table 19. Based on non-responder imputation (NRI) analyses, [redacted] patients were in clinical remission at Week 0 and [redacted] were in clinical remission at Week 16.

Table 19: CDAI Clinical Remission (CDAI < 150) with risankizumab 360 mg OBD at Week 0 and Week 16 (AO) (ITT4 Population)

		Responder	
Visit	**N**	**N (%)**	**95% CI†**
Week 0	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]

Abbreviations: AO, as observed; CDAI, Crohn's Disease Activity Index; CI, confidence interval; ITT, intention-to-treat; OBD, on-body device.
†95% CI for response rate is based on the normal approximation to the binomial distribution.

Administration: Successful self-administration as observed by site staff was analysed on a subject level at Weeks 0 and 16 and occurred for [redacted] of subjects at the Week 0 visit and [redacted] of subjects at Week 16.

Useability: Patient experience and rating of acceptability with OBD was evaluated using the Self-Injection Assessment Questionnaire (SIAQ), which consisted of a pre-module administered at Week 0 before initial OBD injection and a post-module completed by the patient 20–40 minutes after each OBD injection. [redacted] (see Figure 1).

Figure 1: Post Module Mean SIAQ Domain Scores Over Time (AO) (ITT4 Population)

Abbreviations: AO, as observed; ITT, intention-to-treat; SIAQ, the Self-Injection Assessment Questionnaire.

Pharmacokinetics and immunogenicity: Following risankizumab 360 mg SC administration via OBD at Weeks 0 and 8, serum trough concentrations were consistent between the Week 0 and Week 16 time points for both dose arms (geometric mean [arithmetic mean, % coefficient of variation] [redacted] demonstrating that doses administered via the OBD achieved the expected risankizumab exposures for these subjects. There was [redacted] during Weeks 0-16 with risankizumab 360 mg SC administration via OBD indicating no marked impact on immunogenicity by SC administrations via the OBD.

Safety: Overall, treatment emergent adverse events (TEAEs) were reported in [redacted] subjects who received risankizumab 360 mg OBD. [redacted] experienced a TEAEs related to the OBD (dermatitis contact) as assessed by the investigator. No subjects experienced severe AEs or serious AEs and there were no deaths.

Appendix F: Updated cost-effectiveness results

F.1 Revised base-case results

Appendix F and G both present updated cost-effectiveness results, the only setting that differs in the model is the CS risankizumab PAS price.

The risankizumab CD prices used in the updated base-case and scenario analyses presented in this Appendix (F) are as summarised in Table 20.

Table 20: Risankizumab CD prices used in model results Appendix F

Name	Form	Dose per unit	Pack size	List price unit cost	Source	PAS unit cost
Risankizumab (Skyrizi®)	Concentrate for solution for infusion (IV)	600 mg	1	[redacted]	AbbVie	[redacted]
Risankizumab (Skyrizi®)	Solution for injection (SC) in cartridge	360 mg	1	[redacted]	AbbVie	[redacted]

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous.

F.1.1 Conventional care failure population

The fully incremental analysis for the CCF population is presented in Table 21 and Table 22, probabilistic and deterministic results, respectively. The analysis reflects the changes as set out in Table 4. In the CCF patient population, risankizumab was associated with an [redacted] probability of being cost effective at a threshold of £20,000 and [redacted] probability at a threshold of £30,000 (Figure 2).

Table 21: Revised base-case results for the CCF population: fully incremental cost-effectiveness results (probabilistic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 80/40	[redacted]	[redacted]	--	--	--	--
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£710	£710
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	£60,204	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£31,857	£40,970
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£50,184	£2,688,728
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	£71,525	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£205,659	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£225,224	Dominated

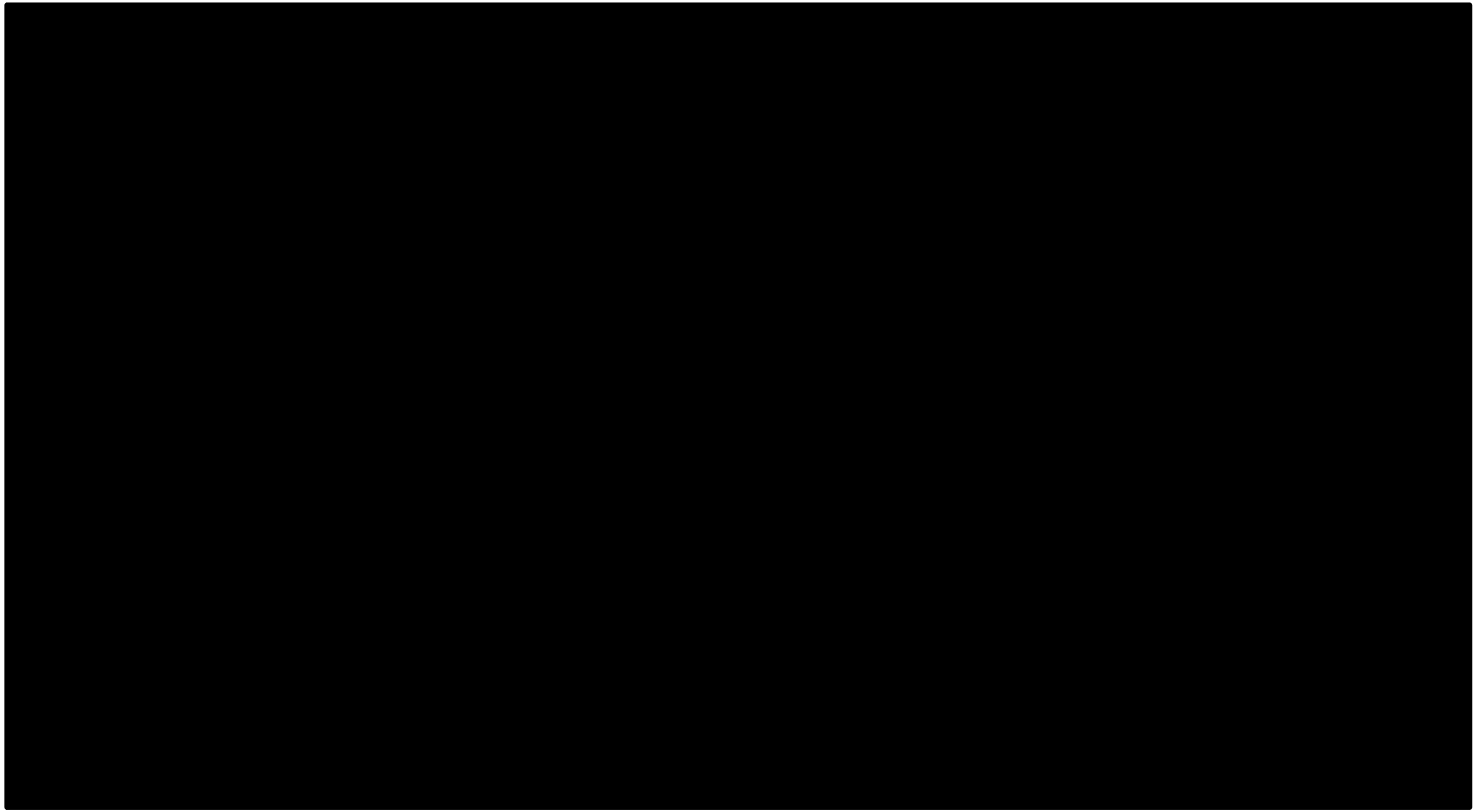
Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 22: Revised base case results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	--	--	--	--
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-2,367	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	42,689	42,689
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	64,019	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	90,079	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	578,589	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	452,058	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Figure 2. Revised cost-effectiveness acceptability curves in CCF population



F.1.2 Biologic failure population

The fully incremental analysis for the BF population is presented in Table 23 and Table 24, probabilistic and deterministic results, respectively. The analysis reflects the changes as set out in Table 4. In the BF patient population, risankizumab was associated with a [redacted] probability of being cost effective at a threshold of £20,000 and [redacted] probability at a threshold of £30,000, (Figure 3).

Table 23: Revised base-case results for the BF population: fully incremental cost-effectiveness results (probabilistic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£34,011	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-£38,164	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£55,209	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Table 24: Revised base-case results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-40,927	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-74,826	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-52,815	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Figure 3. Revised cost-effectiveness acceptability curves in BF population

F.2 Revised scenario analysis 1: 12-month residual treatment effect

F.2.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 25. The analysis reflects the changes of the updated base case, with the change to the residual treatment effect set to 12 months. The consideration of a 12-month residual treatment effect did not change the conclusion of the analysis.

Table 25: Revised scenario 1 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	--	--	--	--
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-4,154	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	35,369	35,369
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	55,242	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	79,548	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	278,009	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	219,629	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

F.2.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 26. The analysis reflects the changes of the updated base case, with the change to the residual treatment effect set to 12 months. The consideration of a 12-month residual treatment effect did not change the conclusion of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population.

Table 26: Revised scenario 1 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
UST	[redacted]	[redacted]	[redacted]	[redacted]	-74,558	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-46,565	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-56,493	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

F.3 Revised scenario analysis 2: NMA outcomes (random effects risk difference model)

F.3.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 27. The analysis reflects the changes of the updated base case, with the change to the NMA outcomes (RE RD model). The changes did not impact the conclusion of the analysis.

Table 27: Revised scenario 2 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	--	--	--	--
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-2,367	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	42,689	42,689
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	64,019	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	90,079	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	578,589	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	452,058	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

F.3.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 28. The analysis reflects the changes of the updated base case, with the change to the NMA outcome (RE RD model). The consideration of changes in the efficacy scenario to a random effects NMA did not change the conclusions of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population.

Table 28: Revised scenario 2 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-40,927	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-74,826	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-52,815	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

F.4 Revised scenario analysis 3: RZB EQ-5D trial data (OLS model)

F.4.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 29. The analysis reflects the changes of the updated base case, with the change to utility score to the risankizumab EQ-5D trial data (OLS model). The consideration of risankizumab EQ-5D trial data utility values did not change the conclusion of the analysis.

Table 29: Revised scenario 3 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	--	--	--	--
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-1,957	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	38,373	38,373
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	57,558	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	80,989	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	721,070	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	407,643	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

F.4.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 30. The analysis reflects the changes of the updated base case, with the change to utility score to the risankizumab EQ-5D trial data (OLS model). The consideration of risankizumab EQ-5D trial data utility values did not change the conclusion of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population.

Table 30: Revised scenario 3 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-35,544	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-67,004	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-45,864	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

F.5 Revised scenario analysis 4: Order probit model calibration

F.5.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 31. The analysis reflects the changes of the updated base case, with the change to the order probit model calibration, using a two cutpoint calibration (mild|moderate/severe and remission|mild). The consideration of a two-cutpoint calibration did not change the conclusions of the analysis.

Table 31: Revised scenario 4 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 80/40	[redacted]	[redacted]	--	--	--	--
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	14,095	14,095
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	80,277	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	60,071	74,670
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	83,162	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	131,672	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	108,838	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	119,490	928,224

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

F.5.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 32. The analysis reflects the changes of the updated base case, with the change to the order probit model calibration, using a two cut point calibration (mild|moderate/ severe and remission|mild). The consideration of a two-cutpoint calibration did not change the conclusions of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population.

Table 32: Revised scenario 4 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
UST	[redacted]	[redacted]	[redacted]	[redacted]	-73,040	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-44,064	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-54,834	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Appendix G: Updated cost-effectiveness results with 600mg induction dose at a lower cost

[redacted]. The risankizumab CD prices used in the updated base-case and scenario analyses presented in this Appendix (G) are as summarised in Table 33.

Table 33: Risankizumab CD prices used in model results Appendix G

Name	Form	Dose per unit	Pack size	List price unit cost	Source	PAS unit cost
Risankizumab (Skyrizi®)	Concentrate for solution for infusion (IV)	600 mg	1	[redacted]	AbbVie	[redacted]
Risankizumab (Skyrizi®)	Solution for injection (SC) in cartridge	360 mg	1	[redacted]	AbbVie	[redacted]

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous.

G.1 Revised base-case results

G.1.1 Conventional care failure population

The fully incremental analysis for the CCF population is presented in Table 34 and Table 35, probabilistic and deterministic results, respectively. The analysis reflects the changes as set out in Table 4. In the CCF patient population, risankizumab was associated with [redacted] net monetary benefit at values of the ICER willingness-to-pay threshold above £20,000. Risankizumab was associated with an [redacted] probability of being cost effective at a threshold of £20,000 and [redacted] probability at a threshold of £30,000 (Figure 4).

Table 34: Revised base-case results for the CCF population: fully incremental cost-effectiveness results (probabilistic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£41,478	Dominated
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-£90,080	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	-£161,145	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£83,384	£83,384
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£114,653	£114,653
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	£149,833	£149,833
UST	[redacted]	[redacted]	[redacted]	[redacted]	£5,802,173	£5,802,173

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 35: Revised base case results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-72,648	Dominated
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-31,250	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	-149,148	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	73,708	73,708
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	100,939	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	134,040	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	1,224,401	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Figure 4. Revised cost-effectiveness acceptability curves in CCF population

G.1.2 Biologic failure population

The fully incremental analysis for the BF population is presented in Table 36 and Table 37, probabilistic and deterministic results, respectively. The analysis reflects the changes as set out in Table 4. In the BF patient population, risankizumab was associated with [redacted] net monetary benefit at values of the ICER willingness-to-pay threshold above £20,000. Risankizumab was associated with a [redacted] probability of being cost effective at a threshold of £20,000 and £30,000, (Figure 5).

Table 36: Revised base-case results for the BF population: fully incremental cost-effectiveness results (probabilistic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£239,406	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-£162,131	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£178,910	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Table 37: Revised base-case results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-165,715	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-287,894	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-176,960	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Figure 5. Revised cost-effectiveness acceptability curves in BF population

G.2 Revised scenario analysis 1: 12-month residual treatment effect

G.2.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 38. The analysis reflects the changes of the updated base case, with the change to the residual treatment effect set to 12 months. The consideration of a 12-month residual treatment effect did not change the conclusion of the analysis, with risankizumab remaining cost effective compared with all comparators, in the CCF population.

Table 38: Revised scenario 1 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-77,895	Dominated
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-44,782	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	-119,702	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	99,578	99,578
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	131,106	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	169,263	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	697,747	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

G.2.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 39. The analysis reflects the changes of the updated base case, with the change to the residual treatment effect set to 12 months. The consideration of a 12-month residual treatment effect did not change the conclusion of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population.

Table 39: Revised scenario 1 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
UST	[redacted]	[redacted]	[redacted]	[redacted]	-261,351	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-150,900	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-160,351	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

G.3 Revised scenario analysis 2: NMA outcomes (random effects risk difference model)

G.3.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 40. The analysis reflects the changes of the updated base case, with the change to the NMA outcomes (RE RD model). The changes did not impact the conclusion of the analysis, with risankizumab remaining cost effective compared with all comparators, in the CCF population.

Table 40: Revised scenario 2 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-72,648	Dominated
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-31,250	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	-149,148	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	73,708	73,708
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	100,939	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	134,040	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	1,224,401	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

G.3.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 41. The analysis reflects the changes of the updated base case, with the change to the NMA outcome (RE RD model). The consideration of changes in the efficacy scenario to a random effects NMA did not change the conclusions of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population.

Table 41: Revised scenario 2 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-165,715	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-287,894	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-176,960	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

G.4 Revised scenario analysis 3: RZB EQ-5D trial data (OLS model)

G.4.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 42. The analysis reflects the changes of the updated base case, with the change to utility score to the risankizumab EQ-5D trial data (OLS model). The consideration of risankizumab EQ-5D trial data utility values did not change the conclusion of the analysis, with risankizumab remaining cost effective compared with all comparators, in the CCF population.

Table 42: Revised scenario 3 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-90,539	Dominated
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-29,978	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	-185,877	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	61,637	61,637
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	84,401	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	112,079	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	784,778	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

G.4.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 43. The analysis reflects the changes of the updated base case, with the change to utility score to the risankizumab EQ-5D trial data (OLS model). The consideration of risankizumab EQ-5D trial data utility values did not change the conclusion of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population.

Table 43: Revised scenario 3 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-143,917	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-257,801	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-153,671	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

G.5 Revised scenario analysis 4: Order probit model calibration

G.5.1 Conventional care failure population

The fully incremental analysis for the CCF population (deterministic results) is presented in Table 44. The analysis reflects the changes of the updated base case, with the change to the order probit model calibration, using a two cutpoint calibration (mild|moderate/severe and remission|mild). The consideration of a two-cutpoint calibration did not change the conclusions of the analysis, with risankizumab remaining cost effective compared with all comparators, in the CCF population.

Table 44: Revised scenario 4 analysis results for the CCF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-42,839	Dominated
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	-68,651	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	-98,656	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	409,692	409,692
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	516,935	Dominated
IFX IV	[redacted]	[redacted]	[redacted]	[redacted]	631,008	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	536,312	928,224

Abbreviations: ADA, adalimumab; CCF, conventional care failure; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

G.5.2 Biologic failure population

The fully incremental analysis for the BF population (deterministic results) is presented in Table 45. The analysis reflects the changes of the updated base case, with the change to the order probit model calibration, using a two cut point calibration (mild|moderate/ severe and remission|mild). The consideration of a two-cutpoint calibration did not change the conclusions of the analysis, with risankizumab remaining cost effective compared with all comparators, in the BF population (Table 45).

Table 45: Revised scenario 4 analysis results for the BF population: fully incremental cost-effectiveness results (deterministic results)

Technology	Total discounted costs	Total discounted QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
RZB	[redacted]	[redacted]	--	--	--	--
UST	[redacted]	[redacted]	[redacted]	[redacted]	-265,578	Dominated
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-148,516	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-158,385	Dominated

Abbreviations: BF, biologic failure; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Appendix H: Company Response to EAG's Additional Clarifications

Questions from EAG:

1. **Please clarify whether the company made further changes to the model other than those reported in Table 4 of your TE response.**

   Company response

   The company can confirm that the main amendments made to the company's base case are those described in Table 4, which were made in accordance with the EAG report ("ID3986-Risankizumab-Crohns-EAGReport v0.1 01.09.22 ACIC"). In addition to these changes, the company also added the two-cutpoint adjustment scenario for the ordered probit model and removed the option of the two NMA scenarios provided during the clarification questions phase since they were not considered appropriate for decision-making (due to the reasons described as a response to clarification questions A15 and B12); however, these two changes do not impact the company base-case results.

   Upon receipt of the EAGs modelling-related clarification questions, the company checked their cost-effectiveness model and uploaded an updated version ("6a. ID3986_Risankizumab CD_NICE_CEM_Final_ACIC_cal_options_v2.1") to the NICE Docs portal. The updated model corrects an error from the previously submitted version ("6a. ID3986_Risankizumab CD_NICE_CEM_Final_ACIC_cal_options_v2.0. xlsm") pertaining to incorrect baseline characteristic inputs which deviate from the default values.

2. **Please confirm that the EAG have correctly implemented the company's documented changes to the company base case in the model including EAG assumptions (version shared at TE fact check) and confirm that the resulting company base case ICERs reported in the EAG response to the company TE response are correct.**

   Company response

   The company can confirm that the use of the EAG model with the model switches set to the company's (previous and updated) base case draw comparable results to the updated company model ("6a. ID3986_Risankizumab CD_NICE_CEM_Final_ACIC_cal_options_v2.1"). However, to note, there is a small difference in the company base-case cost-effectiveness results between the two models due to the changes made in the updated company model to incorporate the different cutpoint assumptions requested by the EAG during technical engagement. Specifically, to add the new cutpoint assumptions, the company had to re-run the goal-seek Excel function that generates the coefficients of the ordered probit model (for both the base case and two-cutpoint adjustment scenario) and subsequently the transition probabilities of the

Markov part of the model. The goal-seek function inherently draws ordered probit coefficient values which due to rounding will differ (in the order of $X10^{-5}$) across files, leading to similar discrepancies in the transition probabilities and consequently differences in the low order of magnitude in the produced ICERs across the company and EAG models (i.e., the differences in the total costs and QALYs of the intervention and comparators across the two models are less than £20 and 0.002, respectively). These slight differences in the cost-effectiveness outcomes are expected given the small changes in the ordered probit model coefficients described above. The company maintain that the EAG use the updated company model ("6a. ID3986_Risankizumab CD_NICE_CEM_Final_ACIC_cal_options_v2.1") since it incorporates the amendments suggested by the EAG during technical engagement as well as additional scenarios that the EAG model does not include and will help with the final NICE decisions.

References

1. NICE. Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy STA (TA456). 2017. Available at: https://www.nice.org.uk/guidance/ta456/documents/committee-papers (Accessed June 2022)
2. NICE. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [TA352]. 2014. Available at: https://www.nice.org.uk/guidance/ta352/documents/crohns-disease-moderate-to-severe-vedolizumab-committee-papers2 (Accessed June 2022).
3. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011.
4. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model. 2011.
5. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-analysis for decision-making: John Wiley & Sons; 2018.
6. Gelman A, Rubin DB. Markov chain Monte Carlo methods in biostatistics. Stat Methods Med Res. 1996;5(4):339-55.
7. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 3: Heterogeneity—Subgroups, Meta-Regression, Bias, and Bias-Adjustment: National Institute for Health and Clinical Excellence; 2011.
8. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in medicine. 2015;34(6):984-98.
9. Cameron C, Hutton B, Druchok C, McElligott S, Nair S, Schubert A, et al. Importance of assessing and adjusting for cross-study heterogeneity in network meta-analysis: a case study of psoriasis. Journal of comparative effectiveness research. 2018;7(11):1037-51.
10. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Alimentary pharmacology & therapeutics. 2009;30(3):265-74.
11. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. The New England journal of medicine. 2016;375(20):1946-60.
12. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. The New England journal of medicine. 2013;369(8):711-21.
13. Freeman HJ. Use of the Crohn's disease activity index in clinical trials of biological agents. World journal of gastroenterology. 2008;14(26):4127-30.
14. Gastro training. Activity Index (CDAI). Available from: http://www.gastrotraining.com/calculators/cdai (Accessed June 2022).

15. Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Alimentary pharmacology & therapeutics. 2015;41(1):77-86.
16. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1-s106.
17. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw Index. Inflammatory bowel diseases. 2006;12(4):304-10.
18. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2010;8(4):357-63.
19. NICE. Ustekinumab for moderately to severely active Crohn’s disease after previous treatment: final appraisal determination. TA456. 2017.
20. Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet (London, England). 2022;399(10340):2031-46.
21. Chhatwal J, Jayasuriya S, Elbasha EH. Changing Cycle Lengths in State-Transition Models: Challenges and Solutions. Med Decis Making. 2016;36(8):952-64.
22. Srivastava T, Latimer NR, Tappenden P. Estimation of Transition Probabilities for State-Transition Models: A Review of NICE Appraisals. PharmacoEconomics. 2021;39(8):869-78.
23. AbbVie. A Phase 1, Pharmacokinetic Comparability Study of Intravenous and Subcutaneous Administration of Risankizumab in Healthy Subjects (M19-128) Clinical Study Report. 2021.
24. AbbVie. MHRA Day 180 Clinical Assessment Report Bioequivalence excerpt. 2022;Data on file.
25. AbbVie. EMA Day 173 overview Bioequivalence excerpt. 2022;Data on file.
26. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease (ADVANCE [M16-006]). Clinical Study Report. Risankizumab. 2021.
27. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment (MOTIVATE [M15-991]). Clinical Study Report. Risankizumab. 2021.

28. AbbVie. Multicenter, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Crohn's Disease (FORTIFY [M16-000]). Clinical Study Report. Risankizumab. 2021.
29. AbbVie. Multicenter, Randomized, Double-Blind, Placebo-Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Crohn's Disease – Sub-Study 4 (M16-000) Clinical Study Report. 2022.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in section 1.3 in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **21st October 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating Crohn's disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Guy's & St Thomas' NHS Foundation Trust
3. Job title or position	[redacted]
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Crohn's disease? ☒ A specialist in the clinical evidence base for Crohn's disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
8. What is the main aim of treatment for Crohn's disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	As set out by the International Organisation for the study of IBD (IOIBD) in their Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative, the main aims of treating Crohn's fall into two domains: 1) symptom resolution and 2) resolution of objective markers of inflammation. It is believed

	that by achieving resolution of inflammatory activity, progression of disease to complications (such as penetration and/or stricture formation) can be prevented. Beyond these main aims, restoration of quality of life is also crucially important. As is restoration of normal growth and maturation when treating children and adolescents.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Again, as set out by STRIDE, clinical remission can be defined using the novel Patient Reported Outcome-2 (PRO2) measure, or by using the Harvey Bradshaw Index (HBI). The suggested threshold for PRO2 is an abdominal pain score of </=1 and a stool frequency score of </=3. For HBI a score of <5 was suggested and generally used in clinical practice. In terms of resolution of objective markers of inflammation, assessment with ileocolonoscopy was recommended using a target based on the Simple Endoscopic Score for CD (SES-CD) of <3 points. Alternatively, resolution of ulceration could be considered as a definition of endoscopic remission (the two are effectively equivalent). However, in terms of minimum clinically significant treatment response there is reasonably strong data (from a post-hoc analysis of the SONIC trial) that a 50% drop in SES-CD following treatment predicts a favourable treatment outcome. Our own group has also generated recent data supportive of this as a minimum threshold (published in abstract form with full manuscript currently under review, https://academic.oup.com/ecco-jcc/article/16/Supplement_1/i408/6512882?login=false)
10. In your view, is there an unmet need for patients and healthcare professionals in Crohn's disease?	Yes, absolutely.
11. How is Crohn's disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	There exists significant variability in access to and use of advanced therapies for IBD. However, anecdotally, this variation would seem less marked between specialist IBD units and is probably more relevant for UC than Crohn's. The most widely used national guidance comes from the British Society of Gastroenterology and the most recent iteration was published in 2019

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	(https://gut.bmj.com/content/gutjnl/68/Suppl_3/s1.full.pdf). This is largely in keeping with international guidance from the European Crohn's and Colitis Organisation. Beyond this, many CCGs (now ICSs) will have local pathways, for example ours in South East London is published online (https://selondonccg.nhs.uk/wp-content/uploads/dlm_uploads/2021/09/IBD-pathways-with-Fe-deficiency-pathway-June-2019-FINAL.pdf). In general, the pathway is relatively well defined, in that most clinicians would choose to use an anti-TNF agent as first line. Following non-response, depending on a number of factors including therapeutic drug monitoring, one may consider trying another anti-TNF agent, but most would switch to ustekinumab as a second line agent and then finally to vedolizumab as third line. As per my answer above, there is significant unmet need as many patients will fail to respond to all three mechanisms of action and develop progression of disease and complications requiring surgical intervention. Risankizumab would appear to offer the potential to reduce this unmet need by controlling disease in patients refractory to other therapies. There is an ongoing head-to-head trial comparing ustekinumab to risankizumab (SEQUENCE) and this may help to determine whether risankizumab would become the most common second line agent. Until this reports there is equipoise in this regard.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	It is already in use in the NHS for other immune mediated inflammatory diseases and our own centre has already treated approximately 30 patients with Crohn's (initially via Abbvie's Pre-Approval Access Program (PAAP) and more recently via the Extending Access to Medicines Scheme (EAMS)). The healthcare resource will be very much in keeping with currently used biologic drugs for Crohn's disease. The induction doses are administered via IV infusion (as per ustekinumab, vedolizumab and infliximab) and will be given in infusion units which are already entirely accustomed to providing this service. Maintenance treatment will be self-administered using a subcutaneous delivery device, which will be delivered by a dedicated (third-party) homecare service. Again, this is as

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	per standard care for currently available agents (ustekinumab, adalimumab, subcutaneous infliximab and vedolzumab). The drug would only be initiated and managed in secondary care and by a Gastroenterologist with experience of managing IBD.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, based on the available trial data I would expect that this treatment would have the potential to control Crohn's disease inflammatory activity and reduce symptoms and complications, where other therapies have failed to do so. As such, I would expect it to increase health-related quality of life more than current care. As Crohn's is rarely life-threatening/limiting, I'm not sure that I would expect any significant change in length of life. It is very unlikely that there would ever be trial data to support any change in life-expectancy.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Crohn's disease patients with specific contra-indications to anti-TNF (such as multiple-sclerosis or cardiac failure) would be especially likely to benefit from the availability of another effective treatment option. The other group for whom risankizumab may be particularly effective is those with other immune mediated inflammatory diseases for which it has proven efficacy. For example, my understanding is p19 agents (such as risankizumab) are more efficacious for psoriasis (which coexists not infrequently with Crohn's) than anti-TNF agents.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	As per above, the administration would appear to be reasonably straightforward from a healthcare provider perspective. Pre-screening of patients for infective pathogens (e.g. TB and viral hepatitis) will also be as standard for other biologic drugs. The one new practical implication from a patient perspective is that the subcutaneous doses will be administered by an 'on body injector' (OBI) device. This is due to the relatively large volume of solution that needs to be administered, meaning that an injection pen or syringe would not be suitable. It

	remains to be seen whether patients find this more or less preferable than devices they would be more familiar with.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment would most usually require the demonstration of objectively active disease. This may be associated with symptoms but is not necessarily always the case (there is well recognised disconnect between endoscopic activity and symptoms). Treatment response would usually be assessed at 6-12 months and if treatment goals had not been achieved, discontinuation would be considered.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Although subcutaneous formulations of infliximab and vedolizumab are now available, many patients remain on IV infusions on a 4-8 weekly basis. I suppose the benefit of self-administered risankizumab treatment may be missed when comparing to those.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes. Risankizumab is innovative in that it is the first agent in its class for IBD. The endoscopic healing data, in particular, is very impressive and could reasonably be expected to provide a significant and substantial on health-related benefits. There is such a large unmet need in Crohn's currently that no clinician would suggest that risankizumab would completely fulfil this need, but one would expect that it would go some way to addressing it.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The data would suggest that this is a safe and well tolerated treatment. This is particularly the case when comparing it to conventional therapies (thiopurines and methotrexate), corticosteroids and anti-TNF agents (given as monotherapy or in combination with conventional immunosuppressants). It would also have

	appear to have fewer potential adverse events than surgical resection, which is another relevant comparator for this group of patients.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The Bio-IR population would be more representative of the cohort where the drug is likely to be used in UK clinical practice. Outside of the setting of anti-TNF contra-indication, I would imagine it would be rarely used in a bio-naïve population. The chosen endpoints in the phase III trial program appear progressive and directly relevant to clinical practice. They were a step towards aligning clinical trial endpoints with clinical practice treatment targets. The combination of PRO2 and SES-CD, both suggested by STRIDE for use in the setting of routine clinical care, mean that the results can be more readily extrapolated to clinical practice than previous similar phase III trials. There are always groups of CD patients that are not represented adequately in clinical trials and the risankizumab program was no different in this regard. Patients with stomas are almost always considered ineligible, as are those with disease out of reach of an ileocolonoscopy (upper GI disease/isolated mid-small bowel disease). Patients with multiple comorbidities and those on immunosuppressants for other indications would also be underrepresented. Although eligible for inclusion in the trials, patients with perianal fistulation were not systematically re-evaluated (either clinically or with MRI scanning), so robust conclusions are difficult to reach for this disease phenotype. To the best of my knowledge, there are no adverse effects that were not apparent in clinical trials but have come to light subsequently. We have not seen any in our small cohort (30) of risankizumab-treated patients so far.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA352 and TA456?	This head-to-head, randomised, double-blind, phase III trial of ustekinumab vs adalimumab (SEAVUE), published in the Lancet in June 2022 may also be relevant regarding the efficacy of each of those comparator agents: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00688-2/fulltext This study, designed to investigate endoscopic outcomes (which were not included in the phase III, registration trials) for using vedolizumab in Crohn's disease may be relevant as a comparator: https://www.gastrojournal.org/action/showPdf?pii=S0016-5085%2819%2940985-2
23. How do data on real-world experience compare with the trial data?	To the best of my knowledge, there have been two small, real-world studies published and only in abstract form. One comes from Belgium (published at ECCO 2022, https://academic.oup.com/ecco-jcc/article/16/Supplement_1/i516/6513144) and the other from our own centre (published at BSG 2022, https://gut.bmj.com/content/71/Suppl_1/A45.2). Given that these studies include patients with Crohn's that has proved refractory to multiple biologic mechanisms, they provide some initial data that would appear broadly consistent with RCT findings. Clearly, larger and fully described (manuscript format) real-world studies would be more helpful.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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	No.

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Feasibility of exploratory subgroup analysis by CD location	One issue with this approach is that the trials were not designed or powered to identify differences in efficacy based on disease location. Another is that patients with disease proximal to the terminal ileum (i.e. isolated mid-small bowel disease or upper GI disease) would have been excluded from the trial, as disease within reach of a standard ileocolonoscopy was an inclusion criteria. Finally, outside of the context of perianal disease, I'm not entirely sure that disease location is a significant determinant of treatment choice. I'm not sure that the standard treatment algorithms described above put much (if any) emphasis on disease location; indeed, even on the longest standing biologics, we have little robust data that demonstrates variations in efficacy based upon location. On the basis of these factors, I'm not entirely convinced that subgroup analysis by CD location is feasible or clinically valuable.
Unexplored heterogeneity in network meta-analyses in relation to baseline risk	No specific comments

Network structure in maintenance network meta-analyses should be connected	No specific comments
Appropriateness of the model structure	It is quite correct that the CDAI is not used in clinical practice. There are indeed many reasons for this. However, to the best of my knowledge, no phase III registration trials have used HBI to judge efficacy. Rather than HBI, the evaluation of clinical disease activity in trials is moving towards patient reported outcomes (such as PRO2, collected as part of the risankizumab program) in conjunction with endoscopic outcomes. Although HBI is the most commonly used score in clinical practice, in reality, even this is used infrequently. Over time, clinical disease assessments in both clinical practice and trials may converge upon measurement of PROs.
Treatment duration and residual treatment effect assumptions	No specific comments
Estimation and application of maintenance treatment effectiveness assumptions	No specific comments
Health state utility value estimation	No specific comments
Method of administration for risankizumab	Discussed above – IV induction followed by the novel on body injector for maintenance. From a healthcare delivery point of view, this is effectively identical to IV induction and subcutaneous maintenance using a pen device or needle and syringe. Patient experience of the device remains to be seen.

Are there any important issues that have been missed in EAR?	Not that I have identified

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. There is, unquestionably, unmet need in the treatment of Crohn's disease; it appears highly likely that risankizumab will help us start to meet this need.
2. The data demonstrate that risankizumab can help patients achieve clinically meaningful goals, such as clinical remission and endoscopic healing. This is true both for biologic experienced patients as well as those who are naïve to biologics.
3. The safety profile of risankizumab over the course of a year seems favourable and it would appear to be well tolerated.
4. Low rates of immunogenicity suggest that combination therapy, with a conventional immunosuppressant (as is often the case with infliximab and adalimumab), will not be necessary.
5. My own personal experience, in a small cohort of highly treatment refractory patients, has been that even amongst this, difficult-to-treat group with few other options, there have been some significant improvements.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with Crohn's disease or caring for a patient with Crohn's disease. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in section 1.3 in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **21st October 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Living with this condition or caring for a patient with Crohn's disease

Table 1 About you, Crohn's disease, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with Crohn's disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Crohn's disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Crohn's and Colitis UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Crohn's disease? **If you are a carer (for someone with Crohn's disease) please share your experience of caring for them**	I was diagnosed with Crohn's disease in July 2018, having already suffered symptoms for around seven years. Since diagnosis, I achieved remission for one year before having a severe flare-up that I have just got under control after 3 years. During those 3 years, I had a 10-day hospital stay and 13 weeks off work. I had intestinal bleeding, malnutrition, rapid weight loss, five courses of steroids (and associated adverse effects), agonising pain, uncontrollable diarrhoea, and debilitating fatigue. I have spent weeks bed-bound and months house-bound. I have at times been so weak that my parents have had to help me eat and get to the toilet. Over the three years, I have tried various combinations, dosages, and preparations of Pentasa, Mercaptopurine, Prednisolone, IV hydrocortisone, Budesonide, Colesevelam, adalimumab, and ustekinumab. Unfortunately, the standard dosing of ustekinumab – one injection every 8 weeks – is not enough to control my condition, and my local clinical commissioning group has declined to provide the funding I need to inject every 5 weeks. My godfather is therefore paying for me to have additional injections privately, at the cost of £2,500 per injection. It has given me back my life and I am profoundly grateful. Crohn's disease has had an impact on my life that is difficult to fully describe. Before my severe flare-up. I would run, dance, and kayak; I had a high-pressure job at the heart of government; I had lived in six countries, pursuing challenging opportunities wherever they came up. During my 3-year flare-up, my life shrank to one room. I had to give up the job I'd worked towards for ten years, I had to move back in with my parents for 2 years so there would be someone to care for me, I was completely shielded because of Covid, I spent around 22 hours a day in bed, and I was intensely lonely.

	But the aspect that is most frightening is the lack of options. At the moment, my options are eye-wateringly expensive extra ustekinumab injections, vedolizumab (with a roughly 15% efficacy rate), or life-changing surgery. If Risankizumab were approved, it would give me, like thousands of other patients, that crucial extra option. It could be the difference between a life well lived and a lifetime of ill health. I have so much I could, and want, to contribute to the world. I want to be part of society, to work, to meet a partner, to see my friends, to go for a run, to volunteer, to look after my family, to play with my nephew, to make art, to play my violin – but I can't do it without drugs like Risankizumab. I therefore ask you to consider patients like me when you are assessing its approvability.
7a. What do you think of the current treatments and care available for Crohn's disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a) To someone who doesn't have Crohn's disease, it probably looks as though there are a lot of treatments currently available. However, once you start treatment, you quickly discover that isn't the case. For example, I stopped responding to Pentasa, Prednisolone, and Budesonide after just a few months; I never responded to Colesevelam or adalimumab; Mercaptopurine gave me liver problems; and I've only remained on ustekinumab because a friend is paying for me to have a high enough dose for it to be effective. The remission rate of each biologic is around 20% and, even if you get into remission, the rate of relapse is high. Even now that I am in (at least temporary) remission, it is not without costs. It has taken months to get here – necessitating a hospital stay in the meantime – and, even now, I still suffer from intermittent fatigue. It is also frustrating to have a suppressed immune system against a backdrop of Covid, although I acknowledge that this would also be the case with Risankizumab. I think it is also worth noting that the care available for Crohn's disease is seriously suffering from NHS cuts. Even when I had been off work for 7 weeks over the summer, with a rapidly deteriorating condition, the earliest 'urgent' appointment my consultant had available was in six months' time. Although Risankizumab can't directly help with this, it could reduce the number of patients in flare-ups and reduce the number of patients needing urgent appointments.

	7b) Every patient I have ever spoken to shares these views. We are all very grateful that biologics have been invented but it feels like just the beginning of proper Crohn's treatment, not the end. Treatments need higher efficacy rates, fewer adverse effects, and to be quicker to kick in.
8. If there are disadvantages for patients of current NHS treatments for Crohn's disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I think there are four main disadvantages to the current biologics – that I recognise Risankizumab would share: 1. The length of time it takes biologics to kick in. 2. The lack of personalised medicine (meaning that a patient might have to try multiple biologics before they find one that works). 3. The fact that there are still relatively high relapse rates even when on a biologic. 4. Their immunosuppressant effects. However, although these disadvantages are frustrating, they are completely outweighed by the drug's potential advantages. The possibility that the drug could lift you out of daily suffering makes all the disadvantages worthwhile.
9a. If there are advantages of Risankizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Risankizumab help to overcome or address any of the**	9a) The main advantage I can see of Risankizumab over other NHS treatments is the relatively high remission rate of 40-60% and the fact that it does not suppress anti-interleukin-12, meaning that it does not suppress parts of the immune system unnecessarily. But even if it didn't have this advantage *over* other treatments, and just had the *same* advantages of current treatments, it should still be approved for all the same reasons that the current treatments were. 9b) Its efficacy rate. I will put up with suppression of my immune system in order to be well. 9c) It helps to overcome the low remission rates of other biologics, both in the sense that Risankizumab's remission rate seems higher than those of other biologics (though I acknowledge there's a lack of head-to-head studies to be sure), but also because it increases the cumulative probability of a patient finding a drug that works for them.

listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of Risankizumab over current treatments on the NHS please describe these. For example, are there any risks with Risankizumab If you are concerned about any potential side effects you have heard about, please describe them and explain why	None that I can think of.
11. Are there any groups of patients who might benefit more from Risankizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I think Risankizumab will particularly be a lifeline for patients who have not responded to any other Crohn's drug, have had surgery, had a relapse, and have no further medications to treat them. Risankizumab might be their only hope of living a healthy and meaningful life.
12. Are there any potential equality issues that should be taken into account when considering Crohn's disease and Risankizumab? Please explain if you think any groups of people	None. But I urge NICE to be generous and clear in its guidance to reduce the chance of different clinical commissioning groups offering different treatment regimes and patients being victims of postcode lotteries.

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.	
13. Are there any other issues that you would like the committee to consider?	I would like NICE to consider the risks of inaction. Not approving Risankizumab would result in surgeries that might otherwise have been unnecessary, and lives that are not fully lived.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Feasibility of exploratory subgroup analysis by CD location	It would obviously be very helpful for patients and clinicians to have analysis on the efficacy of Risankizumab by CD location. This seems like an excellent subject for further study, and it could contribute to ongoing research into the potential for personalised medicine for CD patients. However, the lack of subgroup analysis does not seem a sufficient reason in itself to decline approval for Risankizumab. As far as I understand, no other biologic for treating CD is recommended (or not) for patients depending on the location of their inflammation.
Unexplored heterogeneity in network meta-analyses in relation to baseline risk	Again, this seems like a nice-to-have and potential subject for further exploration rather than a sufficient reason to decline approval when the drug could have such a positive impact.
Network structure in maintenance network meta-analyses should be connected	Same as above.

Patient expert statement

Appropriateness of the model structure • ***The model structure defines health status by Crohn's Disease Activity Index (CDAI) score, because endoscopic data are not available for all treatments. Which measure of disease activity is most relevant for patients?*** • ***After their initial therapy patients move to conventional care – no other active treatment is given. Does this reflect the treatment pathway for people with Crohn's disease?*** **We consider patient perspectives may particularly help to address this issue**	• The CDAI is often a more relevant measure for patients than endoscopic data because it takes account of many more factors, such as extra-gastrointestinal symptoms (such as eye inflammation) and 'general wellbeing' (fatigue). This is very helpful, as these can cause a patient serious problems even if endoscopy data indicates a low level of bowel inflammation. It is also obviously so much easier to use the CDAI than to have an endoscopy. Not only does the CDAI not require any bowel preparation, an endoscopy can trigger a flare-up (as it does for me). • A move from initial therapy to conventional care after 52 weeks does **not** reflect the treatment pathway for people with Crohn's disease and is concerning to read. Although some patients might decide, along with their consultant, to cease biologic treatment after 12 months if they are in stable remission, it is rare for a patient to be compelled to against their wishes, particularly if many other treatments have failed and they have been very unwell. It is not clear, in reading the report, what percentage of patients who came off Risankizumab went on to have another flare-up in the following months. It is also not clear whether patients who go on to have a flare-up would be allowed to resume treatment and, if so, whether they would continue from where they left off or would start again with a new induction treatment. It is particularly important with Risankizumab that patients be allowed to continue treatment for as long as they need it. As Risankizumab will presumably be the drug of last resort, patients will have no other drug to keep them remission if they come off Risankizumab. I urge NICE to clarify these points in any published guidance if Risankizumab is approved or risk a postcode lottery of different clinical commissioning groups deciding on different procedures.

Treatment duration and residual treatment effect assumptions • ***The company assumes that all patients discontinue biologic treatments by 52 weeks. The EAG assumes 20 years maximum treatment duration. If you (or the patients you represent) have experience of stopping biologic treatments which are still working at a year? If so did your symptoms remain controlled for a period of time?*** **We consider patient perspectives may particularly help to address this issue**	My consultant and I have agreed that I will never have to come off ustekinumab unless I get another flare-up. We agree that the risk of another severe flare-up is too high and that it would be dangerous and unjust. I urge NICE to do the same for patients on Risankizumab. It would be like someone saying "ok, you've walked halfway across a tightrope over a 20ft drop without falling, so I'm going to take away your balance pole now to save money and we'll see what happens." If a patient has done well, they should keep going as they are. It is not fair to take away someone's medication and risk their life and career collapsing.
Estimation and application of maintenance treatment effectiveness assumptions	It seems concerning that the company assumes that dose escalation affects costs but not patient outcomes. EAG's suspicion seems reasonable that this 'likely biases comparative cost-effectiveness estimates in favour of Risankizumab, as dose escalation applies only to comparator biologics'. Given that dose escalation improves patient outcomes in other biologics, the company's assumption seems unlikely. However, it does not, in itself, seem a reason to deny approval for the drug – merely a reason for further study.
Health state utility value estimation	I don't have any views on this.
Method of administration for Risankizumab ***The company explains that Risankizumab maintenance treatment***	I have no preference for an OBD or a subcutaneous injection. I prefer doing a syringe injection (such as Stelara) rather than a pen injection (such as Imraldi), because the latter requires more force to inject and tends to hurt more. I prefer to inject slowly and in a way that makes me feel in

will be administered through the on-body-device (OBD) subcutaneously either at home or in clinic, however clinical evidence comes from a clinical trial where it was administered by subcutaneous injection by a clinician. Do you have any comments on the advantages or disadvantages of an on-body device compared with subcutaneous injection for patients? **We consider patient perspectives may particularly help to address this issue.**	control. Although an OBD wouldn't give me that control, it would certainly have the huge advantage that I wouldn't have to look at the needle. I'd be very happy to use an OBD.
Are there any important issues that have been missed in the EAR?	Not that I can see.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The current treatments are not enough for many patients with Crohn's disease, leaving thousands of people leading painful, miserable lives.
- The issues found in the EAR suggest the need for further study but do not seem sufficient reasons, even considered together, to decline approval for Risankizumab.
- Risankizumab appears to have an efficacy rate and safety profile that Crohn's patients would be very willing to try.
- Risankizumab could be the difference between a person struggling to get through a daily fog of pain, exhaustion, and uncontrollable diarrhoea, and a person living their life happily and healthily to the full.
- Please give patients that chance.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

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

A Single Technology Appraisal

Addendum #1

[ERG Technical Engagement Response]

November, 2022

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU

Authors

Maxwell S. Barnish[1]
Jae Naik[2]
Will Sullivan[2]
Amanda Brand[1]
Emma Hook[2]
Justin Matthews[1]
Mark Edmondson-Jones[2]
Sophie Robinson[1]
Jonathan Digby-Bell[3]
G.J. Melendez-Torres[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
[2] Delta Hat Limited, Nottingham
[3] Royal Devon and Exeter Hospital, Exeter

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter

Correspondence to Dr Maxwell S. Barnish

3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk

Source of funding This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/56/25.

Declared competing interests of the authors None.

Rider on responsibility for document The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This addendum is linked to ERG report Barnish MS, Naik J, Sullivan W, Brand A, Hook E, Matthews J, Edmondson-Jones M, Robinson S, Digby-Bell J, Melendez-Torres GJ.Risankizumab for previously treated moderately to severely active Crohn's disease [ID3986]. Peninsula Technology Assessment Group (PenTAG), 2022.

INTRODUCTION

The purpose of this addendum is to critique the company's responses and additional data provided at Technical Engagement, Key Issue by Key Issue.

Not specific to any one Key Issue, the EAG is minded to note that the company's updated cost-effectiveness model was received by the EAG three working days after the technical engagement response deadline, and only after a follow-up request was made. When received, not only was the company's updated model not set up to allow the user to move between (30 June) company submission, EAG report and updated company results; the model had been hard coded with inputs that contradict those used in the company submission.

1. KEY ISSUE 1: FEASIBILITY OF SUBGROUP ANALYSIS BY CD LOCATION

The company provided exploratory subgroup analyses by CD location as requested by the EAG. The company stated that based on clinical advice from 6 UK gastroenterologists, CD location was not a relevant factor for treatment choice, except for perianal disease which is outside of the present scope. This does not necessarily mean that CD location is not a determinant of outcomes. Clinical advice to the EAG was that CD location was an important prognostic factor, although it should be noted that the EAG was only able to recruit one clinical expert for this topic. The company stated that the patient numbers are quite low for the subgroup analysis, limiting the inference that can be drawn. The EAG agreed that the numbers were suboptimal, although noted that low numbers were also an issue for the company subgroup analysis by patient age.

Across analyses, the EAG considered that generally the results for ileal only patients differed from those in the other patient groups. In ADVANCE, for CDAI clinical remission at Week 12, the response rate difference for risankizumab versus placebo was [redacted] for colonic only, [redacted] for ileal only, and [redacted] for ileal-colonic patients. For endoscopic remission at Week 12, the response rate difference for risankizumab versus placebo was [redacted] for colonic only, [redacted] for ileal only, and [redacted] for ileal-colonic patients. In MOTIVATE, for CDAI clinical remission at Week 12, the response rate difference for risankizumab versus placebo was [redacted] for colonic only, [redacted] for ileal only, and [redacted] for ileal-colonic patients. For endoscopic remission at Week 12, the response rate difference for risankizumab versus placebo was [redacted] for colonic only, [redacted] for ileal disease, and [redacted] for ileal-colonic patients. In FORTIFY, CDAI clinical remission at Week 52 was [redacted] for colonic only, [redacted] for ileal only, and [redacted] for ileal-colonic patients. Endoscopic response at Week 52 was [redacted] for colonic only, [redacted] for ileal only, and [redacted] for ileal-colonic patients. Statistical significance of the differences by CD location was not tested.

The company stated that it was not possible to conduct a network meta-analysis (NMA) by CD location since studies identified in the systematic literature review did not report outcomes by

outcome location. The EAG agreed with this assessment. Therefore, CD location may not be a factor that can be fruitfully explored further in the context of this appraisal.

2. KEY ISSUE 2: UNEXPLORED HETEROGENEITY IN NETWORK META-ANALYSES IN RELATION TO BASELINE RISK

In TE the company examined three adaptations to the risk difference (RD) analyses: adjustment for temporal effect, use of informative priors, and baseline risk adjustment.

The company supplied results as absolute risks for the first two of these when applied to the single network for maintenance (EAG preference) in TE Appendix B. Results from these adaptations to the split network (company preference) were not given in TE response.

As explained further in Key Issue 3, the EAG believes that it is the relative risks (in this case, risk differences), not absolute risks, that should have been presented in order to assess the use of informative priors and/or adjustment by meta-regression. The remainder of this section contains other more specific comments.

2.1. Temporal Effect

The company carried out modelling of relative risk and the baseline model separately, stating *'The absolute effect of the reference treatment (placebo in all instances) were modelled using a baseline natural history model that was constructed independently from the model of relative treatment effects as per NICE DSU TSD5'.* The EAG confirmed that coding for relative effects is independent of the coding for the absolute risk of the reference treatment, and control arm terms are given uninformative priors in the NMA. The EAG agrees strongly with the company's approach.

Because of this the EAG believes the 'temporal effect' analysis, in which the reference treatment prior probabilities are altered, does not affect efficacy results. The choice of reference treatment risk remains an important aspect of cost-effectiveness however (EAG report section 6.2.5). The analysis introduces a higher reference treatment response representing improvements in 'standard care' over time (EAG report fig. 3), with consequences for cost-effectiveness.

The EAG agrees with the company that '*the heterogeneity across the relevant comparator trials a complex combination of the differences (e.g., in study designs, duration of induction phase, drug mechanisms of action, drug half-lives etc.) and not just limited to the time at which the different trials were conducted'.* This would have been the rationale for a meta-regression for

baseline risk had it been successfully carried out taking account of all relevant variables, including potentially time.

2.2. Informative Priors

The company explained that identifying a plausible informative prior in the disease area is difficult. As a fallback, the EAG had suggested the possible use of the generic priors offered by Turner et al. 2015, but the company pointed out that these priors were devised for the logit-link not the RD approach. The EAG agrees that they are not amenable without adaptation to the RD method chosen by the company, though they remain an option for an alternative logit-link analysis. Devising a prior with clinical expertise was not discussed by the EAG or the company.

2.3. Baseline Risk Adjustment

The company indicated that baseline risk adjustment by meta-regression was attempted but problematic for both logit-link and RD approaches.

It goes on to say in TE that '*RD results approximate those of baseline risk adjustment*'. The EAG maintains its view (EAG report section 3.4.5) that while the RD approach implemented in the CS accommodates variations in control arm risk within relative risk analysis, it does not adjust in a meta-regression sense (where adjustment is made for the difference in a trial's specific control arm risk from the average).

3. KEY ISSUE 3: NETWORK STRUCTURE IN NETWORK META-ANALYSIS

The company maintain in TE that the 'approach of a split-network maintenance NMA is most appropriate due to the deficiencies of the single-network maintenance NMA and methodological challenges in accounting for the heterogeneity by means other than splitting the network'.

Many of the original arguments in favour of the split network presented in the CS, and the EAG responses to those, were not revisited by the company. In TE the company focused on extended single-network maintenance NMA results, applying a 'temporal effect' with and without random effects (TE response, Tables 11 and 12) and random effects modelling with vague or informative priors (TE response, Tables 13 and 14). The company reports 'unfeasibly wide CrIs' in all cases, as can be seen in the tabled results. It also notes that these results 'lack face validity when compared against the clinical trial data that are available for each biologic therapy'.

The EAG understands that the company has presented absolute risks in Tables 11-14 of TE Appendix B, in which the relative risks from the NMA have been combined with absolute baseline/ reference treatment risks. The EAG notes that it is the relative risks that represent the efficacy results of the NMA. Absolute not relative risks were also given previously in the CQ response (Tables 24-25). As the relative treatment effects have not been supplied, any changes to efficacy cannot be properly interpreted under these extended analyses.

In summary, the EAG outlined several reasons for preferring a single-network maintenance NMA. In TE, the company argued that doing so leads to absolute risks with very large CrIs, and therefore a split-network maintenance NMA is preferable. The EAG considers that efficacy results (relative risks) are required to assess whether single-network maintenance results have face validity and acceptable precision.

4. KEY ISSUE 4: APPROPRIATENESS OF THE MODEL STRUCTURE

In their technical engagement response to EAG Key Issue 4, the company maintain that their chosen cost-effectiveness model structure is the most appropriate for decision-making, while recognising that the approach is limited in the extent to which it reflects clinical practice. The company comment on four structural and data issues, the first two of which the EAG highlighted as core issues within Key Issue 4: (i) Use of CDAI; (ii) Transition to conventional care after biologic failure; (ii) Defining conventional care after no response; and (iv) Dose escalation and use of standard-dose efficacy. Here, the EAG respond to these company comments in order, before drawing an updated conclusion on Key Issue 4.

4.1. Use of CDAI

In their response, the company reiterate that use of CDAI states facilitates indirect comparisons and has precedent in appraisals of Crohn's Disease. The EAG recognise these points, but reiterate the EAG's central point that despite these relative merits, the EAG feel it is important to stress that CDAI outcomes are not used in clinical practice, and as such, the model is of limited use for decision-making.

The company acknowledge that the Harvey Bradshaw Index (HBI) and endoscopic assessments are measures of relevance in UK clinical practice. In a separate response to technical engagement, a Guy's and St Thomas's NHS Foundation Trust Consultant Gastroenterologist noted a movement towards the inclusion of patient reported outcomes including PRO2 in clinical trials, alongside endoscopic outcomes.

The company note that they consider the use of CDAI outcomes in the model to be aligned with those from the HBI, with the rationale that the measures share several common items and published studies have shown HBI is correlated with CDAI score (correlation coefficient = 0.93).[1] However, the EAG note that in the same study, it is stated that correlation coefficients are not sufficient instruments for deciding whether one method of clinical measurement may logically be substituted for another. The company argue in their technical engagement response that estimating HBI based on CDAI scores would lack credibility, because of increased uncertainty within the model. The EAG note that the company could have explored models which aim to map between CDAI and HBI, like that reported by Best (2006)[1], and captured parametric and methodological uncertainty through a range of sensitivity and scenario analyses.

The company report that health states could not be defined using endoscopic outcomes, as in practice these procedures are conducted “perhaps 1-2 times per year, if not less” (company technical engagement response form). Although this may be the case, the EAG reflect on whether an outcome measure that is used infrequently is arguably more suitable for defining health status than an outcome measure that is not used in clinical practice. Nevertheless, the EAG acknowledge the challenges faced by the company due to limited reporting of endoscopic outcome data for all relevant comparators, which the company describe as only being available for risankizumab and ustekinumab.

4.2. Transition to conventional care after biologic failure

The company cite a lack of available data and consistency with prior NICE appraisals as justification for assuming all patients receive CC upon discontinuation of biologic therapy. While the EAG appreciate there may be a lack of data available for patients with CD who receive multiple lines of biologic therapy, the EAG believe the company could have presented exploratory analyses which attempted to model the treatment pathway more accurately. The EAG feel this is important to highlight, as the addition of a treatment option to the Crohn’s Disease pathway extends the total number of sequential treatments a patient may receive, with cost and potential patient health implications. The company’s analysis in no way captures implications of extending the treatment pathway.

The EAG questions whether data from patients in the biologic failure group could have been used to inform treatment effectiveness estimates for subsequent lines of treatment in the conventional care failure population. Furthermore, the company highlight in their response to technical engagement that response rates are typically lower in patients who are refractory to other biologic therapies, which suggests evidence from the literature could have been leveraged to support subsequent treatment effectiveness estimates in an exploratory analysis. The company note that the current assumptions result in all patients (across treatment arms) experiencing the same outcomes following discontinuation of initial biologic therapy; however, the EAG believe the company could have conducted analyses in which subsequent biologic treatment costs were captured more accurately, even if no data-driven efficacy adjustment was possible.

Finally, the company claim in their response to technical engagement that the purpose of the cost-effectiveness model is to compare the cost effectiveness of individual biologics and not of treatment sequences. The EAG reject this statement and assert that the purpose of the cost-

effectiveness analysis should be to assess the lifetime cost and health implications of introducing risankizumab to the existing treatment pathway for patients with moderately to severely active Crohn's disease in NHS England practice.

4.3. Defining conventional care after no response

In response to the EAG's concern on estimating conventional care effectiveness outcomes from the n = 24 "true placebo" group in the FORTIFY trial, the company note that the EAG maintain use of these data in the EAG-preferred base case. In reply to this, the EAG would like to remind the company that the EAG specifying a preferred analysis within the feasible remit of correcting and adapting the company's model is not an implicit endorsement of every company choice and assumption that the EAG have not corrected nor amended. In this case, the EAG used the company's conventional care after no response transitions in the EAG preferred base case in absence of alternative data *available to the EAG*. The EAG note that alternative and more suitable data may have been available to the company, through systematic search and review of published literature before submission.

4.4. Dose escalation and use of standard-dose efficacy

The company defend their dose escalation and use of standard dose efficacy assumptions in response to EAG Key Issue 4, but the EAG raised this sub-issue within Key Issue 6. For consistency with the EAG Report, the company's comments on this sub-issue are addressed alongside other Key Issue 6 comments, in Section 6 of this document.

4.5. Conclusion

Regarding use of CDAI health states and the structural assumption that all patients transition to conventional care after one modelled treatment line, the EAG recognise the data limitations and precedent that informed the company's structural decision, but stress that the impact of using a model structure that is not reflective of relevant patient outcomes or the real-world treatment pathway on the expected incremental cost-effectiveness ratio (ICER) is unknown, and the Committee may wish to take this important layer of uncertainty into consideration during its decision-making process.

Regarding the company's use of outcomes from the n = 24 "true placebo" patients in the FORTIFY trial to inform "conventional care" health state transitions, the EAG note that as no alternative data were identified by the company, while there are no readily available options for

analysis, the conventional care outcomes in the model are highly uncertain. This adds another layer of uncertainty to the cost-effectiveness results.

5. KEY ISSUE 5: TREATMENT DURATION AND RESIDUAL TREATMENT EFFECT ASSUMPTIONS

5.1. Biologic treatment duration

In the company's FORTIFY study, >[redacted]% of patients in the ITT1A population remained on treatment after 52-weeks, as shown in the company response to EAG Clarification Question B8. Clinical advice received by the EAG is clear, unequivocal and consistent with these data: if a Crohn's disease treatment is working, treatment continues. When asked explicitly about the validity of the company's 52-week treatment cessation assumption, the EAG's expert considered it "unrealistic", noting that biologics are long-term treatments. In short, the company's assumption that all patients will discontinue treatment at 52 weeks is difficult to understand. Despite this, in response to technical engagement, the company continue to argue that their assumption is the most appropriate in the absence of long-term data.

The EAG position on this issue remains unchanged; in absence of long-term treatment discontinuation data, and in line with clinical expectations, the EAG do not consider the need to extrapolate beyond the trial period as sufficient justification for assuming a universal maximum treatment duration across biologic therapies, at the end of the observed data: the company's base case analysis adopts a lifetime horizon - by design, and in line with the NICE Reference Case, expected costs and outcomes are extrapolated beyond the trial period.

5.2. Residual treatment effect

The company's revised base case following technical engagement assumes a 6-month residual treatment effect following discontinuation of biologic therapy, which is in line with the EAG's preferred assumption as reported in Section 6.2.2 and Section 6.3 of the EAG report. With the company's acceptance of the EAG's preferred approach to residual treatment effect length assumptions, the EAG consider this sub-issue resolved.

6. KEY ISSUE 6: ESTIMATION AND APPLICATION OF MAINTENANCE TREATMENT EFFECTIVENESS ASSUMPTIONS

6.1. Between-study heterogeneity in placebo remission rates

The company provide revised maintenance NMA results incorporating EAG baseline-risk model estimates and the company's single network RD maintenance NMA framework. These results are given in an Appendix B to their response document. The company state that these estimates contain CrI's that are unfeasibly wide. The EAG was unable to replicate these results, as modified code was not provided. EAG analyses based on the company's original code did not have wide CrIs.

6.2. Calibration approach (ordered probit model)

It is noted that the company has included the option of adjusting both ordered probit cutpoints in the calibration as a scenario in the CEM. The EAG maintains that this approach is more justifiable, in terms of an ordered probit model, than adjusting just one cutpoint, in relation to the interpretation of the underlying latent variable construct. While not perfect, it is a pragmatic solution given the available data. The company proposes simplicity as a motivation for preferring adjustment of only the remission|mild cutpoint, but this argument is spurious, as an equal adjustment to both cutpoints is equivalently parsimonious being specified by a single variable to be estimated.

The company claims that the goal of calibration is to align the Markov transition matrices with the NMA results at 52 weeks. The EAG asserts that it should also consider alignment with the 26-week estimates obtained from the ordered probit model. The company's approach is guaranteed to hit the NMA target values for remission, as this is its explicit criterion, but the EAG asserts that the exponential assumption method will, in the process, ensure that the results do not align with the ordered probit results. This can be seen most clearly where no calibration is required to meet the remission target, but the exponential approximation will ensure that, in all but the most trivial cases, the proportion with moderate-to-severe disease, for example, will be incorrect. The company's calibration approach masks this when only attending to the remission proportion.

As an example, consider the case for risankizumab where, according to the company's original submission, [redacted] [redacted] and [redacted] of patients enter maintenance in remission, mild and

moderate-to-severe health states respectively. Applying the given ordered probit estimates at 13 weeks for two cycles (to 52) weeks yields [redacted], [redacted] and [redacted] of patients in remission, mild and moderate-to-severe health states respectively at 52 weeks. This requires no adjustment of cycle length to 2-weeks. For illustration we assume that no calibration is required to hit a remission target (i.e. that the target is [redacted] at 52 weeks). If the exponential approximation is used to obtain a 2-week transition matrix, and this is used for 26 cycles to 52 weeks, then we obtain [redacted], [redacted] and [redacted] of patients in remission, mild and moderate-to-severe health states. The company suggests that calibration is then applied to match the remission target of [redacted] a discrepancy introduced by the exponential approximation. This approach, adjusting the remission|mild cutpoint, applying the exponential assumption, and iterating to 52 weeks, yields [redacted], [redacted] and [redacted] respectively. The remission proportion is, by definition, correct, but absolute discrepancies of [redacted] and [redacted] are introduced for mild and moderate-to-severe disease respectively. (Relative errors of [redacted] and [redacted] respectively.)

In practice, it will frequently be the case that a solution does not exist that is faithful to both the NMA target and the results of the ordered probit model. This is a mathematical reality, and in these cases a balance must be struck. The EAG's preferred approach takes one possible approach which minimises the discrepancies necessarily introduced in the 26-week transition matrix, which strikes one possible compromise. (The company incorrectly term these 'inaccuracies'.) Alternative approaches could attach more weight to approximating the NMA targets or to approximating the ordered probit results. The company's approach focuses entirely on the NMA remission targets, but non-transparently.

6.3. Cycle length and transition matrix estimation

The company suggests that exponential approximation is required to obtain a solution that can be practically run in a self-contained manner within Microsoft Excel. Due to practical constraints, the EAG's cost-effectiveness model (CEM) adopted an approach of pre-calculating deterministic values in R and holding them in an Excel CEM to be referenced. A downside of this approach is that it would be unwieldy to implement for probabilistic analyses. Alternative approaches may give a tractable solution solely within Excel.

The cycle length problem comes about as a result of:

- CEM cycle length being 2-weeks
- Ordered probit estimates obtained at 26 weeks

- NMA remission estimates relating to 52 weeks

As noted by Chhatwal et al. (2016) it may be the case that it is not possible to find a 2-week transition matrix, which, when iterated, will yield a pre-specified 26-week transition matrix. The exponential approximation will always yield a 2-week transition matrix. However, in all but the simplest of cases, it will not scale up to the desired 26-week transition matrix. Yet this is masked (not corrected) by the company's 'calibration' process, as illustrated above.

The computationally problematic challenge is in reducing cycle length to a fraction, not in increasing it to a multiple. The company suggest that the required algorithm would take ordered probit results (26-week), find the CEM cycle solution/root (2-week) and then project this to the NMA timescale (52 week). The company rightly suggests that the computationally intensive activity is in finding a 2-week root, unless the simplistic exponential assumption is adopted. It would be possible to mitigate this by iterating between the 26-week ordered probit results (with adjusted cutpoints) and the 52-week results for matching with the NMA remission target. This is computationally trivial, as 52 is a multiple of 26. The problem would then remain in finding a suitable 2-week root, according to some criteria, but this would only need to be calculated once for each set of inputs. Such an approach should be feasible within Excel, but it would still suffer from the practical limitation that an exact root may not exist.

The most appropriate solution would be to modify the ordered probit analysis to directly estimate the 2-week transition probabilities. (I.e. if $\boldsymbol{t}_2(\boldsymbol{\theta})$ is the 2-week transition matrix defined using parameters $\boldsymbol{\theta}$, then $\widehat{\boldsymbol{\theta}}$ is estimated by appropriately fitting $\boldsymbol{t}_2(\boldsymbol{\theta})^{13}$ to the trial data.) Although this is not straightforward with a conventional ordered probit model (it would involve implausible extrapolation of the time covariate out-of-sample), it should be feasible using a modified Bayesian model. This would remove the need to estimate transition probabilities on a shorter cycle length, but would still permit a form of calibration to the NMA results at 52 weeks via adjustment of cutpoints, or any of the relevant parameters to $\boldsymbol{t}_2\left(\widetilde{\boldsymbol{\theta}}\right)^{26}$ and thereby retrieve a 'calibrated' 2-week transition matrix $\boldsymbol{t}_2\left(\widetilde{\boldsymbol{\theta}}\right)$ without the need to shorten the estimated cycle length. Without patient-level data the EAG were unable to undertake such an analysis.

Finally, the company asserts that 'the calibration of Markov matrices to NMA target values is the primary driver of comparative results'. The EAG believe that the company should be more transparent in confirming whether this fidelity to the NMA target should be at the expense of estimates from the ordered probit model.

In summary, the EAG believes that the company's approach to changing cycle length and calibration to NMA results is unreliable, not methodologically justifiable, and is expected to introduce unpredictable errors into the cost-effectiveness model. The EAG-preferred solution aims to mitigate this.

6.4. Dose escalation and use of standard-dose efficacy

The company reiterate the clinical expert input they have received to inform the assumption that dose escalation affects costs but not patient outcomes. This input is from a November 2021 advisory board for which AbbVie provided a brief, partial report as commercial-in-confidence materials in their response to EAG Clarification Question B2. The same clinical experts' input is cited to justify the assumptions that both 92.5% of patients start on high-dose maintenance ustekinumab and that thereafter the annual probability of dose escalation is 92.5%.

The EAG recognises the logic that the aim of dose escalation is to achieve the same level of response as those patients who do not need to dose escalate. However, the EAG is cautious in resting on evidence AbbVie have gathered from experts, given limitations in the documentation provided. The document does not explain the criteria for selecting the experts, the number of experts who were approached but did not participate, declarations of potential conflicts of interest, methods and mediums used to collect opinions, nor whether the experts had the opportunity to review the document before it was shared. This is despite both the NICE User Guide containing guidance text requesting such details, and the EAG explicitly including said text in Clarification Question B2. Overall, the EAG places little value in the expert evidence the company present, given these limitations, and stresses the outstanding uncertainty around the company's comparator dose escalation assumptions.

7. KEY ISSUE 7: HEALTH STATE UTILITY VALUE ESTIMATION

The company's revised base case following technical engagement uses a linear mixed model to estimate CDAI-based health state utility values from risankizumab trial data. This approach is aligned with the EAG's preferred assumption as reported in Section 6.2.10 and Section 6.3 of the EAG report.

With the company's acceptance of the EAG's preferred approach to health state utility value estimation, the EAG consider Key Issue 7 resolved.

8. KEY ISSUE 8: METHOD OF ADMINISTRATION FOR RISANKIZUMAB

The company has resolved confusion by explaining that the terms 'on-body device' (OBD) in the CS and 'on-body injector' on clinical trial registries refer to the same thing. In response to the EAG's query, the company has clarified that the OBD method of administration was included in the relevant EMA and MHRA submissions, which resolves the EAG's concerns about safety. The EAG's other concerns revolved around efficacy, given the clinical effectiveness parameters for the economic model were derived from trial evidence using a different method of administration for risankizumab. In effect, the company assumed the method of administration is not of importance for efficacy.

The company provides results from a phase-1 pharmacokinetic study (M19-128 sub study 1, n = 258) comparing OBD administration with the pre-filled syringe used in the clinical trial programme. Following administration of a single 360 mg SC dose, risankizumab concentrations in Group 2 (360 mg OBD × 1 SC injection) [redacted] when compared to Group 1 (90 mg PFS × 4 SC injections), [redacted]. Thus, the pharmacokinetic parameters between the 90 mg PFS (4 × 90 mg/mL) and 360 mg OBD groups [redacted]. Relative bioavailability was [redacted] for the parameter C_{max} (µg/mL), [redacted] For the parameter AUC_t (µg•day/mL), and [redacted] For AUC_{inf} (µg•day/mL). The EAG was satisfied that the pharmacokinetic properties between the methods of administration were relatively comparable.

Study M16-000 SS4, which was an open-label OBD extension study, evaluated the usability of the OBD as well as patient outcomes. The company report the Week 0, 8 and 16 summary results from the OBD period of the study, but do not report longer-term open-label-extension "PFS period" results – the company do not explain this omission. The SS4 OBD results the company present are from a total sample of n=[redacted] patients. The EAG agreed with the company that the results do not show any unanticipated clinical concerns or harms associated with OBD use. Around [redacted] Of patients in the OBD extension study achieved CDAI clinical remission at Week 0 and [redacted] achieved this at Week 16. However, these short-term, small-sample data are not sufficient to reassure the EAG that treatment discontinuation and effectiveness rates in clinical practice with OBD administration can be expected to be the same as treatment discontinuation and effectiveness

rates in the FORTIFY study and in the company's economic analysis, with any degree of certainty. Further, actively receiving (subcutaneous) maintenance therapy in study SS3 was an entry criterion for SS4, while at weeks 0 and 16 of SS4, the OBD was administered under direct office supervision. Neither of these attributes reflect anticipated OBD use in practice, and both may have inflated administration success and remission rates in the OBD period of SS4 relative to expectations for clinical practice. Lastly, the EAG note an apparent reporting error in Table 19 of the company's response to technical engagement. The table reports n = [redacted] observations at Week 16, which the EAG suspect should read n = [redacted]. If this is the case, the proportion of patients achieving CDAI clinical remission at Week 16 is [redacted], not [redacted] as reported by the company.

The EAG noted that the UK Clinical Pharmacy Association (UKCPA) has submitted a response in which it addressed the issue of the OBD method of administration. This response stated that the OBD addresses the issue of requiring multiple injections at different sites using the more traditional method of administration, but raised some concerns about tolerability given the large volume of risankizumab administered slowly over 5 minutes. Specifically, "*Poor tolerability due to injection site reactions/adverse effects may impact drug persistence which will not have been captured in the trial.*". While these concerns are not reflected in the company's results from M16-000 SS4, the EAG find little solace in this given the limitations of these data.

The UKCPA response also raises a concern around potential OBD failure: "*There is a risk of the OBD failing. This can be before inserting the drug vial or during the injection phase. If it fails pre-insertion of the vial, it will need to be ascertained if the device itself can be replaced and thereby saving wastage of the drug vial and cost; OR if the OBD is only supplied as package with the drug vial. This should not incur extra cost to the NHS as device failure with pre-filled pens is common too and usually credited*". The EAG are mindful that OBD failure, and its implications for NHS cost and patient outcomes, has not been considered up to now in this appraisal, but may be consequential.

Overall, the while EAG is satisfied that the OBD method of risankizumab administration is safe and pharmacokinetically comparable to SC administration, the EAG is concerned about the tolerability implications of the OBD, the possibility and implications of OBD failure, and the potential implications of both for NHS costs and patient outcomes. All cost-effectiveness results are currently blind to the potential implications of these issues.

9. ADDITIONAL ISSUE 1: INCORRECT COMPARATOR

The company raised one factual accuracy check on the EAG report in the additional issues section of the technical engagement response form. The EAG acknowledge that in the final paragraph of Section 6.2.8 of the EAG report (Page 129) the text should read "*vedolizumab* SC in the BF population" rather than "*infliximab* SC in the BF population" and thank the company for highlighting this.

10. COST-EFFECTIVENESS RESULTS

As noted in the introduction, the cost-effectiveness model provided by the company at technical engagement was not an adaptation of the EAG version of the model, nor is it possible for the user to switch between the company's original base case, revised base case and EAG preferred base case. Further to this, the EAG is unable to match the company's original results using the revised company model. Nor is it possible to match the EAG preferred base case as described in Section 6.3. of the EAG report using the revised company model.

In addition, the EAG notes several hardcoded model inputs have been changed between the model submitted at clarification stage and the model submitted at technical engagement, with no description or rationale documented in the company's response to technical engagement. Table 1 presents one instance of this, where the baseline patient characteristics for the CCF and BF populations differ between company models.

Table 1: Example of undocumented changes to company model

Patient characteristic	Company original model*	Company revised model**
CCF population		
Mean patient age (years)	38.83	39.74
Mean percent male (%)	54.9%	52.0%
Weight (kg) - mean	71.15%	70.72
Weight < 55kg	17.8%	21.3%
55kg < Weight ≤ 85kg	65.5%	60.5%
Weight (kg) > 85kg	16.7%	18.1%
BF population		
Mean patient age (years)	38.22	37.72%
Mean percent male (%)	52.5%	52.2%
Weight (kg) - mean	71.20	71.71%
Weight < 55kg	19.1%	19.5%
55kg < Weight ≤ 85kg	61.1%	59.7%
Weight (kg) > 85kg	19.8%	20.7%

* Company original model refers to file named "6a. ID3986_Risankizumab CD_NICE_CEM v0.2 040822 v1.2 [ACIC]"

* Company original model refers to file named "6a. ID3986_Risankizumab CD_NICE_CEM_Final_ACIC_cal_options_v2.0 - 261022 [ACIC]"

As a result, the EAG has been unable to validate the company's model, and consequently, are unable to place confidence in the company's revised base case and scenario results submitted at technical engagement.

Therefore, the EAG present the "EAG-corrected company revised base case" where the changes described in Table 4 of the company's response to technical engagement have been implemented in the EAG versions of the model: "ID3986_Risankizumab CD_EAG_CEM v2_BF [ACIC]" and "ID3986_Risankizumab CD_EAG_CEM v2_CCF [ACIC]" (note: the only difference between EAG models is the population selected). The EAG versions of the model were adapted from the company model submitted at clarification stage, named "6a. ID3986_Risankizumab CD_NICE_CEM v0.2 040822 v1.2 [ACIC]".

The remainder of this section uses the EAG version of the model to inform the results presented.

10.1. Company revised base case

Table 4 of the company's response to technical engagement describes the changes applied to the company's original base case. The six EAG corrections (described in Section 6.1. of the EAG report) have been accepted by the company, in addition to the following three changes:

- 6-month residual treatment effect duration (EAG preferred assumption)
    - The original base case assumed a 12-month effect
- Linear mixed model used to estimate utilities (EAG preferred assumption)
    - The original base case used an ordinary least squares model to estimate utilities

[redacted]

NICE has instructed the EAG not to use the company's proposed pricing for risankizumab, as such the results reported in this addendum apply the PAS included in the company's original submission only.

Table 2 and Table 3 present the EAG-corrected original and revised company base case results for the CCF and BF populations, respectively. In the CCF population, risankizumab remains dominated (more costly and less effective) when the company's revised assumptions (and EAG

corrections) are applied. In the BF population, risankizumab remains a dominant (less costly and more effective) treatment option when the company's revised assumptions (and EAG corrections) are implemented.

Table 2: Original and revised EAG-corrected company base cases – CCF population

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
Original EAG-corrected company deterministic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£4,229	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£32,556	£32,556
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£57,977	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£329,812	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£211,356	Dominated
Revised EAG-corrected company deterministic base case (following response to technical engagement)						
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£3,400	Dominated
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£43,575	£43,575
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£73,976	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£643,409	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£487,420	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 3: Original and revised EAG-corrected company base cases - BF population

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG-corrected company deterministic base case						
RZB	[redacted]	[redacted]	-	-	-	-
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-£26,902	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£51,865	Dominated

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£34,655	Dominated
Revised EAG-corrected company deterministic base case (following response to technical engagement)						
RZB	[redacted]	[redacted]	-	-	-	-
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	-£22,512	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£56,303	Dominated
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£33,219	Dominated

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; IV, intravenous; QALYs, quality adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

10.2. EAG preferred assumptions

The EAG preferred assumptions remain as described in the EAG report (Section 6.3.). Table 4 and Table 5 demonstrate the deterministic, pairwise, step-by-step impact of the EAG-preferred assumptions, from the EAG-corrected revised company base case to the EAG preferred base case, against the optimal in the CCF (infliximab SC) and BF (vedolizumab SC) populations (as described in Section 1.7 of the EAG report), respectively.

As noted previously in the EAG report, neither the company's revised base case nor the EAG's preferred base case address issues with the company's chosen model structure (Key Issue 4) and approach to dose escalation (Key Issue 6).

Table 4: EAG's preferred model assumptions - CCF population (risankizumab versus infliximab SC)

Preferred assumption	Section in report	Cumulative ICER, £/QALY (stepwise change)
EAG-corrected company revised base case (deterministic)	Section 10.1	Dominated, -£119,972
+ Maximum treatment duration of 20 years for all biologic treatments	Section 4.2.6.7. and 6.2.3. (EAG report)	£62,821 (+£182,792)
+ Single maintenance network, with an estimated maintenance placebo remission proportion that is adjusted for a temporal effect	Section 4.2.6. and 6.2.1. (EAG report)	Dominated, -£90,437 (-£153,258)
+ Transition matrices estimated by adjusting both the remission | mild and mild | moderate-to-	Section 4.2.6. and 6.2.6. (EAG report)	Dominated, -£88,792 (+£1,645)

Preferred assumption	Section in report	Cumulative ICER, £/QALY (stepwise change)
severe cut points, and without an exponential assumption to estimate 2-week transitions		
EAG's preferred base case (deterministic)	Section 6.2 and 6.3. (EAG report)	Dominated, -£88,792
EAG's preferred base case (probabilistic)	Section 6.2 and 6.3. (EAG report)	Dominated, -£90,018

Abbreviations: CCF, conventional care failure; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

Table 5: EAG's preferred model assumptions - BF population (risankizumab versus vedolizumab SC)

Preferred assumption	Section in EAG report	Cumulative ICER, £/QALY (stepwise change)
EAG-corrected company revised base case (deterministic)	Section 10.1	Dominant, -£22,512
+ Maximum treatment duration of 20 years for all biologic treatments	Section 4.2.6.7. and 6.2.3. (EAG report)	£79,559 (+£102,071)
+ Single maintenance network, with an estimated maintenance placebo remission proportion that is adjusted for a temporal effect	Section 4.2.6. and 6.2.1. (EAG report)	£66,543 (-£13,016)
+ Transition matrices estimated by adjusting both the remission | mild and mild | moderate-to-severe cut points, and without an exponential assumption to estimate 2-week transitions	Section 4.2.6. and 6.2.6. (EAG report)	£143,088 (+£76,545)
EAG's preferred base case (deterministic)	Section 6.2 and 6.3. (EAG report)	£143,088
EAG's preferred base case (probabilistic)	Section 6.2 and 6.3. (EAG report)	£142,074

Abbreviations: BF, biologic failure; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SC, subcutaneous.

While the EAG preferred assumptions remain unchanged following the company's response to technical engagement, Table 6 and Table 7 summarise incremental deterministic and probabilistic results for the EAG base case in the CCF and BF populations, respectively for completeness. In the CCF population, risankizumab remains dominated (more costly and less effective) when the EAG's preferred assumptions are applied. In the BF population, risankizumab is associated with an ICER of £143,088 when the EAG's preferred assumptions are implemented.

Table 6: EAG incremental base case results - CCF population

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG preferred deterministic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£5,536	£5,536
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£56,481	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£52,086	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£1,349,539	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£4,358,832	Dominated
EAG preferred probabilistic base case						
ADA 160/80 biosimilar	[redacted]	[redacted]	-	-	-	-
IFX SC	[redacted]	[redacted]	[redacted]	[redacted]	£6,744	£6,744
ADA 80/40	[redacted]	[redacted]	[redacted]	[redacted]	-£55,111	Dominated
IFX IV biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£48,951	Dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£867,497	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	-£91,825,236	Dominated

Abbreviations: ADA, adalimumab; CCF, conventional care failure; EAG, Evidence Assessment Group; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.

Table 7: EAG incremental base case results – BF population

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained	
					Versus baseline	Incremental analysis
EAG preferred deterministic base case						
VDZ SC	[redacted]	[redacted]	-	-	-	-
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£2,198,195	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£252,156	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£143,088	£143,088
EAG preferred probabilistic base case						
VDZ SC	[redacted]	[redacted]	-	-	-	-
VDZ IV	[redacted]	[redacted]	[redacted]	[redacted]	-£1,487,732	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£248,239	Extendedly dominated
RZB	[redacted]	[redacted]	[redacted]	[redacted]	£142,074	£142,074

11. REFERENCES

1. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw index. Inflamm Bowel Dis 2006; 12(4): 304-10.