NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Eli Lilly & Company Limited:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **NICE medicines optimisation briefing**

4. **External Assessment Report** prepared by BMJ Technology Assessment Group

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

Document B

Company evidence submission

June 2024

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Contents

List of Tables

List of Figures

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

B.1.1 Decision problem

Population

Mirikizumab is anticipated to receive a marketing authorisation for the treatment of [redacted]

This submission focusses on a subpopulation of the full anticipated marketing authorisation of mirikizumab. This population is defined as adult patients with moderately to severely active Crohn's disease (CD), *only if*:

- The disease has not responded well enough or lost response to a previous biological treatment, *or*
- A previous biological treatment was not tolerated, *or*
- Tumour necrosis factor alpha (TNF-α) inhibitors are not suitable.

Mirikizumab is positioned for use in adults as an alternative to risankizumab, which has received a positive recommendation by NICE for reimbursement for treating moderately to severely active Crohn's disease in people 16 years and older, only if the disease has not responded well enough or lost response to a previous biological treatment, or a previous biological treatment was not tolerated, or TNF-α inhibitors are not suitable (TA888).[1] Therefore, mirikizumab and risankizumab have the same patient population in adults.[1]

Comparators

Lilly is proposing that the appraisal of mirikizumab be considered under the NICE proportional approach to technology appraisals sub-process, making use of a cost comparison economic evaluation. The NICE user guide states that a cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in published technology appraisal guidance for the same indication.[2]

As outlined above, risankizumab recently received a positive recommendation from NICE in the same adult patient population as that proposed for mirikizumab, although the recommendation for risankizumab includes patients aged 16–17 years old as well (TA888).[1] Indirect treatment comparisons (ITCs) in the form of network meta-analyses (NMAs) in patients with moderately to severely active CD were conducted between mirikizumab and a range of comparators, with mirikizumab demonstrating similar efficacy in these analyses to that of risankizumab (see Section B.3.9). Further to this similarity in clinical efficacy, mirikizumab has the same mechanism of action (anti-IL23p19) and a similar method of administration (intravenous [IV] induction, subcutaneous [SC] maintenance) as risankizumab. Lastly, risankizumab is considered to meet

the criteria for the selection of an appropriate comparator for cost-comparison, which state that the selected comparator must fulfil the following:

- It adequately represents the NICE recommended treatments as a whole, both in terms of costs and effects.
- It has significant market share.
- It is recommended in published NICE technology appraisal guidance for the same indication.

Given the above, risankizumab is deemed the most appropriate primary comparator in this appraisal.

In addition to risankizumab, comparisons of mirikizumab versus ustekinumab and vedolizumab are presented for completeness. Head-to-head data for mirikizumab versus ustekinumab, which has a similar mechanism of action to mirikizumab, are available from the VIVID-1 trial which forms the primary clinical evidence base for mirikizumab in CD (see Section B.3.6.2). In this trial, mirikizumab displayed non-inferiority for clinical remission measured by Crohn's disease activity index (CDAI) versus ustekinumab, justifying its presentation as a supportive analysis. Furthermore, in TA888, the NICE Committee concluded that risankizumab and ustekinumab had similar efficacy, further supporting that the assumptions for a cost comparison of mirikizumab versus risankizumab are met.[1] In addition, vedolizumab was identified as the most appropriate comparator to risankizumab in the appraisal for risankizumab in CD, suggesting its relevance as a supportive analysis in this appraisal in turn.[1] Results from the NMA indicated clinical equivalence of mirikizumab versus ustekinumab and vedolizumab (see Section B.3.9.4). As such, supportive comparisons versus ustekinumab and vedolizumab are presented.

The decision problem addressed by this submission, and as compared with the decision problem defined in the final NICE scope, is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.	Adult patients with moderately to severely active CD, only if: • The disease has not responded well enough or lost response to a previous biological treatment *or* • A previous biological treatment was not tolerated, *or* • TNF-α inhibitors are not suitable	The population addressed in this submission is a subpopulation of the anticipated label for mirikizumab: [redacted] As discussed further in the "Comparators" section below, it is anticipated that mirikizumab will be positioned after conventional care and after first-line biologic treatment options, except in the case of unsuitability to receive such biologic therapies.
Intervention	Mirikizumab	Mirikizumab	As per final scope
Comparator(s)	At least one of the following treatments, according to NICE guidance: • TNF-α inhibitors (infliximab and adalimumab) • Ustekinumab • Vedolizumab • Risankizumab • Upadacitinib	Primary comparator: • Risankizumab Supportive comparators: • Ustekinumab • Vedolizumab	It is anticipated that mirikizumab will be positioned after conventional therapy (best supportive care), which is typically prescribed as a first-line treatment for moderately to severely active CD. Therefore, conventional therapy does not represent a relevant comparator. Mirikizumab is positioned as an alternative to risankizumab in UK clinical practice for the treatment of moderately to severely active CD in patients who are intolerant of, or have failed treatment with, prior biologic therapy. This patient population is in line with the patient population in which risankizumab is recommended by NICE, and with the anticipated use of mirikizumab in UK clinical practice. Risankizumab is considered the relevant primary comparator within the scope of the appraisal for the following reasons: • Risankizumab recently received a positive recommendation from NICE in the same patient population as that proposed for mirikizumab[1]

			• ITCs in patients with moderately to severely active CD were conducted between mirikizumab and a range of comparators, with mirikizumab demonstrating similar efficacy in these analyses to that of risankizumab (see Section B.3.9) • Mirikizumab has the same mechanism of action as risankizumab and they share a similar method of administration: both are delivered intravenously during the induction period and subcutaneously during the maintenance period. In addition to risankizumab, ustekinumab and vedolizumab are considered relevant supportive comparators within the scope of the appraisal for the following reasons: • In the VIVID-1 trial, mirikizumab displayed non-inferiority versus ustekinumab (see Section B.3.6.2) • Mirikizumab has a similar mechanism of action to ustekinumab • Ustekinumab and vedolizumab were identified as the most appropriate comparators to risankizumab in the appraisal for risankizumab in CD • Results from the NMA indicated clinical equivalence of mirikizumab versus ustekinumab and vedolizumab (see Section B.3.9.4)
Outcomes	The outcome measures to be considered include: • Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Hospitalisation rates • Adverse effects of treatment • HRQoL	The outcome measures used in this submission include: • Measures of disease activity (clinical remission and relapse, endoscopic response) • Mucosal healing (endoscopic remission, histologic remission) • AEs	Rates of surgery and hospitalisation were assessed as other secondary endpoints in the VIVID-1 trial. However, ultimately, the proportion of patients reporting CD-related surgery and hospitalisation for mirikizumab were low in the VIVID-1 trial, and similar to those reported for patients who received ustekinumab or placebo. In combination with the NMA for safety outcomes (discussed in Section B.3.9.4.4), it was therefore assumed that treatment with mirikizumab was associated with a similar safety profile to risankizumab, ustekinumab and vedolizumab, Given these assumptions surgery and rates

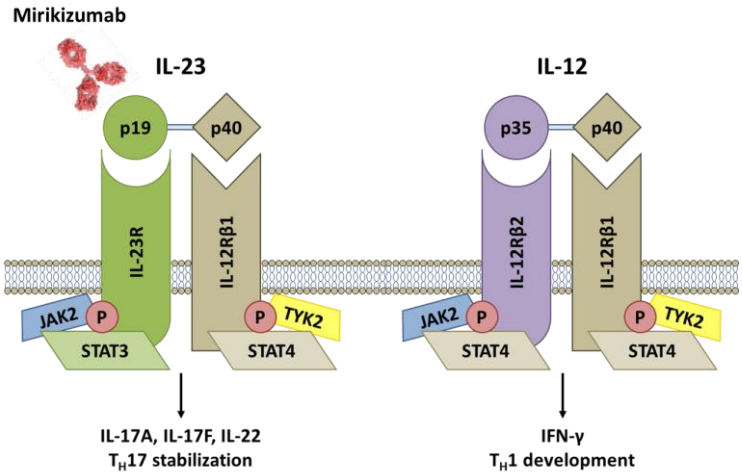
		• HRQoL (EQ-5D-5L, IBD-Q) • Bowel urgency	of hospitalisation are not presented or included in the cost-comparison analyses; this approach is in line with previous cost-comparison analyses in CD (TA905 and TA888).[1, 3]
Economic analysis	This technology has been selected to be appraised as a cost comparison. The time horizon should be sufficient to reflect any differences in costs between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention and comparator technologies will be taken into account.	A cost comparison analysis has been conducted to estimate the incremental costs of mirikizumab versus risankizumab (with supportive comparisons to ustekinumab and vedolizumab also presented). • The base case model time horizon was set as 3 years. This is in line with clinical expert opinion provided to the NICE Committee in TA888 that median duration of treatment persistence with biologic therapies is approximately 2–3 years.[4] Alternate time horizons of 2 years and 5 years were also tested as scenario analyses. • Costs were considered from an NHS and PSS perspective. • A PAS for mirikizumab was included as part of the analysis.	Mirikizumab can be appropriately assessed through the NICE cost-comparison process due to the similarities in terms of both effectiveness and costs with risankizumab. Additionally, it is anticipated that mirikizumab will be positioned similarly to other available therapies, including risankizumab, within the treatment pathway. As such, a cost-comparison has been submitted. The cost-comparison analysis compares the drug acquisition and administration costs for mirikizumab versus risankizumab, with supportive analyses presented for mirikizumab versus ustekinumab and versus vedolizumab.
Subgroups to be considered	None	• People who have previously failed on treatment with one or more biologics (“biologic failure”) • People who have not received a prior biologic (“conventional care failure”)	The VIVID-1 trial, which provides the key clinical evidence base for mirikizumab, included biologic failure and conventional care failure patients. Patients in the conventional care failure subgroup in the VIVID-1 trial had not received a prior biologic and so were biologic-naïve. Separate analyses were conducted in these subpopulations and are presented.

Abbreviations: AE: adverse event; CD: Crohn's disease; EQ-5D-5L: European Quality of Life 5 Dimensions 5 Level; HRQoL: health-related quality of life; IBD-Q: Inflammatory Bowel Disease-Questionnaire; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; PAS: patient access scheme; PSS: Personal and Social Services; QALY: quality adjusted life year; TNF-α: tumour necrosis factor-alpha.

B.1.2 Description of the technology being evaluated

A description of the technology being appraised, mirikizumab, is presented in Table 2, with details on the relevant SmPC provided in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Mirikizumab (Omvoh®)
Mechanism of action	Mirikizumab is a recombinant humanised IgG4 monoclonal antibody that binds to the IL-23 cytokine. IL-23 is a member of the IL-12 family of proinflammatory cytokines and consists of two subunits: the p40 subunit, which is shared with IL-12, and the p19 subunit, which is unique to IL-23.[5] Mirikizumab selectively binds to the p19 subunit of the IL-23 cytokine with high affinity, thus inhibiting its interaction with the IL-23 receptor (IL-23R) (Figure 1).[6] Despite some structural similarity between IL-12 and IL-23, the latter is indicated in the promotion of CD4+ T cells, characterised by the downstream production of IL-17, IL-17F, IL-6 and TNF.[7] IL-23 is mainly secreted by activated macrophages and dendritic cells present in peripheral tissues, including intestinal mucosa, and has been shown to play a crucial role in chronic inflammatory processes and, in particular, intestinal inflammation.[5, 8] As such, the inhibition of IL-23 by mirikizumab acts to reduce the inflammatory processes underlying CD. **Figure 1: Mirikizumab mechanism of action**  **Abbreviations**: IFN: interferon; IL: interleukin; JAK: Janus kinase; STAT: signal transducers and activators of transcription; T_H: T helper cells; TYK: tyrosine kinase. **Source:** Adapted from Teng *et al*., (2015).[9]
Marketing authorisation/CE mark status	Mirikizumab does not currently have a marketing authorisation in the UK for treating moderately to severely active CD. An application to the UK MHRA [redacted] was submitted in [redacted], with a recommendation expected [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	It is anticipated that mirikizumab will receive a marketing authorisation from the MHRA for [redacted] In addition, mirikizumab holds a UK license for treating adult patients with moderately to severely active ulcerative colitis who have had an

	inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.[10]
	Mirikizumab has the following contraindications:[10]
	• Clinically important active infections (active tuberculosis)
	• Hypersensitivity to the active substance or any of the following excipients:
	  ○ Sodium citrate dihydrate
	  ○ Citric acid
	  ○ Anhydrous sodium chloride
	  ○ Polysorbate 80
	  ○ Water for injections

Method of administration and dosage	The recommended dosing regimen for mirikizumab in CD comprises two parts:[10] • **Induction:** 900 mg by IV infusion Q4W (Weeks 0, 4 and 8). Mirikizumab 300 mg (15 ml vial; 20 mg mirikizumab per mL) is available as a concentrate for solution for infusion • **Maintenance:** [redacted]
Additional tests or investigations	No additional tests or investigations are required beyond those that are already part of current clinical practice for NICE recommended biologic treatments in CD.
List price and average cost of a course of treatment	List price per pack, induction dose (300 mg for IV infusion): £2,056.56.[11] List price per pack, maintenance dose ([redacted])[11]
Patient access scheme/commercial arrangement (if applicable)	There is a PAS in place for mirikizumab in its UC presentations. A PAS is planned for mirikizumab for this indication.

Abbreviations: CD: Crohn's disease; IgG4: immunoglobulin G4; IL: interleukin; IV: intravenous; MHRA: Medicines and Healthcare products Regulatory Agency; NICE: National Institute for Health and Care Excellence; PAS: patient access scheme; SC: subcutaneous; SmPC: summary of product characteristics; UK: United Kingdom.

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

B.1.3.1 Disease overview

Disease background

CD is a chronic, inflammatory autoimmune disease of the gastrointestinal (GI) tract.[12] It is classed as an inflammatory bowel disorder (IBD) alongside ulcerative colitis (UC).[12] Unlike UC, which is usually limited to the colon, CD can affect any part of the GI tract from the mouth to the anus, but it is usually characterised by chronic relapsing inflammation of the entire thickness of the small and/or large intestinal walls.[12, 13] In the intestines, inflammation tends to be discontinuous and is characterised by skip lesions, i.e., patches of inflammation interposed between a normal-appearing mucosa.[14, 15] Mucosal ulceration may also be evident, and present

as scattered aphthous ulcers which can often extend the entire thickness of the intestinal walls, leading to the formation of fistulae.[15]

Patients with CD may have chronic symptoms for years before a confirmed diagnosis is established; the symptoms are often insidious, non-specific, and can vary based on disease location and severity.[16, 17] As well as being chronic in nature, the clinical course of CD is also unpredictable, and patients will commonly note the relapsing-remitting nature of their symptoms; between periods of remission or less active disease, patients will usually experience disease flares characterised by abdominal pain, changing bowel frequency and diarrhoea, fatigue, weight loss, anaemia and anorectal dysfunction.[12, 16]

In addition, around 25–40% of patients with IBD, including CD, experience extraintestinal manifestations (EIM) in which the disease may manifest in parts of the body other than the GI tract.[18] EIMs can affect multiple organ systems, including the skin, eyes, liver or spine and may occur as a result of malabsorption, chronic inflammation, medication or genetic risk factors.[19] The risk of developing an EIM increases with duration of the disease and if a patient already has an EIM, and the most common EIM in patients with CD is anaemia in approximately 21% of patients, followed by arthropathy (peripheral and axial) in around 20% of patients.[20, 21]

Epidemiology and diagnosis

An exact cause of CD has not yet been characterised, but it is thought to be the result of an interplay between a range of risk factors including genetic susceptibility, environmental factors, and the intestinal microflora.[13, 14] Other reported risk factors include a history of smoking, appendicectomy and pharmacological treatment history including the use of non-steroidal anti-inflammatory drugs (NSAIDs).[22] It is estimated that approximately one in every 323 people in the UK (approximately 200,000 people) is living with CD, but there is evidence that the prevalence of CD worldwide is increasing in both adults and children.[12, 23, 24] This is supported by data from The Health Improvement Network (THIN) on the prevalence of IBD, which showed an increase in point prevalence from 220 per 100,000 to 400 per 100,000 between 2000 and 2017.[25]

The incidence of CD is slightly higher in women, based on data from the UK IBD registry which found that 53% of patients with CD in the UK were women.[26] This is corroborated by a large UK observational study in which the adjusted incidence rate ratio for women in CD was 1.20 (95% confidence interval [CI]: 1.15, 1.25).[27] Further, it is thought that the estimated incidence of CD may be up to 40% greater in women than men, past the age of 25 years old.[28, 29]

Although it may present at any age, 25% of patients are diagnosed with CD prior to reaching adulthood, and CD symptoms most commonly present before the age of 35.[30, 31] However, timely diagnoses are made difficult due to the indolent, slowly progressing nature of the disease, and the lack of any key differentiating characteristics; symptoms of CD are often confused with other bowel diseases, including UC, irritable bowel syndrome (IBS) or infectious colitis.[32, 33] For this reason, a diagnosis of CD is typically made once other potential causes of symptoms such as infection are excluded.[32] This diagnosis process involves laboratory assessments for faecal pathogens and inflammatory blood biomarkers, and endoscopy is routinely used for confirmation of CD.[32, 34] Though ileo-colonoscopy has previously been considered the gold standard method for diagnosis of CD, guidelines from the European Crohn's and Colitis Organisation (ECCO) note that no gold standard for diagnosis exists and instead recommend that a diagnosis of CD should be based on clinical, biochemical, stool, endoscopic and histological investigations, as well as possible radiological visualisation of the small intestine.[32, 34]

Owing to these factors, the diagnosis of CD is often delayed, which is associated with adverse clinical outcomes in adult patients with CD. Such outcomes include higher likelihood of stricturing (abnormal narrowing of intestinal walls, which may lead to bowel obstruction), penetrating disease (characterised by the formation of fistulae and/or intra-abdominal abscesses) and need for intestinal surgery.[35]

Disease staging

Phenotypic classification

To ensure the clinical management plan is appropriate for the disease presentation of each patient, it is necessary to classify the disease accurately and systematically. In CD, the British Society of Gastroenterology (BSG) highlight the Montreal classification as being widely used to classify the key features of patients with CD.[36] The Paris classification system is also noted, highlighting its development as a modification over the Montreal classification to better capture changes in disease location, behaviour, and growth failure in paediatric patients with CD.[36] Disease extent according to endoscopic or macroscopic features can be defined by the Montreal and Paris classifications, with the Montreal system more commonly used in adult patients (Table 3).[36] However, it has been noted that histological evidence of inflammation may be more extensive than macroscopic features, and thus represent a better indicator for staging CD.[37]

Based on the Montreal classification, younger age at CD diagnosis, more diffuse pathology location, and presentation with stricturing and penetrating behaviour all correlate with higher levels of disease severity.

Table 3: Montreal classification in CD

	Montreal	
Age at diagnosis (years)	A1	<17
	A2	17–40
	A3	>40
Location[a]	L1	Terminal ileal ± limited caecal disease
	L2	Colonic
	L3	Ileocolonic
	L4	Isolated upper disease[b]
Behaviour	B1	Non-stricturing, non-penetrating
	B2	Stricturing
	B3	Penetrating
	P	Perianal disease modifier[c]

Footnotes: [a] Defined as endoscopic or macroscopic extent. [b] Upper disease in Montreal classification describes disease proximal to the terminal ileum. In both Montreal and Paris: L4 and L4a/b may coexist with L1, L2, L3. [c] Perianal abscesses, ulcers or fistulae (but not skin tags or fissures)
Source: Lamb *et al.* (2021)[36]

Disease activity

Disease activity is often considered analogous to disease severity in CD, since patients with highly active disease often report the most severe symptoms including bloody diarrhoea, systemic symptoms, and widespread mucosal stricturing or penetrating disease.[38] Several tools exist to characterise disease activity in patients with CD.

Crohn's Disease Activity Index (CDAI)

The Crohn's Disease Activity Index (CDAI) was developed in 1976 and uses a combination of eight clinical and laboratory parameters, including stool frequency and quality, extent of abdominal mass and pain, anti-diarrhoea drug use, haematocrit deviation, body weight deviation, and measures of general wellbeing to assess the activity of CD in a patient at a given time.[39] The measures used to define CD activity via the CDAI are listed in Table 4, alongside weighting factors, which are multiplied by the score of the respective measure to emphasise the importance of certain CD symptoms to disease activity classification. Based on the total score, the CDAI classifies patients with CD into one of four categories:[39]

- Remission (CDAI score <150)
- Mild to moderate (CDAI score 150–220)
- Moderate to severe (CDAI score 220–450)
- Severe (CDAI score >450)

Due to the extensive and diverse characterisation of CD symptoms in patients, the CDAI has been considered the gold-standard index for use in CD clinical trials.[40]

Table 4: Crohn's Disease Activity Index (CDAI)

Variable	Quantity	Weighting factor	Total
Number of liquid stools per day		x2	
Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)		x5	
General wellbeing (0 = well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)		x7	
Number of complications*		x20	
Opiates for diarrhoea (0 = no, 1 = yes)		x30	
Abdominal mass (0 = no, 2 = questionable, 5 = yes)		x10	
Deviation from normal haematocrit (42 for female, 47 for male)		x6	
% deviation from standard weight		x1	

Total CDAI:	

Footnotes: The quantity of each variable is assessed by a clinician, and multiplied by the respective weighting factor to produce a total score for each variable. These individual scores are totalled to give the overall CDAI score. *One point is added to the CDAI score for the presence of any of the following complications: joint pain or arthritis, iris inflammation or uveitis, presence of erythema nodosum, presence of anal fissures, fistulas or abscesses, presence of other fistulae, or fever during the previous week.[39] CDAI <150 = remission; >450 = severely ill.
Source: Best *et al.* (1976)[39]

Simple Endoscopic Score (SES-CD)

An alternative tool used to characterise CD activity in patients is the Simple Endoscopic Score (SES-CD), developed in 2004.[41] Using the SES-CD, selected colonoscopy parameters (ulcer size, proportion of surface covered by ulcers, proportion of the surface with any other lesions and stenosis) are rated between 0 to 3, based on severity, to define disease activity.[41] This endoscopic characterisation is carried out in different locations (ileum, right colon, transverse colon, left colon and rectum). Higher SES-CD scores indicate more severe disease, whereas lower scores are indicative of mucosal healing. Based on SES-CD score, patients with CD are classified into one of four categories, as follows:[41]

- Inactive (SES-CD score 0–2)
- Mild (SES-CD score 3–6)
- Moderate (SES-CD score 7–15)
- Severe (SES-CD score >16)

Whilst the CDAI and SES-CD are robust measures which are commonly used for CD activity characterisation in clinical settings, other tools such as the Harvey-Bradshaw Index (HBI) are also routinely used.[42]

Harvey Bradshaw Index (HBI)

The HBI is an alternative tool used to measure CD activity, developed in 1980.[42] Using the HBI, patients score different aspects of their wellbeing on a numerical scale including their general wellbeing (scored 0–4), abdominal pain experienced the previous day (scored 0–3) and the presence of an abdominal mass (scored 0–3).[42, 43] In addition, patients record the number of soft or liquid stools passed the previous day and the number of complications they are experiencing (gaining one score per item).[42, 43] Based on HBI score, patients with CD are classified into one of four categories, with lower scores indicating good health and no symptoms and higher scores indicating poorer health with more severe symptoms:[42, 43]

- Remission (HBI <5)
- Mild (HBI 5–7)
- Moderate (HBI 8–16)
- Severe (HBI >16)

B.1.3.2 Burden of disease

Impact on health-related quality of life

The impact of CD on a patient's health-related quality of life (HRQoL) can be vast, severe, and difficult to manage, due to the progressive and lifelong nature of the disease. In studies utilising the Inflammatory Bowel Disease Questionnaire IBD-Q, patients with CD report lower overall HRQoL compared to healthy control subjects in both relapsing and remitting periods, though HRQoL is worsened during intervals of active disease.[44, 45] This was corroborated in a study of 853 patients with CD in the US and the EU5 (France, Germany, Italy, Spain, United Kingdom).[46] Patients with moderate to severely active CD had a EuroQoL-5 dimensions questionnaire (EQ-5D) score that was between 20–25% lower than patients with mild CD (least square [LS] mean: 0.69 vs 0.84, respectively), or those in remission (LS mean: 0.91).[46] A multitude of factors contribute to lowered HRQoL in patients with CD, including heightened disease activity, frequency of relapses, chronic corticosteroid treatment and recurrent need for hospitalisation.[47]

The impacts of CD extend across the daily life and social activities of patients with CD, with patients reporting higher levels of depression and anxiety symptoms when compared to healthy control subjects and patients with UC (odds ratio [OR]: 1.2; 95% confidence interval [CI]: 1.1-1.4).[48] Furthermore, work disability is common in patients with CD, which may contribute to reduced psychosocial wellbeing.[49] Compared to patients in remission, patients with mild CD are more than twice as likely to be work impaired (LS mean: 15.6% vs 37.0%, respectively), with impairment being closer to four times greater in patients with moderately or severely active CD (LS mean: 55.4%).[46]

Bowel urgency

Bowel urgency is defined as the sudden and immediate need to have a bowel movement and is a distinct symptom from stool frequency. Affecting 70% of patients with CD, urgency is an impactful and disruptive symptom which can have a significant negative effect on patient quality of life.[50] Bowel urgency is accompanied by rectal bleeding, abdominal pain, higher CDAI scores and general reduction in wellbeing of patients with CD.[51, 52]

The mechanisms underlying bowel urgency include rectal inflammation and a lack of mucosal healing. The inflammation and alteration in rectal wall functioning is thought to lead to decreased compliance of the rectum, resulting in a propensity for constant rectal spasms. This link between inflammation and bowel urgency may provide an explanation for observations that clinical and endoscopic outcomes are improved in patients exhibiting lower levels of bowel urgency. Bowel urgency is also linked to extensive disease in the small and large intestine, which can cause bowel dysfunction.[53] However, bowel urgency can persist in patients who are receiving medical treatment for CD and in patients with disease considered to be inactive.[54, 55] Despite being a common symptom, bowel urgency is often not discussed by patients due to the associated embarrassment, and it may not be addressed by clinicians due to an expectation for patients to proactively raise this sensitive topic themselves.

Comorbidities

Aside from the classic symptoms of CD, the disease is commonly accompanied by multiple comorbidities affecting many bodily systems.[56] Immune-mediated comorbidities of CD include asthma, rheumatoid arthritis and psoriasis, which is present in 9.6% of patients with CD

compared to 2.2% of healthy control subjects.[57, 58] Metabolic comorbidities of CD include diabetes mellitus, non-alcoholic fatty liver disease, obesity, hepatobiliary conditions, and cardiovascular disorders.[56] Furthermore, psychiatric comorbidities are common in patients with CD, including depression, anxiety, and stress, which greatly reduce quality of life.[48] Psychiatric comorbidity in CD is correlated with increased risk of future surgical intervention, with the presence of anxiety or mood disorders associated with a 28% increase in surgery risk and significantly higher utilisation of healthcare interventions.[59]

Intestinal and extra-intestinal cancers are also comorbid with CD.[60] In particular, a prospective, multicentre study identified penetrating CD as a potential a risk factor for cancer onset.[61] Patients with CD may harbour a long-term invasive cancer risk up to 30% higher than healthy control individuals, including cancers of the small bowel and hepatobiliary malignancies.[62] Further, there may be a higher incidence of cancer in patients with CD compared to those with UC.[61] Importantly, the mortality of patients with CD is 1.4 times higher than that of the general population, which has been associated with this increased risk of cancer in patients with CD.[63] As a result, patients with CD with colonic disease undergo surveillance colonoscopies for colorectal cancer detection in order to increase the chance of diagnosis at an early stage of cancer which is associated with an improved prognosis.[64, 65]

Economic burden

Due to the long-term, progressive, and relapsing nature of CD, the disease is associated with significant economic burden, which is higher for those diagnosed with CD earlier in life.[66] Accounting for the cost of treatment, side effects, disease complications and proportion of time spent in relapse/remission, a study conducted in 2015 estimated the annual cost for patients with CD in the UK to be £6,156.[67] This figure is notably higher for those in active disease periods (£10,513).[67] The recurrent need for patient hospitalisation remains a major source of CD-related economic burden.[68] In addition, workplace absenteeism due to CD and IBD more generally also incurs significant economic cost, the extent of which varies across European countries.[69]

B.1.3.3 Clinical pathway of care

Current pathway of care

Treatments for CD are not curative, with treatment focussed on the induction, and ultimately maintenance, of symptom-free remission to control inflammation and prevent further degradation of patient health. In the UK, CD is treated in a stepwise manner based on factors such as disease severity (mild, moderate, severe), prior medication response, relapse frequency, remission status, and patient suitability for available treatments.[70] Treatment algorithms are available in the form of NICE guidance (NG129) and clinical guidelines by the BSG and by ECCO, and it is recommended that the primary treatment goal for CD is symptomatic remission combined with mucosal healing.[70-72] However, given that treatment decisions are made based on a number of factors there is no single pathway of care adopted by all clinicians and patients.[72]

The treatment pathway options currently available for patients with moderately to severely active CD in the UK are presented in Figure 2. Initially, patients receive conventional therapy, which includes standard corticosteroids such as budesonide. If patients experience two or more CD flares within a 12 month period despite steroid use, add-on treatment in the form of methotrexate/ thiopurines is recommended.[70] However, the effectiveness of these conventional therapies varies

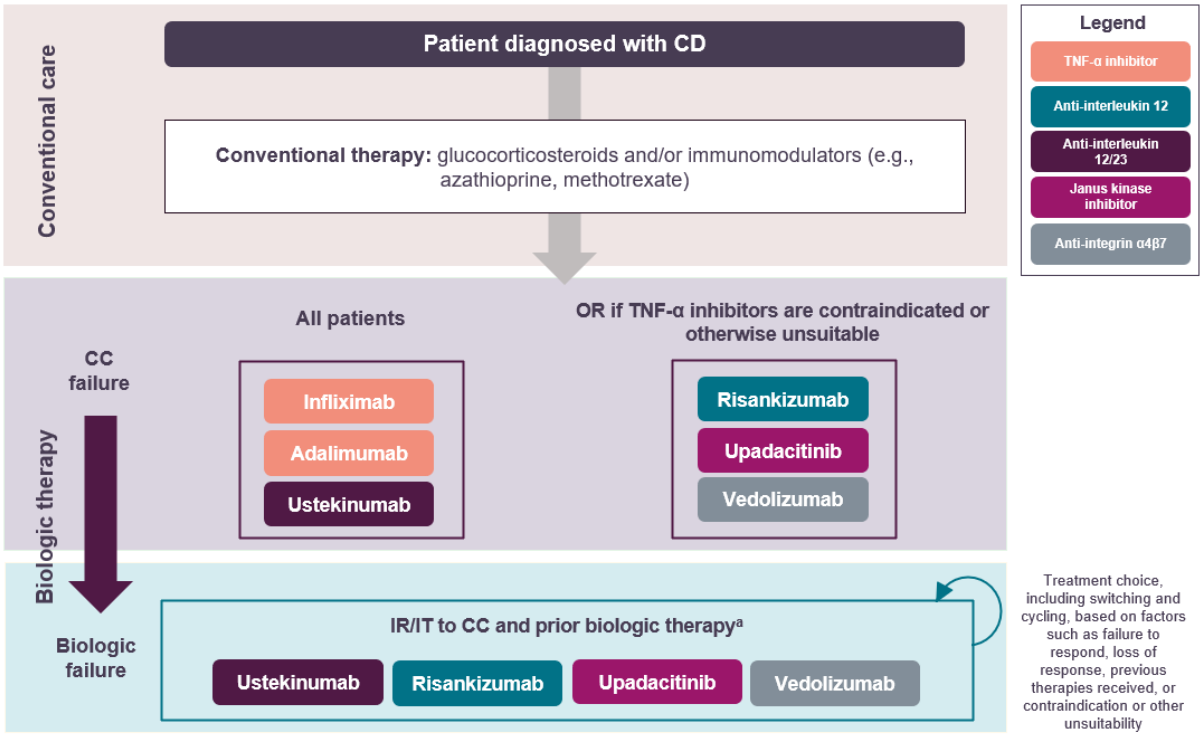
between patients, with a systematic review of conventional therapies in IBD finding that some show no statistical benefit over placebo.[73]

Patients who have had an inadequate response to, lose response to, or are contraindicated or otherwise unsuitable to receive conventional therapies will switch treatments, with the initiation of biologic treatments representing the next line of treatment.[74] As confirmed by clinical experts in the NICE appraisal for risankizumab (TA888), TNF-α inhibitors infliximab and adalimumab (for which lower cost biosimilars are available) typically represent the first biologic treatment received by the majority of patients with CD in the UK.[1] In line with its NICE recommendation, ustekinumab may be prescribed to some patients as the first biologic therapy option.[75] However, the use of ustekinumab at this line of treatment is less common than TNF-α inhibitors because NICE guidance specifies that patients should receive the least expensive treatment option they are eligible to receive.[4, 75] As a result, if a patient is eligible to receive both a TNF-α inhibitor and ustekinumab, they would be expected to receive a TNF-α inhibitor as a first-line therapy ahead of ustekinumab.[75] If first-line biologics fail to produce a clinical response, or the patient has medical contraindications to these therapies, treatment with other biologics such as risankizumab, vedolizumab, ustekinumab (if not already used) and upadacitinib is recommended.[1, 75, 76]

Patients are treated until remission occurs, after which maintenance of the treatment with or without concomitant conventional therapies is used to preserve remission. Medication reviews are recommended to occur every 12 months to assess the suitability of the current treatment.[70] If patients continue to experience inadequate disease control, or are unsuitable to receive these treatment options, patients can receive a range of surgical procedures tailored to the disease severity and location and extent of disease.[72]

In the early stage, surgical options include laparoscopic resections, while wider bowel resection may be considered in later stages.[72] Balloon dilation can be used on an individual basis in cases where strictures are accessible by colonoscopy.[70] Patients may also elect to undergo surgery at an earlier stage if they deem this to be a more suitable option to improve their quality of life or reduce symptoms.[70, 72, 77] However, CD surgery, including bowel resection, can lead to a number of serious complications requiring further treatment, such as postoperative fistulae, therefore preoperative treatment options are crucial in CD.[78]

Figure 2: Current care pathway in CD



Footnote: In line with NICE recommendations, risankizumab, vedolizumab and upadacitinib are considered following initial conventional therapy failure only if patients are considered to be contraindicated to, or unsuitable for TNF-α therapy. Only ustekinumab has received a positive recommendation inclusive of its use as a first-line biologic following initial conventional therapy failure. [a]Following relapse on biologic therapies, patients are switched onto an alternative biologic therapy that has not been used previously.
Abbreviations: CD: Crohn's disease; CT: conventional therapy; IR: inadequate response; IT: intolerant; TNF-α: tumour necrosis factor-alpha.

Limitations of current treatments

At present there are several treatment options for patients with CD and clinicians to consider. Despite this, limitations in the current care pathway of CD are evident. Long-term use of the most common first-line treatment option, corticosteroids, is associated with a multitude of adverse events, such as loss of bone density, metabolic complications, increased intraocular pressure and increased susceptibility to infection.[79] Thus, corticosteroid-free remission is typically sought in CD.[80] Furthermore, corticosteroids are not capable of inducing mucosal healing, which is considered a key treatment goal.[81]

Currently available biologics, which are routinely used following failure of conventional therapy, are also associated with several limitations. Critically, approximately 30% of patients demonstrate primary non-response to TNF-α inhibitors i.e., patients do not respond to these treatments in the first instance.[82] Further, 46% of the patients who do respond to anti-TNF-α therapies lose response over time, thus exhibiting a secondary non-response.[83] Aside from the limited efficacy of TNF-α inhibitors, a link between their use in IBD patients and increased risk of lymphoma has been reported, particularly when co-administered with thiopurines.[84] In addition, concomitant prescription of immunomodulators (such as thiopurines) with TNF-α inhibitors is required to help prevent the development of anti-drug antibodies and thus aim to avoid development of primary non-response or secondary loss of response.[85]

Other biologic treatments with mechanisms of action distinct from inhibition of TNF-α, such as vedolizumab, ustekinumab, risankizumab or upadacitinib, may be used, and changing to other mechanisms of action has been identified as a potential solution to overcome non-response to TNF-α inhibitor therapy in IBD.[83] However, these treatments are also associated with certain disadvantages, including the common prospect of secondary non-response and the continued experience of debilitating CD symptoms, despite ongoing biologic treatment.[86, 87]

Due to these limitations of primary non-response, secondary non-response and continued symptoms, the cycling of several treatment options is required in a significant number of patients resulting in suboptimal treatment outcomes.[88] The frequent use of treatment cycling in CD suggests a need for newer, alternative treatment options for patients.[88]

Unmet need

The combination of factors described above, including the commonplace nature of treatment switching in CD and the suboptimal response achieved by current CD therapies, means that there is currently an unmet need in UK clinical practice for more safe and effective CD treatment options. In recent qualitative studies, patients have described unmet needs in terms of lack of effectiveness and delayed onset of action of medication, fears about potential need for surgery, long-term effects of therapeutics and reduced psychosocial wellbeing.[80, 89]

Additionally, a common symptom of CD which has not been widely addressed with current treatment options, is bowel urgency.[50] As outlined in Section B.1.3.2, bowel urgency affects up to 70% of patients with CD and significantly and negatively impacts the quality of life of patients.[50] Treatment options which reduce the impact of bowel frequency and the associated symptoms of bowel urgency such as rectal bleeding, abdominal pain and higher CDAI scores are required to improve the general wellbeing of patients with CD.[51, 52]

Positioning of mirikizumab

In the current appraisal, mirikizumab is positioned for use in adult patients with moderately to severely active CD, *only if*:

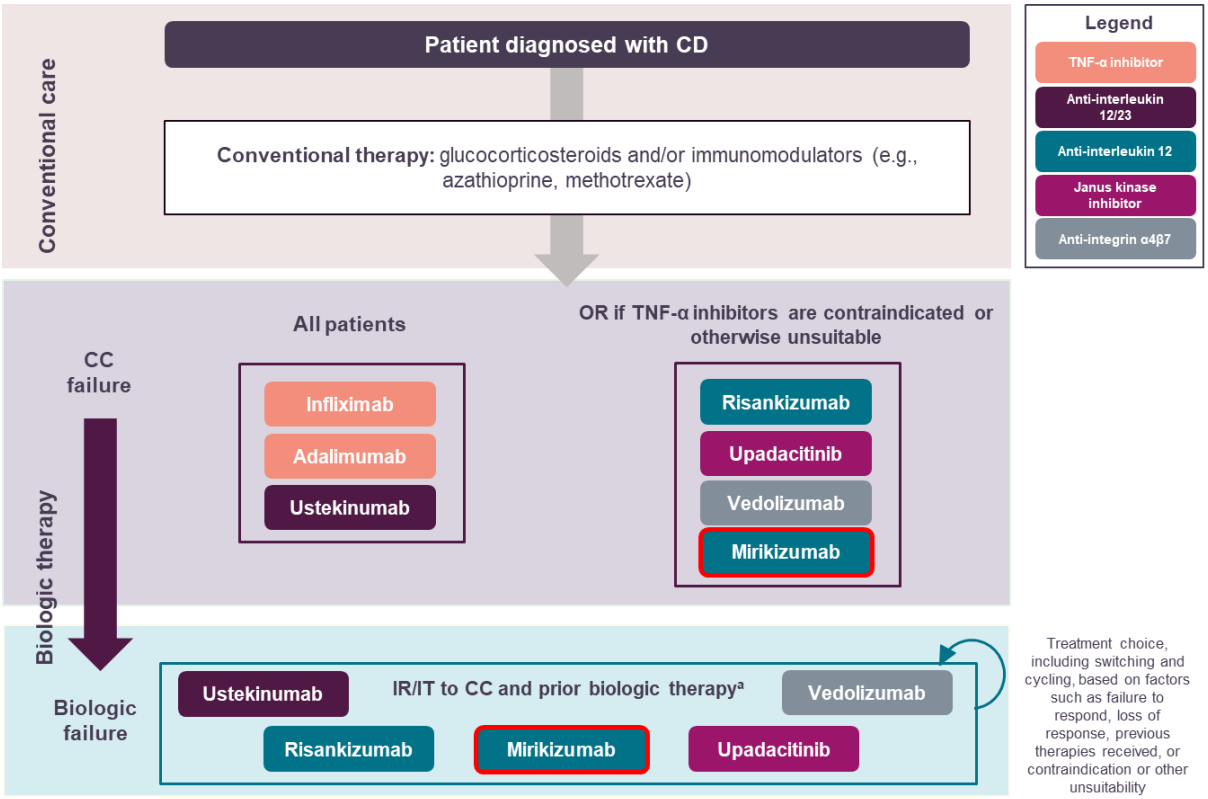
- The disease has not responded well enough, or lost response to, a previous biological treatment, or
- A previous biological treatment was not tolerated, or
- TNF-α inhibitors are not suitable

This positioning is represented in Figure 3. At this point in the treatment pathway, patients in the UK may be eligible to receive a range of biologic treatment options, such as risankizumab, ustekinumab, vedolizumab or upadacitinib. The choice of therapy is likely to depend on any prior treatments received, and the level of response demonstrated i.e., whether a patient has demonstrated a failure to respond or has lost response to previous biologic therapy, including TNF-α inhibitors (termed “biologic failure”), or are contraindicated or unsuitable for TNF-α inhibitor therapy and have not received any other biologic treatment (termed “biologic-naïve”). It is anticipated that the treatment position for mirikizumab will cover both these groups of patients.

The efficacy and safety of mirikizumab versus placebo and ustekinumab has been evaluated in the VIVID-1 trial, wherein mirikizumab demonstrated rapid and sustained induction of clinical remission and a tolerable safety profile (Sections B.3.6 and B.3.10).[90]

Given its clinical efficacy and safety, a NICE recommendation for mirikizumab as a treatment in this population in England and Wales would fulfil a considerable unmet clinical need in this group of patients and provide clinicians with another option for the treatment of adult patients with moderately to severely active CD.

Figure 3: Positioning of mirikizumab in current CD care pathway



Footnotes: In line with NICE recommendations, risankizumab, vedolizumab and upadacitinib are considered following initial conventional therapy failure only if patients are considered to be contraindicated to, or unsuitable for TNF-α therapy. Only ustekinumab has received a positive recommendation inclusive of its use as a first-line biologic following initial conventional therapy failure. [a]Following relapse on biologic therapies, patients are switched onto an alternative biologic therapy that has not been used previously.
Abbreviations: CD: Crohn's disease; CT: conventional therapy; IR: inadequate response; IT: intolerant; TNF-α: tumour necrosis factor-alpha

B.1.4 Equality considerations

Mirikizumab is positioned as an alternative to risankizumab, which has received a positive recommendation by NICE in an adult patient population identical to the population for which mirikizumab is positioned.[1] However, unlike the anticipated treatment population for mirikizumab, risankizumab is also recommended in patients 16–17 years old.[1] Therefore, mirikizumab would not be positioned as an alternative treatment option to risankizumab in adolescents aged 16–17 years old. No other equality considerations have been identified.

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

B.2.1 Clinical outcomes and measures

As discussed in Section B.1.1, three comparators to mirikizumab are considered in the current appraisal: risankizumab (as the primary comparator), and ustekinumab and vedolizumab (as supporting comparators). Additionally, since upadacitinib represents the most recently published NICE appraisal for CD, upadacitinib is also considered in this Section, despite not representing a relevant comparator in the current appraisal. The relevant NICE technology appraisals for these therapies in CD are:

- Risankizumab for previously treated moderately to severely active CD (TA888, published May 2023)[1]
- Ustekinumab for previously treated moderately to severely active CD (TA456, published July 2017)[75]
- Vedolizumab for previously treated moderately to severely active CD (TA352, published August 2015)[76]
- Upadacitinib for previously treated moderately to severely active CD (TA905, published June 2023)[3]

Ustekinumab and vedolizumab were evaluated through the NICE single technology appraisal (STA) process and cost-utility analyses were performed in both submissions.[75, 76] Upadacitinib was evaluated through a cost-comparison approach.[3] Whilst a cost-utility analysis was initially performed in TA888 for risankizumab, a cost-comparison approach was considered more suitable following consultation with the NICE appraisal Committee.[1] Therefore, alongside the clinical outcomes and measures discussed in the Committee papers for ustekinumab, vedolizumab and upadacitinib, only the relevant outcomes and measures from the cost-comparison analysis for risankizumab are considered below. An overview of the clinical outcomes and measures considered in these comparator appraisals are presented in Table 5.

Clinical response and remission

For all presented appraisals, the definitions of clinical response and remission were based on CDAI scores, used to assess disease activity in the respective pivotal trials.[1, 3, 75, 76] The relevant ERGs in TA888, TA456 and TA352 noted concerns on the generalisability of the CDAI for disease activity scoring in each appraisal, due to the relative lack of CDAI use in current UK clinical practice.[1, 75, 76] However, given the use of the CDAI to define treatment response and remission in previous appraisals, as well as the correlation between CDAI scores and metrics more routinely used in the UK, such as the HBI, the Committees of all three appraisals concluded the CDAI to be an acceptable measure of CD activity for decision-making.[1, 75, 76] SES-CD scores were used as a secondary measure of clinical response in TA888 and TA905, representing endoscopic response to treatment.[1, 3] However, as a cost-comparison approach was taken in these appraisals, SES-CD scores were not considered in the final model.[1, 3]

Dose escalation

Dose escalation in the maintenance phase of treatment was considered across all four appraisals; in the base-case analyses in TA888, TA456 and TA905,[1, 3, 75] and in exploratory analyses in TA352.[76] In TA888, TA352 and TA905, patients were modelled to enter the maintenance phase at the escalated dose.[1, 3, 76] In TA456, all patients were considered to start at the lower starting dose, and dose escalation was modelled at a 2-week probability of 2–3% thereafter.[75] Across all appraisals, estimates on the proportion of patients who were dose-escalated were derived from clinical expert opinion.[1, 3, 75, 76] The modelled approaches did not raise any significant concerns with the Committees, and the dose escalation proportions reported in TA888 were considered to be in line with the experiences of clinicians in the UK.[1, 3, 75, 76]

Treatment discontinuation

The approach to modelling treatment discontinuation differed across comparator submissions. Treatment discontinuation was not considered in the cost-comparison models in TA888 and TA905;[1, 3] this was considered appropriate by the Committee in TA888 due to the nature of cost-comparison analyses.[1] Conversely, the cost-effectiveness models in TA456 and TA352 did consider treatment discontinuation.[75, 76] In TA456, the percentage of patients who discontinued ustekinumab due to lack of treatment efficacy was calculated from the total number of patients in the maintenance phase, and converted to a per-cycle probability of discontinuation which was subsequently incorporated into the model.[75] In TA352, treatment discontinuation was modelled only in terms of patients who discontinued vedolizumab use due to AEs, and not due to lack of efficacy, which was critiqued by the ERG.[76] Despite this, it was concluded that how treatment discontinuation was modelled imposed minimal effects on the incremental cost-effectiveness ratio (ICER) in either submission (TA456 or TA352), and both approaches were accepted by the Committees.[75, 76]

Surgery

The cost-comparison approaches utilised in TA888 and TA905 did not consider surgical intervention.[1, 3] In TA905, this was reported to be due to a lack of data available for surgery from the U-EXCEL and U-EXCEED trials.[3] While no rationale was explicitly reported for the exclusion of surgery from TA888, this approach aligns with an assumption of equal efficacy and safety across treatments.[1] Conversely, annual rates of surgery, gathered from Hospital Episode Statistics (HES) NHS data and converted into 2-week cycle rates, were used in TA456.[75] Although the ERG raised concerns regarding the omission of post-surgery prognosis and future surgery rates in TA456, the Committee accepted that models of similar structure had been accepted in previous appraisals, and likewise, accepted the approach taken in TA456 as suitable for decision-making.[75] Rates and costs of surgery were also included in the model in TA352.[76] The ERG noted that the chosen approach to model surgery as a single health state was likely to oversimplify surgery in CD, but ultimately concluded that this may be a necessary assumption given the apparent data limitations.[76] The Committee did not comment on the appropriateness of modelling surgery as a single health state. However, the probability of repeated surgery in the original model was considered to be unreasonably high.[76] Following consultation with the Committee, the approach to modelling repeated surgery was amended in the final model, and per-cycle probabilities for surgery, based on analyses of HES data, were derived. This was accepted as the preferred approach by the Committee.[76]

Adverse events

AEs for use in the model were selected based on expert clinical opinion in the TA352 and included serious infections, tuberculosis, lymphoma, hypersensitivity, and skin reactions.[76] This approach to modelling AEs was mirrored in TA456.[75] Across both TA352 and TA456, the impact of the AEs were considered to be minimal, and no concerns were raised by the Appraisal Committees.[75, 76] AEs were not considered in the cost-comparison models in TA888 and TA905.[1, 3] In TA905, an assumption of equivalent safety was made between upadacitinib and the comparators (ustekinumab and vedolizumab) based on the results of the NMA, thus supporting the approach of excluding AEs from the cost-comparison analysis.[3] While rationale for the exclusion of AEs were not reported in TA888, no queries were raised by the Committee in this regard, and it is in line with the assumption of equal efficacy.[1]

Mortality

Rates of all-cause mortality were extracted from the Office for National Statistics (ONS) life tables for England and Wales and incorporated into the models within TA456 and TA352.[75, 76] In TA352, uncertainties were raised by the ERG regarding the study used in the model, which omitted information regarding mortality in relation to disease severity at baseline, though this was not commented on by the Committee.[76] Mortality was not addressed in the cost-comparison approach used in TA888.[1] In line with this approach, patient mortality in TA905 was assumed to be equal between upadacitinib and the comparators, so considerations for mortality were not included in the cost-comparison analysis in TA905.[3]

Table 5: Clinical outcomes and measures appraised in published NICE guidance for the comparators relevant to the decision problem

Outcome	Measurement scale	Used in model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
Risankizumab, TA888[1] – cost-comparison approach[a]					
Treatment response and remission	CDAI Moderately to severely active CD: defined as a CDAI score between 220 and 450. Clinical response (CDAI-100): a reduction in CDAI score of >100 points from baseline at endpoint measurement. Clinical remission: an absolute CDAI score of <150 points at endpoint measurement.	CDAI scores were used to assess comparative efficacy in the supporting NMA. Based on the results of this NMA, an assumption of clinical equivalence was made, and a cost-comparison was considered more suitable for decision making. As such, CDAI score was not used directly in the cost-comparison model.	N/A – not used directly in cost-comparison analysis.	No alternative assumptions were suggested by the Committee, from the Company-submitted approach.	The EAG noted that the CDAI is not often used in UK clinical practice. However, given its correlation with the HBI which is commonly used, the impact of using the CDAI to inform the model was considered to be minimal. The Committee concluded the measures of response and remission would be likely to reflect the measures used to define these outcomes in clinical practice. Uncertainties were raised by the EAG and Committee regarding whether the NMA results supported clinical effectiveness of risankizumab across
	SES-CD Moderately to severely active CD: SES-CD score of 6 or more (4 or more for isolated ileal disease). Endoscopic response:	NR			

<table>
<tr><td></td><td>decrease in SES-CD score >50% from baseline in patients with a baseline SES-CD score of 6 or more, or a decrease in SES-CD of 2 or more points for patients with a baseline SES-CD score of 4 or 5.</td><td></td><td></td><td></td><td>treatments, particularly due to disparities in trial design and population within the available trial data. However, the Committee ultimately concluded the effectiveness of risankizumab to be similar to that of other treatments based on the available NMA evidence.</td></tr>
<tr><td>Dose escalation</td><td>Loss of response/efficacy to therapy.</td><td>Dose escalation (patients modelled to receive a higher-dose regimen throughout the maintenance phase of treatment) was considered for all comparators in TA888, with rates based on clinical expert opinion:
<table>
<tr><th>Treatment</th><th>Dose escalation</th><th>% dose escalation</th></tr>
<tr><td>Risankizumab</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Adalimumab 160/80</td><td rowspan="3">40 mg SC Q2W to 40 mg SC QW</td><td>50.0</td></tr>
<tr><td>Adalimumab 80/40</td><td>50.0</td></tr>
<tr><td>Adalimumab biosimilar</td><td>50.0</td></tr>
<tr><td>Infliximab IV</td><td rowspan="2">5 mg/kg IV Q8W to 10 mg/kg IV Q8W</td><td>40.0</td></tr>
<tr><td>Infliximab IV biosimilar</td><td>40.0</td></tr>
<tr><td>Infliximab SC</td><td>N/A</td><td>N/A</td></tr>
</table></td><td>Substantial</td><td>No alternative assumptions were suggested by the Committee from the Company-submitted approach.</td><td>The Committee noted that the dose escalation proportions reported in TA888 were in line with the experiences of clinicians in the UK. However, it was noted that the assumptions reflected a simplification of clinical practice.</td></tr>
</table>

		<table><tr><td>Ustekinumab</td><td>90 mg Q12W to 90mg Q8W</td><td>92.5</td></tr><tr><td>Vedolizumab IV</td><td>300 mg Q8W to 300 mg Q4W</td><td>30.0</td></tr><tr><td>Vedolizumab SC</td><td>N/A</td><td>N/A</td></tr></table>			
Treatment discontinuation	The number of patients who discontinued treatment due to lack of treatment efficacy.	Treatment discontinuation was not considered in the cost-comparison analysis.	N/A – not used directly in cost-comparison analysis.	The Committee noted that as a cost-comparison analysis was conducted, it was more appropriate to determine a time horizon sufficient to capture any differences in costs rather than to model treatment discontinuation. To that effect, the Committee agreed that a shorter time horizon than the company's 10 years should be implemented.	The Committee acknowledged that this simplified approach does not reflect true clinical practice in which patients would be expected to discontinue treatments for reasons such as loss of efficacy or adverse events, but was considered appropriate for the cost-comparison approach.
Surgery	Annual surgery rate.	Surgery was not included in the cost-comparison analysis.	N/A – not used directly in cost-comparison analysis.	The Committee did not have any comments on surgery.	N/A
Adverse events	Rate of treatment-related AEs.	AEs were not considered in the cost-comparison analysis.	N/A – not used directly in cost-comparison analysis.	The Committee did not have any comments on AEs.	N/A

Mortality	All-cause mortality.	Mortality was not considered in the cost-comparison analysis.	N/A – not used directly in cost-comparison analysis.	The Committee did not have any comments on mortality.	N/A
Ustekinumab, TA456[75] – cost-effectiveness approach					
Treatment response	CDAI-70 Clinical response: a reduction in CDAI score of >70 points from baseline at endpoint measurement. CDAI-100 Clinical response: a reduction in CDAI score of >100 points from baseline at endpoint measurement.	CDAI-100 was used to define treatment response in the base case. CDAI-70 was used in scenario analyses, based on the approach to treatment response used in TA352. CDAI scores were extracted from relevant study publications.	Substantial	The Committee accepted the use of the CDAI as a validated method for assessing CD activity.	The Committee concluded that the use of the CDAI to assess treatment response was acceptable, given its historic use in assessing response to other biological treatments. However, it was noted that there is now a move towards more objective assessment of disease activity, such as endoscopic evaluation of ulceration.
Remission	CDAI Clinical remission: an absolute CDAI score of <150 points at endpoint measurement.	CDAI measures, extracted from relevant study publications, were used in the model to define clinical remission.	Substantial	The Committee did not have any comments on clinical remission.	N/A – the ERG raised no concerns about the use of CDAI to model remission rates.
Dose escalation	Loss of response/efficacy to therapy.	All patients receiving biologic therapy dose escalation were modelled to be eligible for increased dosage (infliximab) or dose	Minimal	Neither the Committee nor the ERG had any comments on the approach	N/A

		frequency (all other therapies) in cases of inadequate response. 14% and 23% of patients who received ustekinumab following conventional therapy failure and anti-TNF-α failure entered the model at an escalated dose, respectively. For all comparator therapies, all patients were considered to start at the lower starting dose, and dose escalation was modelled at a 2-week probability of 2–3%.		to dose escalation used in the model.	
Treatment discontinuation	The number of patients who discontinued treatment due to lack of treatment efficacy.	Percentage of patients who discontinued the trial due to lack of efficacy during the maintenance phase was calculated and converted to an instantaneous rate, and subsequently to a per-cycle probability of discontinuation using an exponential formula.[b] This per-cycle discontinuation probability was used in the model. Patient data extracted from the IM-UNITI trial (ustekinumab) and the analogous maintenance trials for comparators (vedolizumab: GEMINI II, infliximab: ACCENT I) were used.	Unclear	The Committee did not have any comments on how treatment discontinuation rates were used in the model.	Uncertainties were raised in the company submission regarding patients in the moderate to severe condition transferring to conventional therapy if ustekinumab is discontinued in the final model, which may underestimate the true discontinuation rate.
Surgery	Annual surgery rate.	The annual rate of surgery (7%, taken from NHS HES data) was used in the model, converted to a 2-week cycle rate using an exponential formula.[b] The resulting probability for surgery was 0.28% per cycle.	Moderate	No preferred assumptions were noted by the Committee versus the Company-submitted approach.	The impact of surgery on future prognosis, or the need for further surgery, were not explored in the model. The ERG noted the uncertainty introduced by the lack of exploration

					into these outcomes. The Committee acknowledged these concerns from the EAG, however noted that models of a similar structure had been used, and accepted, in previous CD submissions, and therefore accepted the approach taken in TA456 was suitable for decision-making.
Adverse events	Rate of treatment-related AEs.	AEs were considered in the base case. AEs were selected for use in the model based on clinical expert opinion, mirroring those used in TA352 (including serious infections, tuberculosis, lymphoma, hypersensitivity, and skin reactions). Scenario analyses excluding AEs were performed.	Minimal	The Committee did not have any comments on the AEs used in the model.	N/A
Mortality	All-cause mortality.	Rates of all-cause mortality were extracted from the ONS life tables for England and Wales 2012-2014. To account for gender differences, the model referred to the ratio of males:females at the time to calculate mortality.	Unclear	Neither the Committee, or the ERG, had any critique on the approach to mortality in TA456.	N/A
Vedolizumab, TA352[76] – cost-effectiveness approach					
Treatment response	CDAI-70 Clinical response: a reduction in CDAI score of	CDAI-70 measures, extracted from relevant study publications, were used in the model to define treatment response.	Substantial	The Committee agreed with the comments made by the ERG regarding the timepoints of analysis in the	The ERG noted uncertainty about the use of CDAI as an outcome

	>70 points from baseline at endpoint measurement.			Induction phase of treatment, concluding that analyses should be conducted at Week 10.	measure, as this may not reflect UK clinical practice. Furthermore, the generalisation of trial data to patients with a CDAI score >450 was questioned, since no patients with a CDAI score >450 were recruited in the relevant studies. Whilst the Committee acknowledged these concerns, no revisions were suggested by the Committee. Additionally, clinical response assessments for induction were considered at Week 6 in the original Company model. The ERG preferred these analyses to occur at Week 10, as this was deemed more relevant to the duration of induction of biological therapies, and in line with UK clinical practice.

					In line with Committee preferences, the revised Company model considered induction response at Week 10.
Remission	CDAI Clinical remission: an absolute CDAI score of <150 points at endpoint measurement).	CDAI measures, extracted from relevant study publications, were used in the model to define treatment remission.	Substantial	The Committee did not have any comments on the approach to remission in TA352.	The ERG noted a limitation of the economic model, which resulted in the model estimating a lower proportion of patients to be in remission on conventional non-biologic therapies than was observed in the GEMINI II trial. This was due to the model inaccurately assessing the efficacy of these treatments by utilising data from the maintenance phase in vedolizumab responders instead of incorporating data from patients on placebo. The ERG recommended using observed data from the placebo arm of the GEMINI II trial instead.

Dose escalation	Loss of response/efficacy to therapy.	Dose escalation was considered in an exploratory analysis in the Company ACD response. The company included dose escalation for TNF-α inhibitors (infliximab and adalimumab) but not vedolizumab. The Company cited the differences in mechanism of action between vedolizumab and the TNF-α inhibitors as the rationale for doing so. The escalated dose was applied at the beginning of the Maintenance phase in the model, with estimates for the proportion of patients modelled to receive a dose escalation based on clinical expert opinion. The range of dose estimates from clinicians was wide. Ultimately dose escalation rates of 30% and 100% (for adalimumab), and 15% and 50% (for infliximab) were used in the exploratory analyses.	Unclear	The Committee acknowledged the exploratory analyses including dose escalation but did not comment on the approach taken.	The ERG raised a number of concerns regarding the application of dose escalation in the exploratory analysis. Based on expert clinical feedback, the Company modelled dose escalation for infliximab and adalimumab only. The ERG could not confirm whether this assumption was appropriate.
Treatment discontinuation	The number of patients who discontinued treatment due to AEs.	The data used in the model reflects trials that reported discontinuation due to AEs only.	Minimal	The Committee acknowledged concerns raised by the ERG regarding omission of discontinuation rates due to lack of efficacy but made no further comment on how discontinuation was modelled.	The ERG proposed that as well as discontinuation due to AEs, discontinuation due to lack of efficacy should have been included in the model. It was also assumed that there was no increase in relapse post-biologic withdrawal which did not align with clinical opinion.
Surgery	Rate and costs of surgery.	In the original Company model, surgery was included as a health state in the model, but post-surgical health states were not. The incidence of surgical complications was	Minimal	The Committee considered the probability of repeated surgery in the original model to be unreasonably	The ERG noted that modelling surgery as a single health state was a

		included in the model within the surgery health state. Following consultation with the Committee, the final model derived per-cycle probabilities for surgery based on analyses of HES data. A per cycle rate of 1.11% (equivalent to 7% annually) was used.		high, and preferred the lower HES-derived assumptions in the final model. Based on the changes made to the model following consultation, the Committee concluded that the proportions and costs associated with surgery used in the final model were appropriate.	simplifying assumption, as subsequent surgery depends on the initial procedure. However, it was recognised that this may have been due to data limitations, and concluded that the impact to the ICER would be minimal. The Committee considered the probability of repeated surgery (33.75%) in the original model as an unreasonably high proportion, and so they considered it likely that the model overestimated the proportion of patients having repeated surgery.
Adverse events	AE rates.	AEs in the final model were selected based on clinical expert opinion, including those for serious infections, tuberculosis, lymphoma, hypersensitivity, and skin reactions.	Minimal	The Committee did not have any comments on the rates of AEs presented in the final model.	The ERG noted that it was unclear whether all AEs or only Grade 3 or 4 AEs were considered in the model. The ERG deemed the calculations to be simplistic and prone to inaccuracy as

					they overlooked trial duration. Additionally, it remained unclear why the model did not incorporate the incidence of serious AEs. The Committee did not comment on any of the points discussed above. However, it was noted by the Committee that, the model may not have adequately captured the impact of treating long-term AEs of patients taking corticosteroids (e.g. hip fractures and complications of diabetes). Incorporating these in the model would likely reduce the ICER in favour of vedolizumab.
Mortality	Annual mortality rate.	Rates of all-cause mortality were extracted from the ONS life tables for England and Wales, and adjusted for each model health state to define relative risk.	Minimal	The Committee agreed with the ERG's preference for application of the same excess risk mortality to all health states. No further comments were made by the Committee regarding	The ERG highlighted uncertainties regarding the study used by the company in its model, which did not report differences in

				how mortality was modelled.	mortality according to disease severity at baseline, nor in mortality between patients who did or did not receive infliximab. It was the preference of the ERG to apply the same excess risk mortality to all health states.
Upadacitinib, TA905[3] – cost-comparison approach					
Treatment response	CDAI-100 Clinical response: a reduction in CDAI score of >100 points from baseline at endpoint measurement PRO ≥60% decrease in average daily very soft or liquid SF and/or ≥35% decrease in average daily AP score and both not greater than baseline SES-CD	Since upadacitinib was evaluated via a cost-comparison approach, response outcomes were not used directly in the model. An NMA of comparative efficacy against vedolizumab and ustekinumab was conducted based on CDAI-100 clinical remission and CDAI-100 clinical response. Based on the results of this NMA, an assumption of clinical equivalence was made between upadacitinib, ustekinumab and vedolizumab.	N/A – not used directly in cost-comparison analysis.	No alternative assumptions were suggested by the Committee.	The Committee accepted that the approach taken to comparing the clinical effectiveness of upadacitinib and comparators was the most acceptable option in light of the evidence available.

	Decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline				
Remission	CDAI Clinical remission: an absolute CDAI score of <150 points at endpoint measurement). PRO Average daily very soft or liquid SF ≤2.8 and average daily AP score ≤1.0 and both not greater than baseline SES-CD SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable				
Dose escalation	Loss of response/efficacy to therapy.	Dose escalation was modelled for all treatments (intervention and comparators) in the maintenance phase in TA905, except for	Substantial	No alternative assumptions were suggested by the Committee from the	N/A

<table>
<tr><td></td><td></td><td>the SC regimen of vedolizumab. Dose escalation estimates were based on clinical expert opinion:<table><tr><th>Treatment</th><th>Dose escalation</th><th>% dose escalation</th></tr><tr><td>Upadacitinib</td><td>15 mg QD to 30 mg QD</td><td>30.0</td></tr><tr><td>Ustekinumab</td><td>90 mg Q12W to 90 mg Q8W</td><td>92.5</td></tr><tr><td>Vedolizumab IV</td><td>300 mg Q8W to 300 mg Q4W</td><td>30.0</td></tr><tr><td>Vedolizumab SC</td><td>N/A</td><td>N/A</td></tr></table></td><td></td><td>Company-submitted approach.</td><td></td></tr>
<tr><td>Treatment discontinuation</td><td>The number of patients who discontinued treatment due to AEs.</td><td>An NMA of comparative safety against vedolizumab and ustekinumab was conducted that considered treatment discontinuation due to AEs. Based on the results from this NMA, an assumption of clinical safety equivalence was made between upadacitinib and the comparators (ustekinumab and vedolizumab). Therefore, treatment discontinuation due to AEs was not considered in the cost-comparison analysis.</td><td>N/A – not used directly in cost-comparison analysis.</td><td>No alternative assumptions were suggested by the Committee, from the Company-submitted approach.</td><td>The EAG highlighted that discontinuation of treatment due to AEs occurred more often with upadacitinib than with the comparators in the NMA (ustekinumab and vedolizumab). However, ultimately, the Committee concluded that upadacitinib was likely to have a similar safety profile to ustekinumab and vedolizumab, based on the results from the NMA.</td></tr>
</table>

Surgery	Annual surgery rate.	Surgery was not included in the cost-comparison analysis.	N/A – not used directly in cost-comparison analysis.	The Committee agreed with the EAG regarding limitations of the absence of surgery in the model. However, since no data were available regarding surgery outcomes from the upadacitinib trials, this was not further commented on by the Committee.	The EAG noted that exclusion of surgery from the decision problem, despite it being present in the NICE scope, was a disadvantage with respect to decision-making.
Adverse events	Rate of treatment-related AEs.	AEs were not considered in the cost-comparison analysis.	N/A – not used directly in cost-comparison analysis.	The Committee did not have any comments on AEs.	N/A
Mortality	All-cause mortality.	Mortality was not considered in the cost-comparison analysis.	N/A – not used directly in cost-comparison analysis.	The Committee did not have any comments on mortality.	N/A

Footnotes: [a]Risankizumab was originally evaluated via a cost-utility approach. However, a cost-comparison approach was considered more suitable by the NICE appraisal Committee at the draft guidance stage. [b]The following exponential formulae were used: 1) With probability (P) over time (T), the instantaneous rate (r): $r = - [ln (1 - P))/T$. 2) From r, probability (p) over time period, (t) is: $p = 1 – exp (-r * t)$

Abbreviations: ACD: appraisal consultation document; AE: adverse event; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; EAG: external assessment group; ERG: evidence review group; HBI: Harvey-Bradshaw Index; HES: Hospital Episode Statistics; ICER: incremental cost-effectiveness ratio; IV: intravenous; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; NR: not reported; ONS: Office for National Statistics; QD: once daily; QW: once every week; Q2W: once every two weeks; Q4W: once every four weeks; Q6W: once every six weeks; Q8W: once every eight weeks; Q12W: once every twelve weeks; SC: subcutaneous; SES-CD: Simple Endoscopic Score-Crohn's disease; TA: technology appraisal; TNF-α: tumour necrosis factor alpha; UK: United Kingdom.

B.2.2 Resource use assumptions

The healthcare costs and resource use considered in the relevant appraisals (TA888, TA456, TA352 and TA905), and any Committee comments on these resource use assumptions are presented in Table 6 below.[1, 3, 75, 76] As the original cost-utility model in TA888 was not considered to be suitable for NICE decision making, only the resource use assumptions from the revised cost-comparison approach for risankizumab are discussed below.

Table 6: Resource use considered in relevant NICE technology appraisals

Resource use costs considered	Committee comments
Risankizumab (TA888)[1] – cost-comparison approach[a]	
Intervention and comparator acquisition costs • Drug acquisition costs for the comparators in TA888 were sourced from the BNF	No issues were raised by the Committee regarding treatment acquisition costs in the company's cost-comparison model.
Treatment administration costs • Risankizumab was administered as IV in the induction period and using an on-body device in the maintenance period • Ustekinumab was administered as IV in the induction period and SC in the maintenance period • Vedolizumab was administered as IV in the induction period and either IV/SC in the maintenance period ○ The decision to use the IV or SC regimens of vedolizumab was considered to depend on a range of factors, including clinical judgement, patient preference and resource availability. A blended approach considering 50% IV/50% SC was considered in the cost-comparison model • Administration costs for IV infusions included the costs of administration in a hospital setting (for first and subsequent doses) and were sourced from the NHS schedule of costs. SC administration assumed an administration cost for the first dose only (for training by a nurse) and was not considered for subsequent doses as it was expected that a patient would self-administer. Costs for SC administration were sourced from the PSSRU	No issues were raised by the Committee regarding the treatment administration costs reported in TA888. The Committee also noted that a clinical expert agreed with the blended approach taken for considering IV and SC vedolizumab maintenance therapy.
Drug wastage • The on-body device used to administer risankizumab (at maintenance) in	The Committee did not comment on the appropriateness of this assumption of drug wastage in the cost-comparison model.

clinical practice is a different method of administration to the SC method used in other comparator therapies. The manufacturer argued that the extent of drug wastage with risankizumab in CD is unlikely to differ from that of comparators, noting the single-use formulation of all comparator therapies. It was therefore assumed that any wastage with risankizumab would equally apply to all biologic therapies, negating any impact on economic outcomes	
Ustekinumab, TA456[75] – cost-effectiveness approach	
Intervention and comparator acquisition costs • Drug acquisition costs for the comparators in TA456, were sourced from the MIMS. Dosing information was taken from the respective SmPCs, and combined with unit costs to calculate a cost per model cycle	In their report, the ERG disagreed with the company's assumptions on concomitant therapies and noted potential disconnects between the effectiveness data and cost data used in TA456. However, the ERG acknowledged that the effect of these on the ICER was likely to be negligible. The Committee acknowledged the general limitations of the model highlighted by the ERG, but did not make any explicit mention regarding the intervention and/or comparator costs used in the Company model.
Treatment administration costs • Vedolizumab, infliximab and induction ustekinumab were administered as IV infusion ○ Administration costs of IV infusion were sourced from the NHS Payment by Results tariff 2014/15, and applied every time a dose was administered • Ustekinumab in the maintenance phase and all adalimumab doses were administered by SC injection. This was administered either by a nurse, self-administered (assuming no additional cost to the NHS) or, for ustekinumab, via a homecare service provided by the manufacturer, free of charge to the NHS • In the base case, no adalimumab or ustekinumab administrations were assumed to be provided via hospital, due to the homecare service provided by the respective manufacturers	No issues were raised by the Committee regarding the treatment administration costs reported in TA456.
Surgery • Resource use estimates for surgery were gathered via a Delphi panel with clinicians • Clinicians divided surgical procedure resource use according to length of stay and this was used to calculate a weighted average cost (20% day case; 10%	In the ERG report it was noted that the inclusion of additional surgical costs in the health state costs could lead to the potential double counting of surgery-related costs, given the separate surgery health state in the Company model. These additional

<5 days; 70% >5 days) • The costs of surgical complications were thereafter added to the weighted surgery cost to give a total surgery cost • All unit costs were sourced from NHS Reference costs 2014/2015	costs were excluded in scenario analyses, the results of which were broadly in line with the base-case results. The ERG preferred the base case assumptions for surgery resource use in TA352. However, ultimately, no issues were raised by the Committee regarding the surgery costs reported in TA456.
Drug wastage • Mean baseline patient weight was used to estimate infliximab dosage and vial wastage, but no further details on wastage were reported	No comments were made by the Committee regarding drug wastage in TA456.
AEs • Resource use associated with the treatment of five AEs were included in the company model: serious infection, tuberculosis, hypersensitivity, injection site reactions and lymphoma • The costs for all AEs, except for lymphoma, were sourced from NHS Reference Costs 2014/15 • The cost of lymphoma was given as in TA352, where the average of lymphoma costs from three technology appraisals of rituximab for lymphoma was used, and accepted by the ERG	The ERG noted that the costs associated with injection site reactions were considerably higher than the value used in TA352. However, no issues were raised by the Committee regarding the costs of AEs reported in TA456.
Vedolizumab, TA352[76] – cost-effectiveness approach	
Intervention and comparator acquisition costs • Drug acquisition costs for the vedolizumab and comparators in TA352, were sourced from the BNF 2013 ○ Following the first Committee meeting, drug costs and doses were updated to those in the November 2014 version of the BNF	The calculated drug acquisition costs were conditional on the treatment regimen assumed within the company's model. The ERG had some concerns with the treatment regimen assumed, notably for in the induction phase for vedolizumab and adalimumab. The ERG also noted that the drug acquisition cost for infliximab was conditional on the patient weight. The ERG considered that using the mean weight was not appropriate and that the distribution of patients within a weight band should be used instead; it was unclear whether the drug acquisition for infliximab would be affected by this change. The ERG questioned the assumption that whilst patients are receiving biologic therapy, the costs associated with conventional non-biologic therapy was halved (concomitant therapy).

	A scenario was submitted during the clarification stage with 100% of patients on biologic therapy also receiving conventional therapy; the impact on ICERs was minimal. Ultimately, the Committee acknowledged the concerns raised by the ERG, but were satisfied with the dosing assumptions used in the final model and did not comment on the costs for acquiring the intervention or comparators.
Treatment administration costs • Treatments were administered as IV infusion ○ Administration costs of IV infusion were sourced from the NHS Payment by Results tariff 2013/14, and applied per administration	The ERG was satisfied with the administration cost estimates assumed by the company, and no further comments were noted by the Committee.
Drug wastage • In the final model, vial sharing was not assumed for vedolizumab; any unused medicine in opened vials were discarded. Therefore, the drug costs calculations were based on whole unit costs only • Wastage for the comparators were not discussed	No issues were raised by the Committee regarding the approach to modelling drug wastage in TA352.

Surgery
• The costs of surgery included the surgical procedure itself, and the costs of treating surgical complications (wound infection, prolonged ileus/bowel obstruction, intraabdominal abscess, anastomotic leak)
  ○ The average cost of surgical procedures in the final model were derived from an analysis of the HES dataset
  ○ Costs for treating surgical complications were sourced from NHS Reference Costs 2013/14
	No issues were raised by the Committee regarding the approach to costing surgery in TA352.

Adverse events
• Five AEs were included: serious infection, TB, hypersensitivity, injection site reactions, and lymphoma
  ○ The costs for all AEs, except for lymphoma, were sourced from NHS Reference Costs 2013/14
  ○ The average lymphoma costs from three technology appraisals of rituximab for lymphoma (TA226, TA243 and TA65) informed the cost of lymphoma
	No issues were raised by the Committee regarding the costs to treat AEs reported in TA352.

• It was assumed that all patients with these AEs required hospitalisation ○ All costs pertaining to hospitalisation were sourced from the NHS Reference Costs 2013/14	
Upadacitinib, TA905[3] – cost-comparison approach	
Intervention and comparator acquisition costs • Drug acquisition costs for the comparators in TA905 were sourced from the BNF.	No issues were raised by the Committee regarding the treatment acquisition costs reported in TA905.
Treatment administration costs • No treatment administration costs were assumed for upadacitinib given it is administered orally for both induction and maintenance • Ustekinumab was administered as IV in the induction period and SC in the maintenance period • Vedolizumab was administered as IV infusion in the induction period and either IV/SC in the maintenance period • Administration costs for IV infusions included the costs of administration in a hospital setting (for first and subsequent doses) and were sourced from the NHS schedule of costs. For SC administration, an administration cost for the first dose only (for training by a nurse) was assumed, with no additional cost to the NHS for subsequent doses as patients would self-administer. Costs for SC administration were sourced from the PSSRU	No issues were raised by the Committee regarding the treatment administration costs reported in TA905.
Drug wastage • Drug wastage was not considered in the results presented in the submission • As the IV dose of ustekinumab was weight-based, an option for vial-sharing was included in the model for completeness, but this was unused	No issues were raised by the Committee regarding drug wastage in TA905.

Abbreviations: AE: adverse event; BNF: British National Formulary; CD: Crohn's disease; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; IV: intravenous; MIMS: Monthly Index of Medical Specialities; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; SC: subcutaneous; SmPC: Summary of Product Characteristics; TA: Technology Appraisal

B.3 Clinical effectiveness

Summary of clinical effectiveness evidence

The VIVID-1 trial

- The efficacy and safety data for mirikizumab versus placebo and ustekinumab are derived from the VIVID-1 trial.
- VIVID-1 is a Phase III, multi-centre, randomised, double-blind, double-dummy, parallel group, active- and placebo-controlled, treat-through study designed to evaluate the efficacy and safety of mirikizumab in patients with moderately to severely active CD.
- Baseline demographic characteristics and disease characteristics were well-balanced across treatment arms (mirikizumab: N=579; placebo: N=199; ustekinumab: N=287) in the primary analysis set (PAS) of the study.[91, 92]

Efficacy data from VIVID-1

- A higher proportion of patients receiving mirikizumab achieved clinical response at Week 12 (by PRO) alongside endoscopic response (by SES-CD) at Week 52, as compared with those receiving placebo in the PAS (mirikizumab: 38.0%; placebo: 9.0%), CCF (mirikizumab:39.3%; placebo: 11.8%) and BF (mirikizumab: 36.7%; placebo: 6.2%) populations.
- A higher proportion of patients receiving mirikizumab achieved clinical response at Week 12 (by PRO) alongside clinical remission (by CDAI) at Week 52, as compared with those receiving placebo in the PAS (mirikizumab: 45.4%; placebo: 19.6%), CCF (mirikizumab: 47.3%; placebo: 26.5%) and BF (mirikizumab: 43.4%; placebo: 12.4%) populations.
- A greater proportion of patients who received mirikizumab achieved corticosteroid-free remission at Week 52 as compared with those receiving placebo in the PAS (mirikizumab: 43.7%; placebo: 18.6%), CCF (mirikizumab: [redacted]; placebo: [redacted]) and BF (mirikizumab: [redacted]; placebo: [redacted]).
- Patients in the PAS and BF populations experienced [redacted] ([redacted]) improved fatigue, measured by FACIT-F, at Week 12 compared to baseline. Patients in the CCF subgroup also experienced a reduction in fatigue, but this was [redacted] ([redacted]).
- Patients in the PAS, CCF and BF populations experienced [redacted] ([redacted]) improved fatigue, measured by FACIT-F, at Week 52 compared to baseline.
- The proportion of patients who reported minimal to no bowel urgency (Urgency NRS ≤2) was greater at Week 12 for patients who received mirikizumab compared to placebo in the PAS (mirikizumab: [redacted]; placebo: [redacted]), CCF (mirikizumab: [redacted]; placebo: [redacted]) and BF (mirikizumab: [redacted]; placebo: [redacted]) and at Week 52.
- A similar proportion of patients receiving mirikizumab experienced clinical remission by CDAI at Week 12 compared to ustekinumab in the PAS (mirikizumab: [redacted]; ustekinumab: [redacted]), CCF (mirikizumab: [redacted]; ustekinumab: [redacted]) and BF (mirikizumab: [redacted]; ustekinumab: [redacted]) populations. However, a higher proportion of patients receiving mirikizumab experienced clinical remission by CDAI at Week 52 compared to ustekinumab in the PAS (mirikizumab: [redacted]; ustekinumab: [redacted]), CCF (mirikizumab: [redacted]; ustekinumab: [redacted]) and BF (mirikizumab: [redacted]; ustekinumab: [redacted]) populations.
- A similar proportion of patients who received mirikizumab and ustekinumab experienced endoscopic response by SES-CD at Week 12 in the PAS, CCF and BF. At Week 52 the proportion of patients who achieved endoscopic response by SES-CD was similar in patients who received mirikizumab and ustekinumab in the PAS (mirikizumab:[redacted]; ustekinumab: [redacted]) and CCF (mirikizumab:[redacted]; ustekinumab: [redacted]), but was higher in the patients who received mirikizumab in the BF population (mirikizumab:[redacted]; ustekinumab: [redacted]).

Safety data from VIVID-1

- The frequencies of treatment-emergent adverse events (TEAEs) in the mirikizumab-treated patients of VIVID-1 were similar to those for patients receiving placebo or ustekinumab

across both the induction period and the treatment regimen period.

- The majority of TEAEs observed being mild to moderate in nature in all treatment arms in both the induction period and the treatment regimen period.
- Frequencies of serious adverse events (SAEs) were similar for both mirikizumab and ustekinumab, but there was a marginally higher frequency of SAEs observed in the placebo group across both the induction period (placebo: [redacted]%; mirikizumab: [redacted]%; ustekinumab: [redacted]%) and the treatment regimen period (placebo: 17.1%; mirikizumab: 10.3%; ustekinumab: [redacted]%).[91] The frequency of SAEs was also higher for each treatment arm in the treatment regimen period compared to the induction period.
- [redacted] deaths occurred throughout the study: [redacted] deaths in the placebo arm ([redacted] in the induction period and [redacted] in the treatment regimen period) and [redacted] in the ustekinumab arm (in [redacted] in the treatment regimen period).

Efficacy data from the network meta-analyses (NMAs)

- The VIVID-1 trial did not compare the efficacy of mirikizumab in moderately to severely active CD to all comparators relevant to the decision problem.
- Therefore, indirect treatment comparison via an NMA was required to compare the efficacy of mirikizumab to other targeted therapies for treatment of moderately to severely active CD relevant to the decision problem.
- The results of the analyses found that regardless of the subgroup population (BF or CCF) or timepoint (induction or maintenance) mirikizumab offered similar efficacy and safety benefits to all active comparators in the NMA, including against risankizumab, ustekinumab and vedolizumab.

Conclusion

- Clinical effectiveness and safety evidence from VIVID-1 demonstrates that treatment with mirikizumab provides a clinically meaningful benefit to patients with moderately to severely active CD and is well-tolerated.
- Compared to relevant comparators, indirect treatment comparisons show that mirikizumab offers greater clinical benefits than placebo and similar benefit to other active treatments.

B.3.1 Identification and selection of relevant studies

A *de novo* systematic literature review (SLR) was conducted in March 2020 to identify all relevant clinical evidence from randomised controlled trials (RCTs), describing the clinical efficacy and safety of both induction, and maintenance, treatment regimens for patients with moderately to severely active CD. The SLR was updated in December 2020, April 2021, October 2021, May 2022, October 2022, April 2023, October 2023 and January 2024, using identical methodology to ensure recently published evidence was included.

In total, the overall SLR, including all updates, included 157 publications reporting on 95 unique studies. Full details of the SLR search strategy, study selection process, and results can be found in Appendix D.

B.3.2 List of relevant clinical effectiveness evidence

The SLR identified one randomised, double-blind, placebo-controlled Phase III trial (VIVID-1) for mirikizumab in moderately to severely active CD. The results of this trial are presented from the full clinical study report (CSR).[93] A summary of the clinical effectiveness evidence from VIVID-1 is presented in Table 7.

Table 7: Clinical effectiveness evidence

Study	VIVID-1 (NCT03926130)[93, 94]
Study design	A Phase III, multicentre, randomised, double-blind, double-dummy, parallel group, active- and placebo-controlled, treat-through study designed to evaluate the efficacy and safety of mirikizumab in patients with moderately to severely active CD.
Population	Adult patients between 18 and 80 years old with an established diagnosis of CD at least three months prior to baseline. Patients had moderately to severely active CD, defined by: • An unweighted daily average stool frequency (SF) ≥4, and/or an unweighted daily average abdominal pain (AP) score ≥2, as per the self-report measures of the CDAI • An SES-CD score ≥7 in participants with ileal-colonic CD or ≥4 in participants with isolated ileal disease within 21 days prior to randomisation Patients must have had an inadequate response to, loss of response to, or intolerance to corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, a combination of thiopurine and allopurinol), or an approved biologic therapy for CD.
Intervention(s)	During the induction period (Weeks 0 to 12): • 900 mg mirikizumab administered IV once every 4 weeks (Weeks 0, 4 and 8) During the maintenance period (Weeks 12 to 52): • 300 mg mirikizumab administered SC once every 4 weeks
Comparator(s)	Placebo During the induction period (Weeks 0 to 12): • Placebo administered IV once every 4 weeks (Weeks 0, 4 and 8) During the maintenance period (Weeks 12 to 52): • Responders continued to receive IV and SC placebo dosing, as applicable, at Weeks 12 to 20, then SC placebo Weeks 24 to 52 • Non-responders received blinded mirikizumab therapy: 3 doses of 900 mg IV once every 4 weeks followed by 300 mg SC once every 4 weeks Ustekinumab During the induction period (Weeks 0 to 12): • ~6 mg/kg ustekinumab administered IV at Week 0 • 90 mg ustekinumab administered SC once every 8 weeks starting at Week 8 During the maintenance period (Weeks 12 to 52): • 90 mg ustekinumab administered SC once every 8 weeks
Indicate if study supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	The outcome measures used in this submission include: • Rates of and durability of response and remission by CDAI and PRO (clinical response, clinical remission) • Mucosal healing (endoscopic response and remission by SES-CD,

Study	VIVID-1 (NCT03926130)[93, 94]
	histologic remission) • Measures of disease activity • Corticosteroid-free remission • HRQoL (EQ-5D) • Bowel urgency numeric rating scale • AEs

Abbreviations: AE: adverse event; AP: abdominal pain; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; IV: intravenous; PRO: patient-reported outcomes; SC: subcutaneous; SES-CD: Simple Endoscopic Score-Crohn's disease; SF: stool frequency.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report.[93]

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

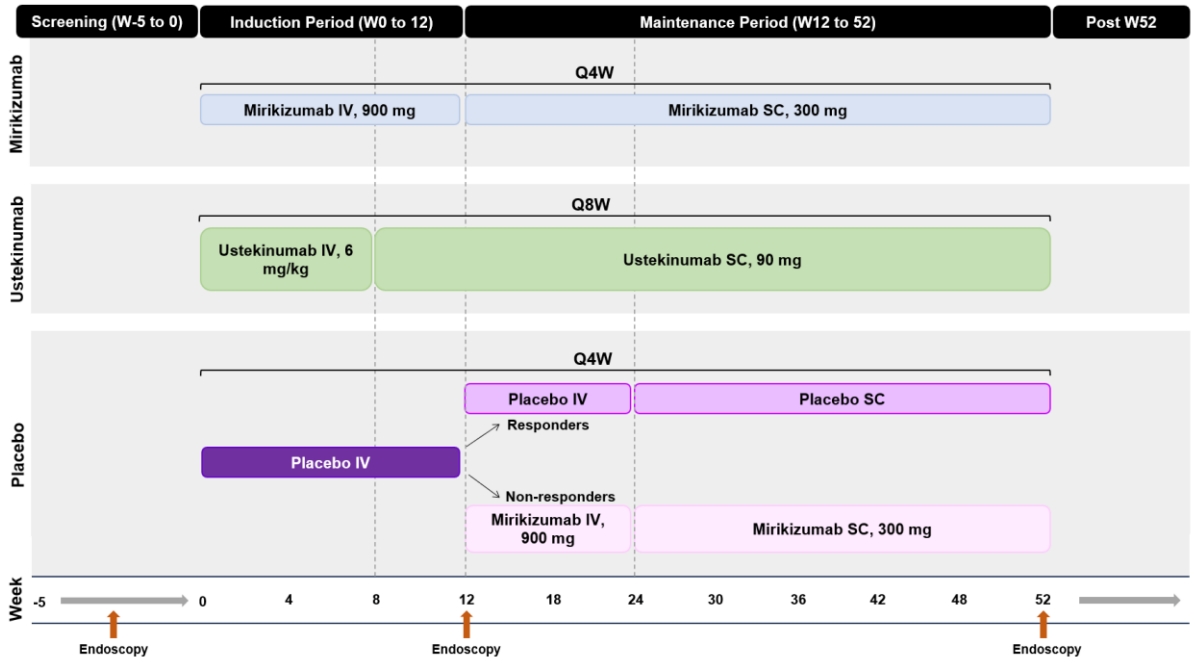
B.3.3.1 Trial design and methodology

A Phase III study, VIVID-1, was conducted to evaluate the clinical efficacy and safety of mirikizumab in adult patients with moderately to severely active CD. VIVID-1 was a randomised study, comprised of a 12-week induction period (Weeks 0 to 12), followed by a treat-through 40-week maintenance period (Weeks 12 to 52). Further details of the VIVID-1 trial are presented below.

Trial design

The trial design of VIVID-1 is shown in Figure 4. VIVID-1 was a multicentre, randomised, double-blind, parallel, placebo and active controlled, treat-through trial designed to evaluate the efficacy and safety of mirikizumab, compared with placebo or ustekinumab, over a 12-week induction period (Weeks 0 to 12) and 40-week maintenance period (Weeks 12 to 52). The trial was conducted at 328 centres that screened 2,665 patients; screening assessments were required to be completed no earlier than 35 days prior to trial baseline. After screening, 1,152 patients were randomised in the study. As outlined in Section B.3.2, the study population consisted of patients with moderately to severely active CD who had an inadequate response to, loss of response to, or intolerance to corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate, a combination of thiopurine and allopurinol), or an approved biologic therapy for CD.

Figure 4: Trial design of VIVID-1



Abbreviations: IV: intravenous; Q4W: once every four weeks; Q8W: once every eight weeks; SC: subcutaneous; W: Week.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Figure AMAM.3.1 (page 53).[93]

Induction period

In the induction period (Weeks 0 to 12), patients were randomised 6:3:2, respectively, to receive:

- IV mirikizumab 900 mg once every 4 weeks (Q4W) at Week 0, 4 and 8, or
- IV placebo (Q4W) at Week 0, 4 and 8, or
- IV ustekinumab ~6 mg/kg at Week 0 and SC ustekinumab 90 mg Q8W starting at Week 8

Maintenance period

In the maintenance period (Weeks 12 to 52), there were four intervention groups, as follows:

- Patients who received mirikizumab in the induction period: Received SC mirikizumab 300 mg Q4W during the maintenance period
- Patients who demonstrated a response to placebo in the induction period: Continued to receive IV and SC placebo dosing, as applicable, between Weeks 12 to 20, followed by SC placebo between Weeks 24 to 52
- Patients who did not demonstrate a response to placebo in the induction period (defined as being no worse than baseline and failing to achieve at least a 30% reduction in stool frequency [SF], abdominal pain [AP], or both): Received blinded mirikizumab therapy. Blinded mirikizumab was delivered as 3 doses of IV mirikizumab 900 mg Q4W, followed by SC mirikizumab 300 mg Q4W, until study completion
- Patients who received ustekinumab in the induction period: Received SC ustekinumab 90 mg Q8W during the maintenance period

Trial methodology

The VIVD-1 trial had two co-primary endpoints. Both were composite endpoints and were designed to evaluate the efficacy of mirikizumab in comparison to placebo by:

- The proportion of patients achieving a clinical response by patient-reported outcomes (PRO) of the CDAI at Week 12 (defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline) *and* endoscopic response by SES-CD at Week 52 (defined as a ≥50% reduction from baseline in SES-CD Total Score)
- The proportion of patients achieving clinical response by PRO of the CDAI at Week 12 *and* clinical remission by CDAI at Week 52 (defined as a total CDAI score of <150)

Major secondary endpoints comparing mirikizumab to placebo included further assessments of clinical response and remission by PRO/CDAI at Weeks 12 and 52, endoscopic response and remission by SES-CD at Weeks 12 and 52, change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores at Week 12 and measures of corticosteroid-free remission. Major secondary endpoints comparing mirikizumab to ustekinumab included clinical remission by CDAI at Week 52, and endoscopic response by SES-CD at Week 52. A summary of the methodology of the VIVID-1 trial is presented in Table 8.

Table 8: Summary of VIVID-1 trial methodology

Trial name	VIVID-1
Location	The study was conducted at 328 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, France, Germany, Hungary, India, Israel, Italy, Japan, Latvia, Lithuania, Mexico, The Netherlands, Poland, Romania, Russian Federation, Serbia, Slovakia, South Korea, Spain, Switzerland, Turkey, Ukraine, United Kingdom ([redacted]), and the United States.
Trial design	A Phase III, multicentre, randomised, double-blind, parallel, placebo- and active-controlled, treat-through study of mirikizumab in moderately to severely active CD compared to placebo or ustekinumab, over a 12-week induction period and subsequent 40-week maintenance period.
Eligibility criteria for participants	A summary of the key inclusion and exclusion criteria is provided below. Full details of the eligibility criteria are presented in Appendix J. **Inclusion criteria:** • Aged ≥18 and ≤80 years • An established diagnosis of CD at least 3 months prior to baseline, confirmed by clinical, endoscopic, and histological criteria • Moderately to severely active CD at baseline (defined by SF and AP patient reported items of CDAI) • Endoscopic assessment with an SES-CD score ≥7 (ileal-colonic disease) or ≥4 (isolated ileal disease) within 21 days prior to randomisation **Prior medication failure inclusion criteria:** Patients must have previously had an inadequate response to, loss of response to, or intolerance to: • Corticosteroids *or* • Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) *or* • An approved biologic therapy for CD (such as anti-TNF therapies or anti-integrin antibodies) **Exclusion criteria:** • Having a current diagnosis of UC or IBD-unclassified • Currently, or were suspected to have, an abscess

	○ Recent cutaneous and perianal abscesses were not exclusionary if drained, adequately treated and resolved at least 3 weeks prior to baseline or 8 weeks prior to baseline for intra-abdominal abscesses, provided that there was no anticipated need for any further surgery • Have a stoma, ileoanal pouch or ostomy • Have undergone bowel resection within 6 months of baseline • Have undergone any kind of intra-abdominal or extra-abdominal surgery within 3 months of baseline • Have discontinued use of an anti-IL 12/23p40 antibody due to primary nonresponse or secondary loss of response or intolerance, or who received more than the IV induction dose and one SC dose • Have complications of CD such as symptomatic strictures or stenosis, short bowel syndrome or any other manifestation that may confound treatment effect • A history or current evidence of GI tract cancer • Current infections such as tuberculosis, hepatitis B/C, *C. difficile* and opportunistic extraintestinal infection
Study drugs	**Intervention – mirikizumab** • Induction period (Weeks 0 to 12): 900 mg IV Q4W (Weeks 0, 4 and 8) • Maintenance period (Weeks 12 to 52): 300 mg SC Q4W **Comparator – placebo** • Induction period (Weeks 0 to 12): IV placebo Q4W (Weeks 0, 4 and 8) • Maintenance period (Weeks 12 to 52): ○ Responders: IV/SC placebo Q4W Weeks 12 to 20, SC placebo Q4W Weeks 24 to 52 ○ Non-responders: 3 doses of 900 mg IV mirikizumab Q4W, followed by 300 mg SC mirikizumab Q4W **Comparator – ustekinumab** • Induction period (Weeks 0 to 12): ~6 mg/kg IV ustekinumab at Week 0, 90 mg SC ustekinumab Q8W starting at Week 8 • Maintenance period (Weeks 12 to 52): 90 mg SC ustekinumab Q8W
Permitted and disallowed concomitant medication	Stable doses of the following medications were permitted: • Oral aminosalicylates (5-ASAs) • Oral corticosteroids (prednisone ≤30 mg/day or equivalent, or budesonide ≤9 mg/day) • Immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate) • Antibiotics (for treatment of CD) The use of the following medications were prohibited during the treatment phase of the study and during washout periods prior to the screening endoscopy, if applicable: • Anti-TNF antibodies (for example, infliximab, adalimumab, or certolizumab pegol) • Anti-integrin antibodies (e.g. natalizumab, vedolizumab) • Agents depleting B or T cells (for example, rituximab, alemtuzumab, or visilizumab) • Immunomodulatory medications, including oral cyclosporine, IV cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, or Janus kinase inhibitors • Rectally administered corticosteroids or 5-ASA therapies

	• IV corticosteroids • Systemic corticosteroids for non-CD indication • Any investigational biologic or non-biologic therapy • Leukocyte apheresis • Interferon therapy • Anti-IL-23p19 antibodies for any indication (for example, risankizumab) • Anti-IL-12/23p40 antibodies for any indication (for example ustekinumab) within 16 weeks prior to screening endoscopy
Co-primary outcomes	The VIVID-1 trial had two co-primary endpoints: 1) The proportion of patients achieving clinical response by CDAI PRO at Week 12 (defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline) and endoscopic response at Week 52 (defined as a ≥50% reduction from baseline in SES-CD Total Score) 2) The proportion of patients achieving clinical response by CDAI PRO at Week 12 and clinical remission by CDAI at Week 52 (defined as a total CDAI score of <150). See Section B.3.3.3 (Table 11) for further information regarding primary outcomes in VIVID-1.
Secondary outcomes	**Mirikizumab versus placebo** The major secondary endpoints of the VIVID-1 trial for mirikizumab versus placebo included: • Proportion of patients achieving clinical response by PRO at Week 12 • Proportion of patients achieving clinical remission by CDAI at Week 12 • Proportion of patients achieving endoscopic response by SES-CD at Week 12 • Proportion of patients achieving endoscopic remission by SES-CD at Week 12 • Proportion of patients showing significant FACIT-Fatigue change from baseline at Week 12 • Proportion of patients achieving clinical remission by CDAI at Week 52 • Proportion of patients achieving endoscopic response by SES-CD at Week 52 • Proportion of patients achieving clinical response by PRO at Week 12 and clinical remission by PRO at Week 52 • Proportion of patients achieving clinical response by PRO at Week 12 and corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI at Week 52 • Proportion of patients achieving clinical response by PRO at Week 12 and endoscopic remission by SES-CD at Week 52 Other secondary endpoints of the VIVID-1 trial for mirikizumab versus placebo included: • The proportion of patients achieving: ○ Clinical remission by PRO at Week 12 ○ Clinical response by CDAI at Week 12 ○ Endoscopic remission at Week 12 ○ Endoscopic response and clinical response by CDAI at Week 12 ○ Endoscopic response and clinical remission by CDAI at Week 12 ○ Urgency NRS ≤2 at Week 12 in patients with baseline Urgency NRS ≥3

- The proportion of patients achieving clinical response by PRO at Week 12 and each below, individually:
  - Clinical response by CDAI at Week 52
  - Clinical response by PRO at Week 52
  - Endoscopic remission at Week 52
  - Stability of clinical remission by CDAI from Week 12 to Week 52
  - Durability of endoscopic response at Week 12 and Week 52
  - Durability of endoscopic remission at Week 12 and Week 52
  - Endoscopic remission and clinical remission by CDAI at Week 52
  - Endoscopic response and clinical remission by CDAI at Week 52
  - Corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI at Week 52 in patients who used corticosteroids at baseline
  - Urgency NRS ≤2 at Week 52 in patients with baseline Urgency NRS ≥3
- Change from baseline in Urgency NRS at Week 52
- The proportion of patients achieving the below, over time:
  - Clinical remission by CDAI
  - Clinical response by CDAI
  - Clinical remission by PRO
  - Clinical response by PRO
- Change from baseline at Week 12 and Week 52 of the below:
  - C-reactive protein
  - Faecal calprotectin
  - FACIT-Fatigue (Week 52 only)
  - EQ-5D-5L
  - WPAI:CD
  - Medical Outcomes SF-36 Version 2
  - IBDQ

Exploratory secondary endpoints of the VIVID-1 trial for mirikizumab versus placebo included:

- Histologic response at Week 52

Mirikizumab versus ustekinumab

The major secondary endpoints of the VIVID-1 trial for mirikizumab versus ustekinumab included:

- Proportion of patients achieving clinical remission by CDAI at Week 52
- Proportion of patients achieving endoscopic response by SES-CD at Week 52

Other secondary endpoints of the VIVID-1 trial for mirikizumab versus ustekinumab included:

- Endoscopic response by SES-CD at Week 12
- Endoscopic remission SES-CD at Week 52
- Clinical remission by CDAI at Week 12
- Clinical response by CDAI at Week 12
- Clinical response by CDAI at Week 52
- Corticosteroid-free clinical remission by CDAI at Week 52

See Section B.3.3.3 (Table 11) for further information regarding secondary

	outcomes in VIVID-1, including outcome definitions.
Pre-specified subgroups	Subgroup analyses for all primary and major secondary endpoints were conducted for the following: • Demographics • Previous CD therapy (including biologic-failed and non-biologic-failed; see Section B.3.4.1 for definitions) • Baseline CD therapies • Baseline disease characteristics • Baseline patient-reported outcomes • Treatment-emergent anti-mirikizumab antibody status

Abbreviations: 5-ASA: aminosalicylates; AP: abdominal pain; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; EQ-5D-5L: EuroQoL five-dimensional instrument; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; GI: gastrointestinal; IBD: inflammatory bowel disease; IBDQ: Inflammatory Bowel Disease Questionnaire; IL: interleukin; IV: intravenous; NRS: numeric rating score; PK: pharmacokinetic; PRO: patient-reported outcome; Q4W: once every 4 weeks; Q8W: once every 8 weeks; SC: subcutaneous; SF: stool frequency; SF-36: Medical Outcomes Study 36-Item Short Form Health Survey; SES-CD: Simple Endoscopic Score-Crohn's disease; TNF: tumour necrosis factor; UC: ulcerative colitis; WPAI:CD: Work Productivity and Activity Impairment Questionnaire: Crohn's Disease.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report.[93]

B.3.3.2 Baseline characteristics

Summaries of the demographic characteristics and baseline disease characteristics for patients included in the VIVID-1 trial are provided below in Table 9 and Table 10, respectively.

Overall, demographic characteristics were well-balanced across treatment groups within the primary analysis set (PAS) population (see Section B.3.4.1 for definition). Respectively, patients in the PAS population receiving mirikizumab, placebo and ustekinumab had a mean age of 36.0 years, 36.3 years and 36.6 years, and 57.3%, 59.3% and 47.7%, were male.[92] A similar proportion of patients in each arm had severe disease at baseline, defined by a CDAI score ≥300 ([redacted] for the mirikizumab arm, [redacted] for the placebo arm and [redacted] for the ustekinumab arm). The mean CDAI scores at baseline were 323.1, 318.9 and 318.5 in the mirikizumab, placebo and ustekinumab groups, respectively.[92] Additionally, the mean SES-CD scores at baseline were 13.5, 13.1 and 13.9 in the mirikizumab, placebo and ustekinumab groups, respectively, indicating consistently severe endoscopic measures of CD across all trial arms.[92]

Table 9: Baseline demographic characteristics for patients in the PAS population of the VIVID-1 trial

Characteristics	PBO (N=199)	Miri (N=579)	Uste (N=287)
Age (years), mean (SD)	36.3 (12.7)	36.0 (13.2)	36.6 (12.7)
Male, n (%)	118 (59.3)	332 (57.3)	137 (47.7)
Weight (kg), mean (SD)	69.6 (19.0)	68.0 (18.3)	66.9 (17.6)
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	144 (74.6)	408 (71.5)	201 (70.3)
Black or African American	5 (2.6)	10 (1.8)	8 (2.8)
Asian	42 (21.8)	148 (25.9)	74 (25.9)
American Indian or Alaska Native	2 (1.0)	2 (0.4)	2 (0.7)
Multiple	0	3 (0.5)	1 (0.3)

Geographical region, n (%)			
Asia	[redacted]	[redacted]	[redacted]
North America	27 (13.6)	77 (13.3)	37 (12.9)
Central/South America	[redacted]	[redacted]	[redacted]
Europe/Rest of World	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; Miri: mirikizumab; PAS: primary analysis set; PBO: placebo; SD: standard deviation; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.4.2 (page 74).[93] Ferrante et al. (2024).[91] Jairath et al. (2024)[92]

Table 10: Baseline disease characteristics and prior therapies of patients in the PAS population of the VIVID-1 trial

Characteristics	PBO (N=199)	Miri (N=579)	Uste (N=287)
Duration of CD (years), mean (SD)	7.8 (7.4)	7.4 (8.2)	7.2 (7.7)
Disease location, n (%)			
Ileal	19 (9.5)	65 (11.2)	29 (10.1)
Colonic	77 (38.7)	225 (38.9)	120 (41.8)
Ileal-colonic	103 (51.8)	289 (49.9)	138 (48.1)
Prior surgical bowel resection			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
CDAI measures			
CDAI, mean (SD)	318.9 (86.2)	323.1 (85.8)	318.5 (93.2)
CDAI ≥300, n (%)	[redacted]	[redacted]	[redacted]
SES-CD measures			
SES-CD, mean (SD)	13.1 (6.0)	13.5 (6.6)	13.9 (6.6)
SES-CD ≥12, n (%)	[redacted]	[redacted]	[redacted]
Patient-reported outcomes (PRO)			
AP, mean (SD)	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)
AP average ≥2, n (%)	[redacted]	[redacted]	[redacted]
SF, mean (SD)	5.8 (3.2)	5.7 (3.0)	5.7 (2.9)
SF average ≥7, n (%)	[redacted]	[redacted]	[redacted]
Disease biomarkers			
CRP (mg/L), median (range: Q1, Q3)	[redacted]	[redacted]	[redacted]
Faecal calprotectin (µg/g), median (range: Q1, Q3)	[redacted]	[redacted]	[redacted]

Abbreviations: AP: abdominal pain; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; Miri: mirikizumab; PAS: primary analysis set; PBO: placebo; PRO: patient-reported outcomes; Q1: quartile 1; Q3: quartile 3; SD: standard deviation; SES-CD: Simple Endoscopic Score-Crohn's disease; SF: stool frequency; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.4.3 (page 75).[93] Ferrante et al. (2024).[91] Jairath et al. (2024)[92]

B.3.3.3 Outcome definitions

Definitions for the clinical effectiveness outcomes used in the VIVID-1 trial are presented in Table 11.

Table 11: Definitions of clinical effectiveness outcomes used in the VIVID-1 trial

Outcome	Definition
Clinical response by CDAI	Clinical response was defined by CDAI measures as a decrease in CDAI score from baseline ≥100 and/or CDAI <150
Clinical remission by CDAI	Clinical remission by CDAI was defined as a total CDAI score <150
Clinical response by PRO	From the CDAI, AP and SF are 2 of the 3 patient-reported items that form the PRO (see Section B.1.3.1 for details on how CDAI scores were calculated). Clinical response by PRO was defined as ≥30% decrease in SF and/or AP with neither score worse than baseline
Clinical remission by PRO	Clinical remission by PRO was defined as: • An unweighted daily average SF≤3, and not worse than baseline (as per Bristol Stool Scale Category 6 or 7) *and* • An unweighted daily average AP ≤1 and not worse than baseline
Endoscopic response	Endoscopic response was defined as a ≥50% reduction from baseline in total SES-CD score
Endoscopic remission	Endoscopic response was defined as an SES-CD total score ≤2
Endoscopic remission - alternative definition	An alternative definition of endoscopic response was also reported, in order to prevent misclassification of participants who have only 1 aphthous ulcer with otherwise normal mucosa. Alternative endoscopic response was defined as: • An SES-CD total score ≤4 *and* • At least a 2-point reduction in SES-CD score from baseline *and* • No sub-score of each individual variable in any ileocolonic segment >1
Fatigue change from baseline	Change from baseline in FACIT-Fatigue score
Corticosteroid-free clinical remission	Corticosteroid-free clinical remission was defined as a patient: • Being corticosteroid-use-free from Week 40 to Week 52 *and* • Achieving clinical remission by CDAI at Week 52

Abbreviations: AP: abdominal pain; CDAI: Crohn's Disease Activity Index; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; PRO: patient-reported outcome; SES-CD: Simple Endoscopic Score-Crohn's disease; SF: stool frequency.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 Trial populations

The description and number of patients in each analysis population for the VIVID-1 trial is presented in Table 12. The PAS population was used in the analysis of patient disposition and demographics, efficacy and health outcomes. The safety population was used for safety-related analysis.

Table 12: Trial populations used for the analysis of outcomes in the VIVID-1 trial

Population	Description	N

Screening Population	All patients who signed informed consent.	2,665
PAS (primary population used in efficacy analyses)	All randomised patients who had baseline SES-CD ≥7 (or ≥4 for isolated ileal disease) and took at least 1 dose of study intervention, even if the patient did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol.	1,065
PAS, exclude patients impacted by crisis	All patients in PAS, excluding all affected patients at affected sites by crisis (i.e., specific to Russia-Ukraine war).	975
PAS, Not-Biologic-Failed Population	All patients in PAS who had not failed any biologic medication regardless of prior biologic exposure.	548
PAS, Biologic-Failed Population	All patients in PAS who had failed at least 1 biologic medication	517
mITT Population	All randomised patients who took at least 1 dose of study intervention, even if the patient did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol.	1,150
ITT Population	All randomised patients, even if the patient did not take the assigned study intervention, did not receive the correct study intervention, or otherwise did not follow the protocol.	1,152
Safety Population (primary population used in safety analyses)	Same as mITT population.	1,150
All Active Treatment Safety Population	All randomised patients who received at least 1 dose of mirikizumab or ustekinumab, including • patients randomised to mirikizumab arm from Weeks 0 to 52 and patients randomised to placebo arm and were placebo non-responders by PRO at Week 12 and switched to mirikizumab (from Week 12 to Week 52), and • patients randomised to ustekinumab arm from Weeks 0 to 52	1,024

Abbreviations: AP: abdominal pain; CDAI: Clinical Disease Activity Index; ITT: intent-to-treat; mITT: modified intent-to-treat; N: number of participants in a population; PAS: Primary Analysis Set; PRO: 2 of the patient-reported items of the CDAI (SF and AP); SES-CD: Simple Endoscopic Score for Crohn's Disease; SF: stool frequency
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report. Table AMAM.4.1 (page 72).

Subgroup definitions

Subgroup analyses based on a failure of prior conventional or biological therapy use were performed. As per the inclusion criteria for the VIVID-1 trial, all patients were required to have previously had an inadequate response to, loss of response to, or intolerance to corticosteroids, immunomodulators or an approved biologic therapy for CD. In line with the trial definition, the **"biologic-failed" (BF)** population discussed henceforth included patients who had failed and thus discontinued prior biologic therapy, due to loss of response, inadequate response, or intolerance.

Patients referred to as **"conventional care-failed" (CCF)** in this submission included patients who had an inadequate response to, loss of response to, or were intolerant to conventional therapy (corticosteroids and/or immunomodulators), and did not report any previous failure on biologic treatment. In the CSR, the data for these patients are reported as the "Not-biologic-failed" population, with further data reported in the Tables, Figures and Listings (TFL) under the "Prior biologic-failure: Never" subgroup. This definition of the CCF subgroup presented in this submission aligns with the proposed positioning of mirikizumab as a potential treatment option in patients who are contraindicated, are intolerant to or have lost response to CC (see Section B.1.3.3).

The BF and CCF subgroups are in line with that defined in the NICE final scope (Section B.1.1), and the efficacy data for these subgroups are presented alongside the results from the PAS population throughout Section B.3.6.

B.3.4.2 Patient disposition

The patient flow diagram for VIVID-1 is presented in Appendix D.2.

B.3.4.3 Statistical methods

The statistical methods employed for the VIVID-1 trial are presented in Table 13 below.

Table 13: Summary of the statistical methods employed in the VIVID-1 trial

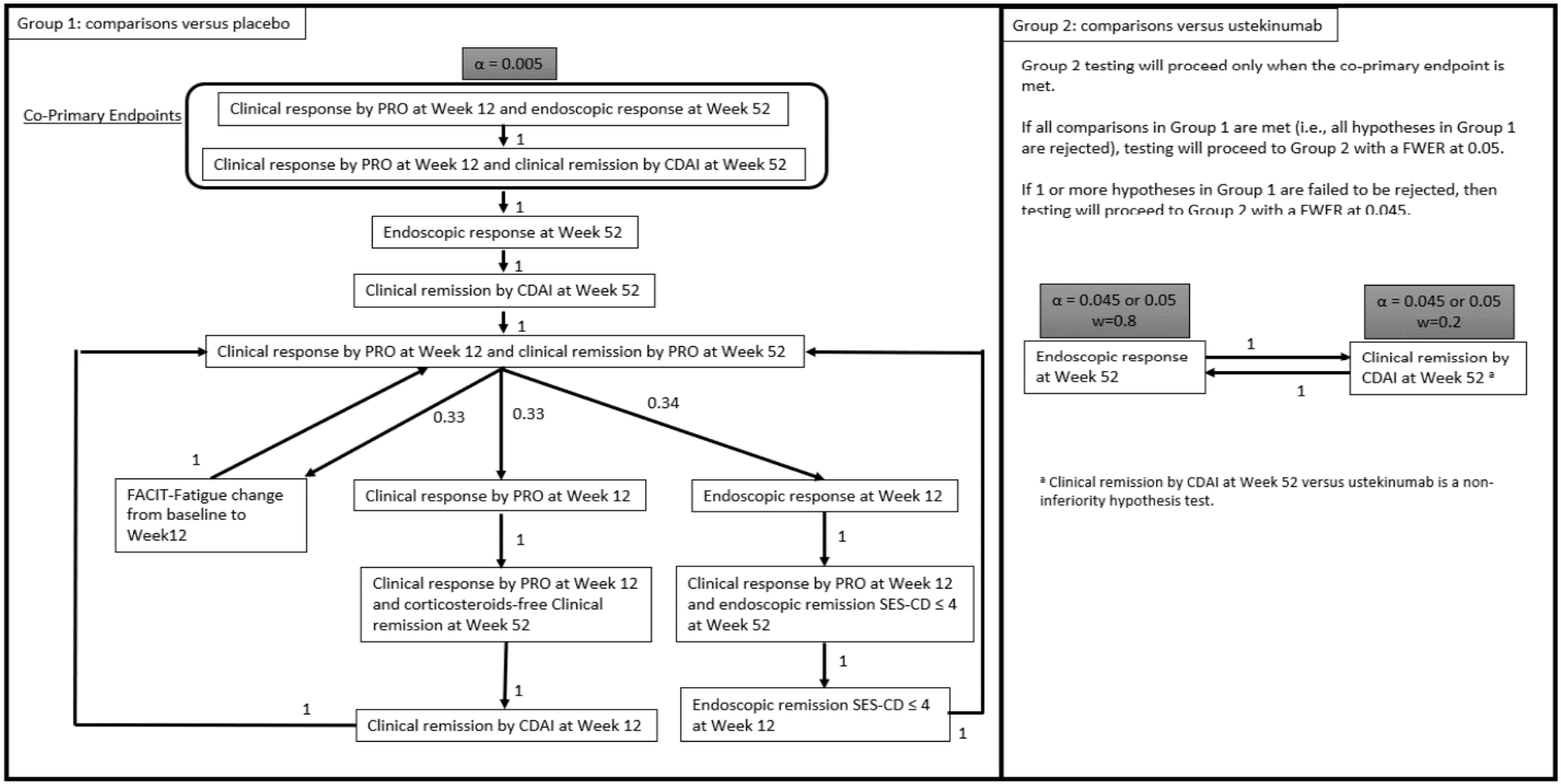
	VIVID-1
Primary hypothesis objective	To test the hypothesis that mirikizumab is superior to placebo in patients achieving the co-primary endpoints (see Section B.3.3.1) .
Multiple comparisons and multiplicity	A pre-specified graphical multiple testing scheme was implemented to control the overall family-wise error rate (FWER) at a two-sided alpha of 0.05, for all co-primary and major secondary endpoints (Figure 5). Two groups including co-primary and major secondary hypotheses were used: • Group 1 included the co-primary endpoints and all major secondary endpoints that involved comparisons versus placebo, and • Group 2 included all major secondary endpoints that involved comparisons versus ustekinumab Within each group, the graphical scheme controlled the FWER at a prespecified level. For Group 1, an FWER at 0.005 was used. If all comparisons in Group 1 were met (i.e., all hypotheses in Group 1 were rejected), testing proceeded to Group 2 with a FWER at 0.05. If one or more hypotheses in Group 1 failed to be rejected, while the comparisons on the co-primary endpoints must be met, then testing proceeded to Group 2 with a FWER at 0.045. More specifically, multiple testing adjusted p-values were calculated using "Algorithm 2" described by Bretz *et al.* (2009),[95] and any hypothesis tests with a multiple testing adjusted p-value <0.05 was considered statistically significant. This graphical approach was a closed testing procedure; hence, it strongly controlled the family-wise error rate across all endpoints.[95-97]
Statistical analysis	Co-primary endpoints: the Cochran–Mantel–Haenszel (CMH) chi-square test was used to compare mirikizumab to placebo adjusting for the selected stratification factors with non-responder imputation (NRI). Stratification factors adjusted for included: • biologic-failed status (yes/no),

	• baseline SES-CD total score (<12, ≥12), • either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown/no) Secondary endpoints: secondary endpoints that were part of the defined multiple testing procedure are referred to as major secondary endpoints. The analyses for superiority of major secondary binary endpoints utilised the CMH test similar to the primary analysis. The analysis for non-inferiority utilised a 10% non-inferiority margin for the common risk difference. The analyses for superiority of major secondary continuous endpoints utilised the analysis of covariance (ANCOVA) test. Other secondary endpoints: P-values reported for other secondary endpoints (those that were neither primary nor major secondary endpoints and not multiplicity-controlled) were nominal p-values, and statistical significance was nominal significance, unless otherwise specified. Similar analysis methods were used as for the major secondary endpoints.
Sample size, power calculation	The study was planned to randomise approximately 1100 patients in a 6:3:2 ratio for mirikizumab (600 patients), ustekinumab (300 patents) and placebo (200 patients), assuming that approximately 90% of randomised patients would meet the PAS definition, and complete the study. A sample size of 990 patients (540 patients in mirikizumab and 180 patients in placebo) provides >90% power to demonstrate that mirikizumab is superior to placebo for the co-primary endpoints of: (1) clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52, and (2) clinical response by PRO at Week 12 and endoscopic response at Week 52. This estimated power is based on a 2-sided chi-square test with α= 0.005 and assuming treatment response rates of the co-primary endpoints are 33% for mirikizumab and 10% for placebo. The sample size based on the PAS also provides >90% power to demonstrate that mirikizumab is superior to ustekinumab for endoscopic response at Week 52. This calculation is based on a 2-sided chi-square test with α= 0.045 and assuming a difference of at least 16% between mirikizumab and ustekinumab in endoscopic response at Week 52.
Data management, patient withdrawals	Clinical data management Study centre personnel entered case report from (CRF) data in a sponsor database system. The clinical data representative applied data quality checks using manual and/or electronic verification methods. The system maintained an audit trail to support data query resolution and any modification to the data. Patient withdrawals Dropouts and missing data were handled as follows: • Binary endpoints: missing data were imputed using non-responder imputation (NRI) • Continuous endpoints: primary analysis was ANCOVA with mBOCF using the missing at random assumption for handling missing data • Patients discontinuing due to an AE or lack of efficacy: missing data due to patient discontinuation due to AEs or a lack of efficacy was imputed using NRI • Patients with sporadically missing data (i.e. when a patient was still in the treatment period but data was not collected): multiple imputation (MI) was used • Patients affected by the COVID-19 pandemic or the Russia/Ukraine crisis, or treatment discontinuation due to “lost to follow-up” or pregnancy: Imputed using MI

Abbreviations: AE: adverse event; ANCOVA: analysis of covariance; CDAI: Crohn’s Disease Activity Index; CMH: Cochran–Mantel–Haenszel; CRF: case report form; FWER: family-wise error rate; MI: Multiple Imputation; mBOCF: modified Baseline Observation Carried Forward; NRI: Non-Responder Imputation; PAS: Primary Analysis Set; PRO: Patient-Reported Outcome; SES-CD: Simple Endoscopic Score for Crohn’s Disease

Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report. Eli Lilly (Data on File). VIVID-1 Statistical Analysis Plan

Figure 5: Graphical approach to controlling FWER in VIVID-1



Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Figure AMAM.5.1 (page 80).[93]

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

RCTs captured in the clinical SLR were assessed for quality using the NICE clinical effectiveness quality assessment checklist. The results of these quality assessments are presented in Appendix D.3, and a summary of the quality assessment for VIVID-1 is presented in Table 14.

Table 14: Quality assessment results for the VIVID-1 trial

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

B.3.6 Clinical effectiveness results of the relevant studies

Summary of key efficacy outcomes from the VIVID-1 trial

- A higher proportion of patients receiving mirikizumab achieved clinical response at Week 12 (by PRO) alongside endoscopic response (by SES-CD) at Week 52, as compared with those receiving placebo in the PAS (mirikizumab: 38.0%; placebo: 9.0%), CCF (mirikizumab: 39.3%; placebo: 11.8%) and BF (mirikizumab: 36.7%; placebo: 6.2%) populations.
- A higher proportion of patients receiving mirikizumab achieved clinical response at Week 12 (by PRO) alongside clinical remission (by CDAI) at Week 52, as compared with those receiving placebo in the PAS (mirikizumab:45.4%; placebo: 19.6%), CCF (mirikizumab: 47.3%; placebo: 26.5%) and BF (mirikizumab: 43.4%; placebo: 12.4%) populations.
- A greater proportion of patients who received mirikizumab achieved corticosteroid-free remission at Week 52 as compared with those receiving placebo in the PAS (mirikizumab: 43.7%; placebo: 18.6%), CCF (mirikizumab: [redacted]; placebo: [redacted]) and BF (mirikizumab: [redacted]; placebo: [redacted]).
- Patients in the PAS and BF populations experienced [redacted] ([redacted]) improved fatigue, measured by FACIT-F, at Week 12 compared to baseline. Patients in the CCF subgroup also experienced a reduction in fatigue, but this was [redacted] ([redacted]).
- Patients in the PAS, CCF and BF populations experienced [redacted] ([redacted]) improved fatigue, measured by FACIT-F, at Week 52 compared to baseline.
- The proportion of patients who reported minimal to no bowel urgency (Urgency NRS ≤2) was greater at Week 12 for patients who received mirikizumab compared to placebo in the PAS (mirikizumab: [redacted]; placebo: [redacted]), CCF (mirikizumab: [redacted]; placebo: [redacted]) and BF (mirikizumab: [redacted]; placebo: [redacted]) and at Week 52.
- A similar proportion of patients receiving mirikizumab experienced clinical remission by CDAI at Week 12 compared to ustekinumab in the PAS (mirikizumab: [redacted]; ustekinumab: [redacted]), CCF (mirikizumab: [redacted]; ustekinumab: [redacted]) and BF (mirikizumab: [redacted]; ustekinumab: [redacted]) populations. However, a higher proportion of patients receiving

mirikizumab experienced clinical remission by CDAI at Week 52 compared to ustekinumab in the PAS (mirikizumab: [redacted]; ustekinumab: [redacted]), CCF (mirikizumab: [redacted]; ustekinumab: [redacted]) and BF (mirikizumab: [redacted]; ustekinumab: [redacted]) populations.

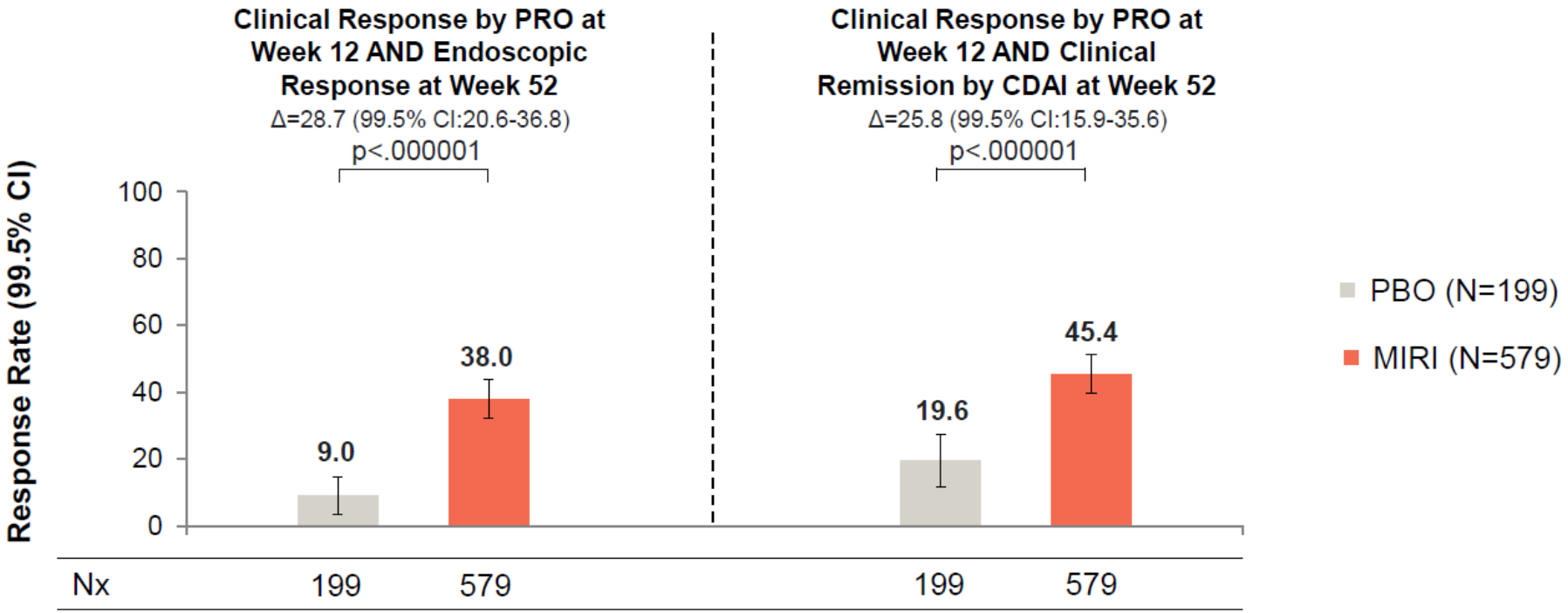
- A similar proportion of patients who received mirikizumab and ustekinumab experienced endoscopic response by SES-CD at Week 12 in the PAS, CCF and BF. At Week 52 the proportion of patients who achieved endoscopic response by SES-CD was similar in patients who received mirikizumab and ustekinumab in the PAS (mirikizumab: [redacted]; ustekinumab: [redacted]) and CCF (mirikizumab: [redacted]; ustekinumab: [redacted]), but was higher in the patients who received mirikizumab in the BF population (mirikizumab: [redacted]; ustekinumab: [redacted]).

B.3.6.1 Mirikizumab vs. placebo

B.3.6.1.1 Co-primary endpoint: Clinical response by PRO at Week 12 and endoscopic response at Week 52 (composite endpoint)

In VIVID-1, a higher proportion of patients receiving mirikizumab achieved clinical response at Week 12 (by PRO) alongside endoscopic response (by SES-CD) at Week 52, as compared with those receiving placebo in the PAS: 38.0% versus 9.0%, respectively. This translated to a common risk difference (RD) of 28.7 (99.5% CI: 20.6, 36.8) which was statistically significant (p<0.001) (Table 15 and Figure 6).[91] In the BF subgroup, the proportion of patients who achieved clinical response at Week 12 and endoscopic response at Week 52, was similarly higher in those treated with mirikizumab compared to the placebo group (RD: 30.5; 95% CI: 23.1, 37.9; p<0.001) (Table 15 and Figure 6).[91] Similarly, in the CCF subgroup, a higher rate of clinical response at Week 12 and endoscopic response at Week 52 was achieved by patients receiving mirikizumab than those receiving placebo (RD: 27.5; 95% CI: 19.1, 35.9; p<0.001) (Table 15 and Figure 6).[91]

Figure 6: Co-primary endpoints[a] of the VIVID-1 trial, NRI (PAS population)[b]



Footnotes: [a]Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline and endoscopic response is defined as ≥50% reduction from baseline in total SES-CD score. Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline and clinical remission by CDAI is defined as a total CDAI score <150 at time of measurement. [b] All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease).
Abbreviations: Δ: adjusted risk difference in all participants; AP: abdominal pain; CDAI: Crohn's disease activity index; CI: confidence interval; MIRI: mirikizumab; mITT: modified intention to treat; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; PRO: patient reported outcomes; SES_CD: simple endoscopic score Crohn's disease; SF: stool frequency.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Table 15: Clinical response by PRO at Week 12, and endoscopic response by SES-CD at Week 52 (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[c] vs placebo (CI[d]) [p-value]
	Placebo IV	Miri IV/SC[b]	
PAS	18/199 (9.0)	220/579 (38.0)	28.7 (20.6, 36.8) [p<0.001]
BF	6/97 (6.2)	103/281 (36.7)	30.5 (23.1, 37.9) [p<0.001]
CCF	12/102 (11.8)	117/298 (39.3)	27.5 (19.1, 35.9) [p<0.001]

Footnotes: [a] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline and endoscopic response is defined as ≥50% reduction from baseline in total SES-CD score. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [d] 99.5% CI for PAS population, 95% CI for BF and CCF subgroups.
Abbreviations: AP: abdominal pain; BF: biologic-failed; CI: confidence interval; CCF: conventional care failed; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PRO: Two of the patient-reported items of the CDAI (SF and AP); Q4W: every 4 weeks; SES-CD: Simple Endoscopic Score for Crohn's Disease; SC: subcutaneous; SF: stool frequency.
Source: Ferrante et al. (2024).[91] Jairath et al. (2024).[92]

B.3.6.1.2 Co-primary endpoint: Clinical response by PRO at Week 12 and clinical remission by CDAI at Week 52 (composite endpoint)

Similarly, in the PAS, a higher proportion of patients receiving mirikizumab achieved clinical response at Week 12 (by PRO) alongside clinical remission (by CDAI) at Week 52, as compared with those receiving placebo: 45.4% versus 19.6%, respectively. This translated to a common RD of 25.8 (99.5% CI: 15.9, 35.6) which was statistically significant (p<0.001) (Table 16 and Figure 6).[91] In the BF subgroup, the proportion of patients who achieved clinical response at Week 12 and endoscopic response at Week 52, was similarly higher in those treated with mirikizumab compared to the placebo group (RD: 31.0; 95% CI: 22.3, 39.8; p<0.001) (Table 16).[91] Similarly, in the CCF subgroup, a higher rate of clinical response at Week 12 and endoscopic response at Week 52 was achieved by patients receiving mirikizumab than those receiving placebo (RD: 20.8; 95% CI: 10.6, 31.1; p<0.001) (Table 16).[91]

Table 16: Clinical response by PRO at Week 12, and clinical remission by CDAI at Week 52 (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[c] vs placebo (CI[d]) [p-value]
	Placebo IV	Miri IV/SC[b]	
PAS	39/199 (19.6)	263/579 (45.4)	25.8 (15.9, 35.6) [p<0.001]
BF	12/97 (12.4)	122/281 (43.4)	31.0 (22.3, 39.8) [p<0.001]
CCF	27/102 (26.5)	141/298 (47.3)	20.8 (10.6, 31.1) [p<0.001]

Footnotes: [a] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline and clinical remission by CDAI is defined as a total CDAI score <150 at time of measurement. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [d] 99.5% CI for PAS population, 95% CI for BF and CCF subgroups.

Abbreviations: AP: abdominal pain; BF: biologic-failed; CDAI: Crohn's disease activity index; CI: confidence interval; CCF: conventional care failed; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PRO: Two of the patient-reported items of the CDAI (SF and AP); Q4W: every 4 weeks; SC: subcutaneous; SF: stool frequency.
Source: Ferrante et al. (2024).[91]

B.3.6.1.3 Major secondary endpoint: Clinical response by PRO at Week 12

A greater proportion of patients who received mirikizumab in the PAS achieved clinical response at Week 12 (by PRO) as compared with those receiving placebo: 70.6% versus 51.8%, respectively. This translated to a common RD of 18.9 (99.5% CI: 7.5, 30.3) which was statistically significant (p<0.001) (Table 17 and Figure 7).[91] Similarly, in the BF subgroup, the proportion of patients who achieved clinical response at Week 12 was higher in those treated with mirikizumab compared to the placebo group (RD: [redacted]; 95% CI: [redacted]; [redacted]) (Table 17 and Figure 7). Similar trends were observed in the CCF subgroup for mirikizumab versus placebo (RD: [redacted]; 95% CI: [redacted] [redacted]) (Table 17 and Figure 7).

Figure 7: Clinical response by PRO at Week 12[a] (treatment regimen period; PAS population, BF and CCF sungroups, NRI)[b]

Footnotes: [a] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline. [b] All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease).
Abbreviations: Δ: adjusted risk difference in all participants; AP: abdominal pain; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; MIRI: mirikizumab; mITT: modified intention to treat; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Table 17: Clinical response by PRO at Week 12 (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[c] vs placebo (CI[d]) [p-value]
	Placebo IV	Miri IV/SC[b]	
PAS	103/199 (51.8)	409/579 (70.6)	18.9 (7.5, 30.3) [p<0.001]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [d] 99.5% CI for PAS population, 95% CI for BF and CCF subgroups.
Abbreviations: AP: abdominal pain; BF: biologic-failed; CI: confidence interval; CCF: conventional care failed; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PRO: Two of the patient-reported items of the CDAI (SF and AP); Q4W: every 4 weeks; SC: subcutaneous; SF: stool frequency.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.5.2 (pages 83) and AMAM.5.5 (pages 86).[93] Ferrante et al. (2024).[91]

B.3.6.1.4 Major secondary endpoints: Clinical remission by CDAI at Week 12 and Clinical remission by CDAI at Week 52

At Week 12, a greater proportion of patients in the PAS who received mirikizumab achieved clinical remission by CDAI as compared with those receiving placebo: 37.7% versus 25.1%, respectively. This translated to a common RD of 12.4 (99.5% CI: 2.2, 22.7) which was statistically significant (p=0.001) (Table 18 and Figure 8).[91] In the BF subgroup, the proportion of patients who achieved clinical remission by CDAI at Week 12 was higher in those treated with mirikizumab compared to the placebo group (RD: [redacted]; 95% CI: [redacted]) (Table 18 and Figure 8). Similarly, in the CCF subgroup, a higher rate of clinical remission by CDAI at Week 12 was achieved by patients receiving mirikizumab than those receiving placebo (RD: [redacted]; 95% CI: [redacted]; [redacted]) (Table 18 and Figure 8).

Figure 8: Clinical remission by CDAI at Week 12[a] (PAS[b], BF and CCF populations, NRI)

Footnotes: [a] Clinical remission by CDAI is defined as a total CDAI score <150 at time of measurement. [b] All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in subgroups; BF: biologic failed; CCF: conventional care failed; CDAI: Crohn's disease activity index; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; MIRI: mirikizumab; mITT: modified intention to treat; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

At Week 52, a greater proportion of patients who received mirikizumab in the PAS achieved clinical remission by CDAI as compared with those receiving placebo: 54.1% versus 19.6%, respectively. This translated to a common RD of 34.6 (99.5% CI: 24.7, 44.4) which was statistically significant (p<0.001) (Table 18 and Figure 9).[91] In the BF subgroup, the proportion of patients who achieved clinical remission at Week 52 was higher in those treated with mirikizumab compared to the placebo group (RD: [redacted]; 95% CI: [redacted]) (Table 18 and Figure 9). Similarly, in the CCF subgroup, a higher rate of clinical remission at Week 52 was achieved by patients receiving mirikizumab than those receiving placebo (RD: [redacted]; 95% CI: [redacted]) (Table 18 and Figure 9).

Figure 9: Clinical remission by CDAI at Week 52[a] (PAS[b], BF and CCF populations, NRI)

Footnotes: [a] Clinical remission by CDAI is defined as a total CDAI score <150 at time of measurement. [b] All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CDAI: Crohn's disease activity index; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; MIRI: mirikizumab; mITT: modified intention to treat; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

These statistically significant benefits for mirikizumab over the placebo group in inducing clinical remission by CDAI were realised as early as Week 4, and maintained until Week 52 (Figure 10).

Table 18: Clinical remission by CDAI (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[c] vs placebo (CI[d]) [p-value]
	Placebo IV	Miri IV/SC[b]	
Week 12			
PAS	50/199 (25.1)	218/579 (37.7)	12.4 (2.2, 22.7) [p=0.001]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	39/199 (19.6)	313/579 (54.1)	34.6 (24.7, 44.4) [p<0.001]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Clinical remission by CDAI is defined as a total CDAI score <150 at time of measurement [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [d] 99.5% CI for PAS population, 95% CI for BF and CCF subgroups.
Abbreviations: BF: biologic-failed; CDAI: Crohn's disease activity index; CI: confidence interval; CCF: conventional care failed; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.5.2 (pages 83) and AMAM.5.5 (pages 86–87).[93] Ferrante et al. (2024).[91]

Figure 10: Clinical remission by CDAI by week (treatment regimen period; PAS population; NRI)[a, b]

Footnotes: *p<.05, **p<.01, ***p<.001 vs placebo [a] Clinical remission by CDAI is defined as a total CDAI score <150 at time of measurement [b] After Week 12, placebo-responders continued receiving placebo; placebo-non-responders switched to mirikizumab, remained included in the placebo group and were imputed as non-responders.
Abbreviations: CDAI: Crohn's Disease Activity Index; CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Pbo: placebo; SC: subcutaneous
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Figure AMAM.5.2 (page 93).[93]

B.3.6.1.5 Major secondary endpoint: Clinical response by PRO at Week 12 and corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI at Week 52 (composite endpoint)

Clinical remission following the discontinuation of concomitant corticosteroid-therapy (between Weeks 40 and 52), hereafter referred to as corticosteroid-free remission, was measured for both the placebo and mirikizumab arm of patients in the treatment-regimen period of the VIVID-1 trial. A greater proportion of patients who received mirikizumab in the PAS achieved corticosteroid-free remission at Week 52 as compared with those receiving placebo: 43.7% versus 18.6%, respectively. This translated to a common RD of 25.0 (99.5% CI: 15.2, 34.7) which was statistically significant (p<0.001) (Table 19).[91] In the BF subgroup, the proportion of patients who achieved corticosteroid-free remission at Week 52, was similarly higher in those treated with mirikizumab compared to the placebo group (RD: [redacted]; 95% CI: [redacted]) (Table 19). Similarly, in the CCF subgroup, a higher rate of corticosteroid-free remission at Week 52 was achieved by patients receiving mirikizumab than those receiving placebo (RD: [redacted]; 95% CI: [redacted]) (Table 19).

Table 19: Clinical response by PRO at Week 12 and corticosteroid-free from Week 40 to Week 52 and clinical remission by CDAI at Week 52 (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[c] vs placebo (CI[d]) [p-value]
	Placebo IV	Miri IV/SC[b]	
PAS	37/199 (18.6)	253/579 (43.7)	25.0 (15.2, 34.7) [p<0.001]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP with neither score worse than baseline. Corticosteroid-free clinical remission is defined as a patient being corticosteroid-free from Week 40 to Week 52 *and* achieving clinical remission by CDAI at Week 52, (defined as a total CDAI score <150 at time of measurement). [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [d] 99.5% CI for PAS population, 95% CI for BF and CCF subgroups.
Abbreviations: AP: abdominal pain; BF: biologic-failed; CDAI: Crohn's disease activity index; CI: confidence interval; CCF: conventional care failed; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PRO: Two of the patient-reported items of the CDAI (SF and AP); Q4W: every 4 weeks; SC: subcutaneous; SF: stool frequency.
Source: Eli Lilly (data on file): VIVID-1 Clinical Study Report, Tables AMAM.5.2 (page 83) and AMAM.5.5 (page 88).[93] Ferrante et al. (2024).[91]

B.3.6.1.6 Secondary endpoints: Endoscopic remission by SES-CD ≤4 at Week 12 (major) and at Week 52 (other)

A higher proportion of patients who received mirikizumab in the PAS demonstrated endoscopic remission by SES-CD ≤4 at Week 12 as compared with those receiving placebo: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (99.5% CI: [redacted]) which was [redacted] ([redacted]) (Table 20 and Figure 11). In the BF subgroup, the proportion of patients who demonstrated endoscopic remission at Week 12, was similarly higher in those treated with mirikizumab compared to the placebo group (RD: [redacted]; 95% CI: [redacted]; [redacted]) (Table 20 and Figure 11). Similarly, in the CCF subgroup, a higher rate of endoscopic remission at Week 12 was achieved by patients receiving mirikizumab than those receiving placebo (RD: [redacted]; 95% CI: [redacted]; [redacted]) (Table 20 and Figure 11).

Figure 11: Endoscopic remission at Week 12[a] (PAS[b], BF and CCF populations, NRI)

Footnotes: [a] Endoscopic remission is defined as SES-CD Total Score ≤4 and ≥2-point reduction from baseline and no subscore >1. [b] All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; MIRI: mirikizumab; mITT: modified intention to treat; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Figure 12: Endoscopic remission at Week 52[a] (PAS[b], BF and CCF populations, NRI)

Footnotes: [a] Endoscopic remission is defined as SES-CD Total Score ≤4 and ≥2-point reduction from baseline and no subscore >1. [b] All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; MIRI: mirikizumab; mITT: modified intention to treat; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

A higher proportion of patients in the PAS who received mirikizumab demonstrated endoscopic remission by SES-CD ≤4 at Week 52 as compared with those receiving placebo: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (99.5% CI: [redacted]) which was [redacted] ([redacted]) (Table 20 and Figure 12). In the BF subgroup, the proportion of patients who demonstrated endoscopic remission at Week 12, was similarly higher in those treated with mirikizumab compared to the placebo group (RD: [redacted]; 95% CI: [redacted]) (Table 20 and Figure 12). Similarly, in the CCF subgroup, a higher rate of endoscopic remission at Week 52 was achieved by patients receiving mirikizumab than those receiving placebo (RD: [redacted]; 95% CI: [redacted]) (Table 20 and Figure 12).

Table 20: Endoscopic remission by SES-CD ≤4 (treatment regimen period; PAS population, NRI)

Population	Response, n/N (%)		Risk difference[b] vs placebo (CI[c]) [p-value]
	Placebo IV	Miri IV/SC[a]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [b] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups [c] 99.5% CI for PAS population, 95% CI for BF and CCF subgroups.
Abbreviations: BF: biologic-failed; CI: confidence interval; CCF: conventional care failed; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.5.2 (page 83), AMAM.5.5 (page 87) and AMAM.8.27 (page 376).[93]

B.3.6.1.7 Secondary endpoints: FACIT-F change from baseline at Week 12 (major) and Week 52 (other)

As presented in Table 21 and Figure 13, fatigue as measured by the FACIT-F was [redacted] ([redacted]) improved in patients who received mirikizumab compared with those receiving placebo in the PAS: least square mean (LSM) change from baseline, [redacted] versus [redacted], respectively. The LSM difference between mirikizumab and placebo was [redacted] (99.5% CI: [redacted]). In both the CCF and BF subgroups, fatigue was improved at Week 12 in those treated with mirikizumab compared to the placebo; LSM difference [redacted] ([redacted]) and [redacted] ([redacted]), respectively (Table 21 and Figure 13).

Figure 13: FACIT-F[a] change from baseline to Week 12 (treatment regimen period; PAS[b], BF and CCF populations, mBOCF[c])

Footnotes: [a]13-item instrument, total score ranges from 0 to 52 based on a rating of 5-point Likert scale. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). [c]For analyses using mBOCF, an ANCOVA model was used.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; ANCOVA: analysis of covariance; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; LSM: least square mean; mBOCF: Modified Baseline Observation Carried Forward; MIRI: Mirikizumab; PAS: primary analysis set; PBO: Placebo; SE: standard error.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

In the PAS population at Week 52, fatigue as measured by the FACIT-F, was [redacted] ([redacted]) improved in patients who received mirikizumab compared with those receiving placebo: least square mean (LSM) change from baseline, [redacted] versus [redacted], respectively (Table 21). The LSM difference between mirikizumab and placebo was [redacted] (99.5% CI: [redacted]) (Table 21). In both the CCF and BF subgroups, fatigue was improved at Week 52 in those treated with mirikizumab compared to the placebo; LSM difference [redacted] ([redacted]) and [redacted] ([redacted]), respectively (Table 21).

Table 21: FACIT-F change from baseline (treatment regimen period; PAS population, NRI)[a]

Population	LSM change from baseline (SE)		LSM difference vs placebo (CI[c]) [p-value]
	Placebo IV	Miri IV/SC[b]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Analysis method used: ANCOVA with mBOCF. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W. [c] 99.5% CI for PAS population, 95% CI for BF and CCF subgroups. [d] Non-multiplicity-adjusted.
Abbreviations: ANCOVA: analysis of covariance; BF: biologic-failed; CI: confidence interval; CCF: conventional care failed; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; IV: intravenous; LSM: least square mean; mBOCF: modified baseline observation carried forward; Miri: mirikizumab; NR: not reported; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous; SE: standard error.
Source: Eli Lilly (data on file): VIVID-1 Clinical Study Report, Tables AMAM.5.2 (page 83), AMAM.5.5 (page 87), AMAM.5.13 (page 100) and AMAM.8.37 (page 636 and 638).[93]

B.3.6.1.8 Other secondary endpoints: Clinical response by CDAI at Week 12 and clinical response by CDAI at Week 52

In the PAS population at Week 12, a greater proportion of patients who received mirikizumab achieved clinical response as measured by CDAI, compared with those receiving placebo: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 22). In both the CCF and BF a greater proportion of patients achieved clinical response as measured by CDAI compared to placebo (CCF: [redacted]% versus [redacted]%; BF: [redacted]% versus [redacted]%). This translated to a common RD of [redacted] (95% CI: [redacted]) in the CCF population and an RD of [redacted] (95% CI: [redacted]) in the BF population, which were [redacted] for each population (CCF: [redacted]; BF: [redacted]).

At Week 52, a greater proportion of patients in the PAS who received mirikizumab achieved clinical response as measured by CDAI, compared with those receiving placebo: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 22). In both the CCF and BF a greater proportion of patients achieved clinical response as measured by CDAI compared to placebo (CCF: [redacted]% versus [redacted]%; BF: [redacted]% versus [redacted]%). This translated to a common RD of [redacted] (95% CI: [redacted]) in the CCF population and an RD of [redacted] (95% CI: [redacted]) in the BF population, which were [redacted] for each population (CCF: [redacted]; BF: [redacted]).

Table 22: Clinical response by CDAI (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Common risk difference vs placebo (95% CI) [p-value]
	Placebo IV	Miri IV/SC[b]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Clinical response by CDAI is defined as a reduction in CDAI by ≥100 and/or total CDAI score <150 at time of measurement. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
Abbreviations: BF: biologic failed; CCF: conventional care failed; CDAI: Crohn's disease activity index; CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.65 (page 1667) and Table AMAM.8.65 (page 1677).[93]

B.3.6.1.9 Other secondary endpoints: Urgency NRS ≤2 in patients with baseline Urgency NRS ≥3 at Week 12 and Week 52

The proportion of patients who reported minimal to no bowel urgency (Urgency NRS ≤2; see Table 11 and Figure 14) was greater at Week 12 for patients who received mirikizumab compared to those who received placebo in the PAS: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 23 and Figure 14). The proportion of patients who reported minimal to no bowel urgency at Week 12 was greater for patients who received mirikizumab compared to those who received placebo in both the BF ([redacted]% versus [redacted]%) and CCF ([redacted]% versus [redacted]%) subgroups This related to a common RD of [redacted] (95% CI: [redacted]) in the BF subgroup and [redacted] (95% CI: [redacted]) in the CCF subgroup. The common RD was [redacted] in the BF subgroup ([redacted]) [redacted] in the CCF subgroup ([redacted]).

Figure 14: Bowel urgency NRS ≤2[a] at Week 12 (treatment regimen period, PAS[b], BF and CCF populations, NRI)

Footnotes: [a]Bowel urgency NRS ≤2 in patients with Urgency NRS ≥3 at baseline. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test.
Abbreviations: Δ: adjusted risk difference in all participants; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; mITT: modified intention to treat; MIRI: mirikizumab; NRI: non-responder imputation; NRS: Numeric Rating Scale; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

This difference was sustained at Week 52, where again, the proportion of patients who reported minimal to no bowel urgency (Urgency NRS ≤2) was greater for patients who received mirikizumab compared to those who received placebo: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 23 and Figure 15). The difference in proportion of patients who reported minimal to no bowel urgency (Urgency NRS ≤2) was also maintained at Week 52 in the CCF and BF subgroups. In the CCF population, the proportion of patients who reported Urgency NRS ≤2 was greater for patients who received mirikizumab compared to those who received placebo: [redacted] versus [redacted]. This translated to a common RD of [redacted] (95% CI: [redacted]), which is statistically significant ([redacted]). Similarly, in the BF population, [redacted]% of patients who received mirikizumab reported Urgency NRS ≤2 compared to [redacted] of those who received placebo. This translated to a common RD of [redacted] (95% CI: [redacted]), which is statistically significant ([redacted]).

Figure 15: Bowel urgency NRS ≤2[a] at Week 52 (treatment regimen period, PAS[b], BF and CCF populations, NRI)

Footnotes: [a]Bowel urgency NRS ≤2 in patients with Urgency NRS ≥3 at baseline. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test.
Abbreviations: Δ: adjusted risk difference in all participants; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; mITT: modified intention to treat; MIRI=Mirikizumab; NRI: non-responder imputation; NRS: Numeric Rating Scale; PAS: primary analysis set; PBO=Placebo; SES-CD: simple endoscopic score Crohn's disease; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Table 23: Urgency NRS ≤2 in patients with baseline Urgency NRS ≥3 (treatment regimen period; PAS population, NRI)

Population	Response, n/N (%)		Common risk difference vs placebo (95% CI) [p-value]
	Placebo IV	Miri IV/SC[a]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
Abbreviations: BF: biologic failed; CCF: conventional care failed; CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; NRS: Numeric Rating Scale; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.78 (page 1777) and Table AMAM.8.78 (page 1787).[93] Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results (slides 85 and 87). Eli Lilly (Data on File). VIVID-1 2.7.3 Summary of Clinical Efficacy.

B.3.6.1.10 Other secondary endpoint: EQ-5D-5L VAS change from baseline at Week 12 and Week 52

At Week 12, patients who received mirikizumab in the PAS demonstrated a [redacted] improvement in patient HRQoL as compared with those who received placebo, as measured by the EQ-5D-5L VAS. LSM change from baseline was [redacted] versus [redacted], respectively. The LSM difference for mirikizumab versus placebo was [redacted] (95% CI: [redacted]) (Table 24).

This difference in HRQoL-improvement was further emphasised at Week 52. LSM change from baseline in EQ-5D-5L VAS at Week 52 was [redacted] versus [redacted], for patients who received mirikizumab and placebo, respectively. The LSM difference for mirikizumab versus placebo was [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 24).

Table 24: EQ-5D-5L VAS change from baseline (treatment regimen period; PAS population, ANCOVA with mBOCF)

Population	LSM change from baseline (SE)		LSM difference vs placebo (95% CI) [p-value]
	Placebo IV	Miri IV/SC[a]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]

Footnotes: [a] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D-5L: EuroQol 5 dimension 5 level; IV: intravenous; LSM: least square mean; mBOCF: modified baseline observation carried forward; Miri: mirikizumab; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous; SE: standard error; VAS: visual analogue scale.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.81 (page 1889), and Table AMAM.8.81 (page 1891).[93]

B.3.6.2 Mirikizumab vs. ustekinumab

B.3.6.2.1 Major secondary endpoints: Clinical remission by CDAI at Week 12 and clinical remission by CDAI at Week 52

In the PAS population at Week 12, a marginally greater proportion of patients who received mirikizumab achieved clinical remission as measured by CDAI, as compared with those receiving ustekinumab: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (99.5% CI: [redacted]) which was [redacted] ([redacted]) (Table 25 and Figure 16).

At Week 52, a greater proportion of patients who received mirikizumab in the PAS achieved clinical remission as measured by CDAI, compared with those receiving ustekinumab, demonstrating non-inferiority: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 25 and Figure 17). A numerically greater proportion of patients receiving mirikizumab achieved clinical remission by CDAI at Week 52 compared to ustekinumab in the BF population ([redacted]% versus [redacted]%, respectively), although this difference was [redacted] (p=[redacted]) (Table 25). The proportion of patients achieving clinical remission by CDAI [redacted] differ between patients who received mirikizumab and ustekinumab in the CCF population ([redacted]% versus [redacted]%, respectively; p=[redacted]) (Table 25).

Figure 16: Clinical remission by CDAI[a] at Week 12 (treatment regimen period; PAS[b], BF and CCF populations, NRI)

Footnotes: [a]Clinical remission by CDAI is defined as a total CDAI score of <150 at time of measurement. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CDAI: Crohn's disease activity index; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; mITT: modified intention to treat; MIRI: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Figure 17: Clinical remission by CDAI[a] at Week 52 (treatment regimen period; PAS[b], BF and CCF populations, NRI)

Footnotes: [a]Clinical remission by CDAI is defined as a total CDAI score of <150 at time of measurement. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). Clinical Remission by CDAI at Week 52 vs. ustekinumabin all patients is a non-inferiority hypothesis test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CDAI: Crohn's disease activity index; CI: confidence interval; mITT: modified intention to treat; MIRI: mirikizumab; NRI: non-responder imputation; NI: non-inferiority with margin of 10%; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Table 25: Clinical remission by CDAI (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[d] vs ustekinumab (CI[e]) [p-value]
	Miri IV/SC[b]	Ustekinumab IV/SC[c]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted][f,g]
BF	[redacted]	[redacted]	[redacted][h]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Clinical remission by CDAI is defined as a total CDAI score of <150 at time of measurement. [b]Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Ustekinumab dose regimen is ~6mg/kg IV at Week 0, then 90 mg SC Q8W starting at Week 8 [d] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [e] 99.5% CI for Week 12 PAS population, 95% CI for all other risk differences presented [f] p-value for non-inferiority is derived from the common risk difference with margin of 10%. The one-sided p-value was multiplied by 2 to be interpretable at standard alpha levels [g] p-value vs. ustekinumab (superiority) = 0.113117 [h] Fisher's exact test was used.
Abbreviations: BF: biologic failed; CCF: conventional care failed; CDAI: Crohn's disease activity index; CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; Q8W: every 8 weeks; SC: subcutaneous.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.5.3 (page 84), AMAM.5.6 (page 89), AMAM.8.25 (page 327), AMAM.8.34 (pages 571 and 573).[93]

B.3.6.2.2 Major secondary endpoints: Endoscopic response by SES-CD at Week 12 and endoscopic response by SES-CD at Week 52

At Week 12, a numerically greater proportion of patients who received mirikizumab achieved endoscopic response as measured by the SES-CD in the PAS, as compared with those receiving ustekinumab: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (99.5% CI: [redacted]) which was [redacted] ([redacted]) (Table 26 and Figure 18).

At Week 52, a numerically greater proportion of patients who received mirikizumab in the PAS demonstrated endoscopic response by SES-CD as compared to ustekinumab ([redacted] versus [redacted], respectively), however [redacted]. The common RD for mirikizumab versus ustekinumab was [redacted] (95% CI: [redacted]) (Table 26 and Figure 19).

Figure 18: Endoscopic response by SES-CD at Week 12[a] (treatment regimen period; PAS[b], BF and CCF populations, NRI)

Footnotes: [a]Endocscopic response is defined as ≥50% reduction from baseline in SES-CD score. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; mITT: modified intention to treat; MIRI: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Figure 19: Endoscopic response by SES-CD at Week 52[a] (treatment regimen period; PAS[b], BF and CCF populations, NRI)

Footnotes: [a]Endocscopic response is defined as ≥50% reduction from baseline in SES-CD score. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; mITT: modified intention to treat; MIRI: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

Table 26: Endoscopic response by SES-CD at Week 12 and Week 52 (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[d] vs ustekinumab (CI[e]) [p-value]
	Miri IV/SC[b]	Ustekinumab IV/SC[c]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Endocscopic response is defined as ≥50 reduction from baseline in SES-CD score. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Ustekinumab dose regimen is ~6mg/kg IV at Week 0, then 90 mg SC Q8W starting at Week 8 [d] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [e] 99.5% CI for Week 12 PAS population, 95% CI for all other risk differences presented
Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous; SES-CD: Simple Endoscopic Score-Crohn's disease.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.5.3 (page 84), AMAM.8.24 (page 318) and AMAM.8.33 (pages 540 and 542)[93]

B.3.6.2.3 Other secondary endpoints: Clinical response by CDAI at Week 12 and Clinical response by CDAI at Week 52

At Week 12, a marginally greater proportion of patients who received mirikizumab achieved clinical response as measured by CDAI in the PAS, as compared with those receiving ustekinumab: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 27). Similarly, in both the CCF and BF populations, a marginally higher proportion of patients who received mirikizumab achieved clinical response as measured by CDAI as compared with those receiving ustekinumab (CCF: [redacted]% versus [redacted]%; BF: [redacted]% versus [redacted]%) (Table 27). These differences translated to a common RD of [redacted] (95% CI: [redacted]) in the CCF population and [redacted] (95% CI: [redacted]) in the BF population. These differences were [redacted] (CCF: [redacted]; BF: [redacted]) (Table 27).

At Week 52, a greater proportion of patients who received mirikizumab achieved clinical response as measured by CDAI, compared with those receiving ustekinumab in the PAS: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 27). Similarly, in both the CCF and BF populations, a marginally higher proportion of patients who received mirikizumab achieved clinical response as measured by CDAI as compared with those receiving ustekinumab (CCF: [redacted]% versus [redacted]%; BF: [redacted]% versus [redacted]%) (Table 27). These differences translated to a common RD of [redacted] (95% CI: [redacted]) in the CCF population and [redacted] (95% CI: [redacted]) in the BF population. These differences were [redacted] (CCF: [redacted]; BF: [redacted]) (Table 27).

Table 27: Clinical response by CDAI (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)	

	Miri IV/SC[b]	Ustekinumab IV/SC[c]	Common risk difference vs ustekinumab (95% CI) [p-value]
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Clinical response by CDAI is defined as a reduction in CDAI by ≥100 and/or total CDAI score <150 at time of measurement [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Ustekinumab dose regimen is ~6mg/kg IV at Week 0, then 90 mg SC Q8W starting at Week 8.
Abbreviations: CDAI: Crohn's disease activity index; CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; Q8W: every 8 weeks; SC: subcutaneous.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.8.65 (pages 1667, 1677).[93]

B.3.6.2.4 Other secondary endpoints: Endoscopic remission by SES-CD ≤4 at Week 12 and endoscopic remission by SES-CD ≤4 at Week 52

Patients who received mirikizumab demonstrated endoscopic remission by SES-CD ≤4 at Week 12 similarly to those who received ustekinumab in the PAS: [redacted] versus [redacted], respectively. This translated to a common RD of [redacted](99.5% CI: [redacted]) which was [redacted] ([redacted]) (Table 28 and Figure 20). In the CCF subgroup, the proportion of patients who demonstrated endoscopic remission at Week 12, was similar between those treated with mirikizumab compared to the ustekinumab group (RD: [redacted]; 95% CI: [redacted]; [redacted]) (Table 28 and Figure 20). Similarly, in the BF subgroup, a higher rate of endoscopic remission at Week 12 was achieved by patients receiving mirikizumab than those receiving ustekinumab (RD: [redacted]; 95% CI: [redacted] [redacted]) (Table 28 and Figure 20).

Figure 20: Endoscopic remission by SES-CD ≤4 at Week 12[a] (treatment regimen period; PAS, BF and CCF populations, NRI)[b]

Footnotes: [a]Endoscopic remission is defined as a SES-CD score ≤4 and at least a 2-point reduction in SES-CD score from baseline and no sub-score of each individual variable in any ileocolonic segment >1. [b]All participants from mITT population who have baseline SES-CD≥7 (or ≥4 for isolated ileal disease). The comparison in all patients is CMH test and is Fisher's exact test in the subgroups.
Abbreviations: Δ: adjusted risk difference in all participants and is unadjusted risk difference in the subgroups; BF: biologic failed; CCF: conventional care failed; CI: confidence interval; mITT: modified intention to treat; MIRI: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; PBO: placebo; SES-CD: simple endoscopic score Crohn's disease; UST: ustekinumab.
Source: Eli Lilly (Data on File). CD VIVID-1 Ph3 Topline Efficacy Results.[98]

A higher proportion of patients who received mirikizumab in the PAS demonstrated endoscopic remission at Week 52 as compared with those receiving ustekinumab: [redacted] versus [redacted], respectively. This translated to a RD of [redacted] (99.5% CI: [redacted]) which was [redacted] ([redacted]) (Table 28 and Figure 12). In the CCF subgroup, the proportion of patients who demonstrated endoscopic remission at Week 52, was similar between those treated with mirikizumab compared to the ustekinumab group (RD: [redacted]; 95% CI: [redacted]; [redacted]) (Table 28 and Figure 12). In the BF subgroup, a higher rate of endoscopic remission at Week 52 was achieved by patients receiving mirikizumab than those receiving ustekinumab (RD: [redacted]; 95% CI: [redacted]) (Table 28 and Figure 12).

Table 28: Endoscopic remission by SES-CD ≤4 at Week 12 and Week 52 (treatment regimen period; PAS population, NRI)[a]

Population	Response, n/N (%)		Risk difference[d] vs ustekinumab (CI[e]) [p-value]
	Miri IV/SC[b]	Ustekinumab IV/SC[c]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a]Endoscopic remission is defined as a SES-CD score ≤4 and at least a 2-point reduction in SES-CD score from baseline and no sub-score of each individual variable in any ileocolonic segment >1. [b]Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Ustekinumab dose regimen is ~6mg/kg IV at Week 0, then 90 mg SC Q8W starting at Week 8 [d] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [e] 99.5% CI for Week 12 PAS population, 95% CI for all other risk differences presented.
Abbreviations: BF: biologic-failed; CI: confidence interval; CCF: conventional care failed; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; Q8W: every 8 weeks; SC: subcutaneous; SES-CD: Simple Endoscopic Score-Crohn's disease.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.8.27 (pages 375–376), AMAM.8.35 (pages 602 and 604).[93]

B.3.6.2.5 Other secondary endpoint: EQ-5D-5L VAS change from baseline at Week 12 and Week 52

At Week 12, patients who received mirikizumab in the PAS demonstrated a marginal improvement in patient HRQoL over ustekinumab, as measured by the EQ-5D-5L VAS. LSM change from baseline was [redacted] versus [redacted], respectively. The LSM difference for mirikizumab versus ustekinumab was [redacted] (95% CI: ([redacted]) (Table 29).

This difference in HRQoL improvement widened at Week 52. LSM change from baseline in EQ-5D-5L VAS at Week 52 was [redacted] versus [redacted], for patients who received mirikizumab and ustekinumab, respectively. The LSM difference for mirikizumab versus ustekinumab was [redacted] (95% CI: [redacted]) which was [redacted] ([redacted]) (Table 29).

Table 29: EQ-5D-5L VAS change from baseline (treatment regimen period; PAS population, ANCOVA with mBOCF)

Population	LSM change from baseline (SE)	

	Miri IV/SC[a]	Ustekinumab IV/SC[b]	LSM difference vs ustekinumab (95% CI) [p-value]
Week 12			
PAS	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]

Footnotes: [a] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [b] Ustekinumab dose regimen is ~6mg/kg IV at Week 0, then 90 mg SC Q8W starting at Week 8. Please note that of the [redacted] patients receiving mirikizumab and [redacted] patients receiving ustekinumab in VIVID-1, [redacted] and [redacted] of these patients were used in this analysis for mirikizumab and ustekinumab, respectively.
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; IV: intravenous; LSM: least square mean; mBOCF: modified baseline observation carried forward; Miri: mirikizumab; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous; SE: standard error; VAS: visual analogue scale.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.81 (page 1889, 1891). [93]

B.3.7 Subgroup analysis

The pre-specified subgroup analyses relevant to the decision problem (CCF and BF) are presented in Section B.3.6.

B.3.8 Meta-analysis

A meta-analysis was not conducted as there was no head-to-head comparison between mirikizumab and all comparators within the scope of this submission. A network meta-analysis was conducted and is presented in Section B.3.9.

B.3.9 Indirect and mixed treatment comparisons

In the absence of direct head-to-head data for the comparative efficacy and safety of mirikizumab versus relevant comparators, network meta-analyses (NMAs) were performed and are presented below. As outlined in Section B.1.1, risankizumab was selected as the reference comparator for the cost-comparison analysis presented in this appraisal. However, this NMA was conducted from a Global perspective and thus compared the efficacy and safety of mirikizumab to a broad range of treatments for moderately to severely active CD, some of which are not relevant to the current decision problem. Results versus all treatments included in the NMA are presented for completeness.

As outlined in Section B.3.9.3.1, where the evidence base allowed, efficacy analyses were performed for induction and maintenance timepoints separately for two populations of interest: CCF and BF (Sections B.3.9.4.1 and B.3.9.4.3, respectively). NMAs of safety outcomes were performed for the overall mixed population regardless of prior exposure to biologic therapy due to limitations in reporting by prior therapy as per Consolidated Standard of Reporting Trials (CONSORT)[99] recommendations and at the end of the induction period only, due to heterogeneity in the definition of the 'placebo' safety population within maintenance trials (Section B.3.9.4.4).

B.3.9.1 Identification and selection of relevant studies

The basis for the NMA was an SLR originally conducted in March 2020 which has since been regularly updated every six months to identify newly published studies of interest; the most

recent update was conducted in January 2024. Full details on the methodology and the results of the SLR, including a full list of search dates, are presented in Appendix D.

The objectives of the SLR were to identify all eligible RCT evidence on relevant treatments for patients with moderately to severely active CD. To date, a total of 96 studies were considered for inclusion in the NMA (95 studies from the SLR plus VIVID-1). A summary of the overall SLR search results alongside a PRISMA flow diagram is presented in Appendix D.1.4.1.

B.3.9.2 Feasibility assessment

The comparability of the evidence identified in the SLR was investigated extensively through a NMA feasibility assessment. Heterogeneity with respect to patient characteristics, study design, interventions, and outcomes were assessed and the potential implications of identified differences are summarised in the sections below. Further details on the feasibility assessment are provided in Appendix D.1.6.1.

A summary of the PICO criteria for inclusion of studies in the NMA is provided in Table 30 below.

Table 30: PICO criteria for inclusion of studies into the NMA

	Induction period	Maintenance period
Population(s)	• CCF: Patients who have had an inadequate response to conventional care.[a] • BF: Patients who had previously received at least one biologic and had an inadequate response.[a] • Overall population: Entire population enrolled in the trial, may differ between studies according to their trial eligibility.	
Intervention(s)	MIRI 900 mg	MIRI 300 mg
Comparator(s)[b]	• ADA 160/80 mg • ADA 80/40 mg • CZP 400 mg • IFX 5 mg/kg • NTL 300 mg • UST 6 mg/kg • VED 300 mg • UPA 45 mg • UPA 30 mg • RKZ 600 mg	• ADA 40 mg Q2W • ADA 40 mg QW • ADA 80 mg Q2W • CZP 400 mg • IFX 5 mg/kg • NTL 300 mg • UST 90 mg Q8W • UST 90 mg Q12W • VED 300 mg Q8W • VED 300 mg Q4W • VED 108 mg Q2W • UPA 15 mg • UPA 30 mg • RKZ 180 mg • RKZ 360 mg
Outcome(s)	Efficacy outcomes of interest in the CCF and BF: • Enhanced clinical response (decrease in CDAI ≥100) • Clinical remission (CDAI <150) • Endoscopic response • Endoscopic remission • Mucosal/endoscopic healing	

	• PRO-2 defined response • PRO-2 defined remission Safety outcomes of interest in the overall population: • SAEs • All-cause discontinuations

Footnotes: [a]The CCF and BF populations can be the overall trial population (if trial eligibility specified) or a subgroup of the overall trial population. [b]Comparators of interest for this NMA are EMA and FDA approved doses of biologics for the treatment of moderately to severely active CD.
Abbreviations: ADA: adalimumab; BF: biologic failed; CCF: conventional care failed; CDAI: Crohn's disease activity index; CZP: certolizumab pegol; EMA: European Medicines Agency; FDA: Food and Drug Administration; IFX: infliximab; MIRI: mirikizumab; NMA: network meta-analysis; NTL: natalizumab; PRO-2: patient-reported outcomes; RSK: risankizumab; SAE: serious adverse events; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

B.3.9.2.1 Population

As the patient population criteria of the SLR stipulated that patients must be adults and have moderately to severely active CD, all studies included in the SLR have a patient population relevant for inclusion in the NMA.

A summary of baseline characteristics of patients (such as age, the proportion of males, years since diagnosis, baseline CDAI score, concomitant medications and the site of disease) across studies included in the NMA, by population (CCF or BF) and timepoint (induction or maintenance) is available in Appendix D.1.6.1.

A number of population characteristics have previously been shown to impact placebo response rates within trials of patients with CD, including baseline CDAI score, disease duration, colonic disease, age, concomitant medication and prior exposure to biologic therapy at enrolment.[1, 100-105] To reduce heterogeneity observed across population characteristics discussed above and in anticipation of the VIVID-1 trial populations, subgroup populations from the included studies were considered for the NMAs of efficacy outcomes and were explored as described further in Section B.3.9.3.1. In addition, placebo response rates across trials identified for inclusion in the NMA were explored as described further in Appendix D.1.6.2.

B.3.9.2.2 Study design

Induction

Of the 96 studies identified in the SLR, 35 compared an EMA or FDA approved dosing regimen. Most studies were multi-regional, and all included studies were double-blinded, but differences in sample size and length of induction periods were observed which may introduce bias into the results. SEQUENCE was excluded from induction networks due timepoint assessments being incomparable for induction studies (24 weeks as the earliest available timepoint measurement). It was noted that Targan (1997) reporting on infliximab differed from the remaining studies in terms of study age and that substantial variation in study age is known to introduce heterogeneity. However, Targan (1997) was included in the analysis as exclusion of the study would have caused infliximab to be removed from CCF induction networks. Further discussion is presented in Appendix D.1.5 and Appendix D.1.6.1.

Maintenance

Most maintenance studies were multinational, with one single-centre study identified which was conducted in Japan. All included studies were double-blinded, but substantial differences in sample size were observed. The approach to account for heterogeneity arising from the timepoint of assessment in the maintenance phase is discussed in Appendix D.1.6.1.

Trial design heterogeneity

The identified clinical trials for the maintenance phase can be categorised into two groups: treat-through and re-randomised responder trials.

Patients in treat-through trials are randomised at baseline to either the study drug or a comparator (either another active treatment or placebo), and outcomes are measured multiple times thereafter. VIVID-1 with mirikizumab, ustekinumab and placebo arms, SEAVUE and SEQUENCE are treat-through trials.

Patients in re-randomised responder trials, were either randomised at the start of induction to either study drug or placebo, or all patients received induction therapy with the study drug of interest. After induction was completed, responders on the study drug would be re-randomised at the start of the maintenance period to either continue the study drug or discontinue active treatment in favour of placebo. While there are exceptions, for most studies, re-randomisation into the maintenance phase of a study was thus conditional on response to active treatment during induction. Therefore, patients assigned to placebo arms in re-randomised trials present with different treatment histories as they responded to different induction treatments. Almost half of the re-randomised maintenance studies (5 of 11 included in the NMA) defined response at the end of induction as clinical response (CDAI decrease ≥ 70).

The approach to account for heterogeneity arising from these alternative trial designs is discussed in Appendix D.1.6.1.

B.3.9.2.3 Interventions

Only EMA approved doses and regimens of targeted therapies for the treatment of moderately to severely active CD were included in the NMA. Different dosing arms of the same drug were treated as individual comparators within the NMA. Studies from the SLR that did not meet these criteria were not considered in the NMA feasibility assessment. The list of interventions included in the NMA is presented in Table 40 in Appendix D.1.6.1, and a list of all excluded studies, alongside reasons for exclusion, is provided in Table 39 in Appendix D.1.5.

B.3.9.2.4 Outcomes of interest

Efficacy outcomes

The primary goal of treatment for CD is to induce and maintain remission. Rates of enhanced clinical response and clinical remission are the most consistently reported outcomes across studies and are the most relevant efficacy parameters in CD to allow comparative analysis. Therefore, the NMA evaluated clinical response and remission for both induction and maintenance phases. Note that clinical response and enhanced clinical response, defined as a decrease in CDAI≥70 and a decrease in CDAI≥100, respectively, were not evaluated based on feedback from clinical experts that these no longer represent clinically relevant outcomes. For

this reason, endoscopic response and endoscopic remission were included based on being more clinically meaningful and objective. Further, more recent studies have placed increasing importance on achieving endoscopic response and remission as treatment goals. Therefore, where data availability allowed, the NMA evaluated the following efficacy outcomes at induction and maintenance in the CCF and BF populations:

- Enhanced clinical response (decrease in CDAI≥100)
- Clinical remission (CDAI<150)
- Endoscopic response (SES-CD >50% from baseline or 2-point SES-CD reduction if isolated ileal disease and a baseline SES-CD of 4)
- Endoscopic remission (SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no sub-score greater than 1)

The definitions of the efficacy endpoints of interest for the NMA are consistent across the clinical trials identified. Enhanced clinical response was defined as CDAI decrease ≥100 from baseline in most studies. Five studies differed in their definition of enhanced clinical response, allowing inclusion of patients with CDAI<150 to be considered. Targan (1997) did not report enhanced clinical response outcomes but only reported clinical response (decrease in CDAI≥70). Given the study was the only available source of evidence to connect infliximab to the evidence networks, data transformations were applied using reweighted infliximab CDAI-70 data to estimate CDAI-100 data. The estimated data was used in the base case CCF induction network for enhanced clinical response.

Clinical remission was defined as a CDAI score ≤ 150 across all identified trials. Endoscopic response was defined by all studies reporting it as a 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. Endoscopic remission was described by almost all studies reporting it 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.

Safety outcomes

Aggregate safety endpoints (all-cause discontinuations and incidence of serious adverse events [SAEs]) were considered for the overall population in the induction phase only.

Due to limitations in the reporting of safety outcomes which are most commonly reported for the overall study population (i.e., regardless of prior exposure to biologic therapy), NMAs of safety outcomes were performed for the overall population in a single analysis. In the instance that only serious treatment-emergent AEs (TEAEs) were reported, these data were assumed to be comparable to SAEs and were therefore included.

NMAs of safety outcomes were performed for induction only because of considerable differences across the placebo populations in maintenance that were introduced by differences in trial design. Across these studies, for the maintenance phase, some CD patients were assigned to placebo or active treatment for the full length of the trial (treat-through trials), whereas other patients responding to active treatment after induction were re-randomised to active treatment or placebo (re-randomised). Safety outcomes were reported for the following maintenance populations:

- Active treatment induction remitters
- Active treatment induction responders
- Active treatment induction responders and non-responders
- Patients randomised at baseline only (treat-through study)
- Patients from either the double-blind or open-label phases of the study

As a result, the 'placebo' safety populations of these trials consisted of various 'placebo' patients which differ due to the trial designs mentioned above. Considering all these exposure-related differences among placebo-treated patients, no sound and reliable conclusions could be drawn from any maintenance analyses of safety outcomes. Thus, NMAs of safety outcomes following maintenance treatment were not performed.

B.3.9.2.5 Summary of trials included in the NMA

Included studies

Including the VIVID-1 trial, a total of 26 studies were considered for inclusion in the NMA; 22 induction studies (Table 31) and 14 maintenance studies (Table 32). During the induction study period, 18 studies reported data for at least one efficacy outcome for the CCF population, and 18 studies reported data for at least one efficacy outcome for the BF population. Further, 20 studies reported data for at least one safety outcome for the overall population (regardless of prior biologic exposure). For the maintenance study period, 11 and 9 studies reported data for at least one efficacy outcome for the CCF and BF populations, respectively.

The studies included in the induction and maintenance NMAs, and their full publication references, are provided in Tables 33 and 34 in Appendix D.1.5, respectively, and an overview of these included studies by population and outcome of interest is presented in Table 35 (induction) and Table 36 (maintenance) in Appendix D.1.5. Summaries of how the studies included in the NMA defined the presented study population(s) by prior biologic therapy use are presented in Table 37 (induction) and Table 38 (maintenance) in Appendix D.1.5. A summary of the patient baseline characteristics for patients in the CCF and BF populations is presented in Section 1.2 of the NMA report appendices in the reference pack.

Table 31: Overview of studies included by population and outcome of interest, Induction NMAs

Study	Intervention	Included for CCF population?	Included for BF population?	Included for overall (mixed[a]) population (safety)?
ADVANCE	RKZ	✓	✓	✓
CLASSIC I	ADA	✓	–	✓
Faegan 2017	RKZ	–	–	✓
GAIN	ADA	–	✓	✓
GALAXI 1	UST	✓	✓	✓
GEMINI 2	VDZ	✓	✓	✓
GEMINI 3	VDZ	✓	✓	✓
MOTIVATE	RKZ	–	✓	✓
Sandborn 2012	UST	–	✓	✓[c]
SEAVUE	UST/ADA	✓	–	–
Targan 1997	IFX	✓[d]	–	–
U-EXCEED	UPA	–	✓	✓
U-EXCEL Study	UPA	✓	–	✓
UNITI 1	UST	–	✓	✓
UNITI 2	UST	✓	–	✓[c]
VIVID-1	UST/MIRI	✓	✓	✓
Watanabe 2011	ADA	✓	✓	✓
Watanabe 2020	VDZ	✓	✓	✓

Footnotes: [a] Mixed population with regards to prior medication. [b] Studies were not included in base case analysis. [c] Different timepoint of assessment for efficacy data and safety data, ENACT 1 assessed safety data at week 12, Sandborn 2012 and UNITI 2 assessed safety data at week 8. [d] Original CDAI decrease ≥100 outcome data for IFX is not available, included in the base case by reweighting available CDAI decrease ≥70 data, as described in the RKZ NICE submission.
Abbreviations: ADA: adalimumab; BF: biologic failure; CCF: conventional care failure; Clin REM: clinical remission; Clin RES: enhanced clinical response; CZP: certolizumab; disc.: discontinuation; Endo REM: endoscopic remission; Endo RES: endoscopic response; IFX: infliximab; MIRI: mirikizumab; NMA: network meta-analysis; NTL: natalizumab; RKZ: risankizumab; SAE: serious adverse events; TNF: tumour necrosis factor; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 32: Overview of studies included by population and outcome of interest, Maintenance NMAs

Study	Intervention	Maintenance period (weeks)	Study design	Included for CCF population?	Included for BF population?
ACCENT I	IFX	52	RR	✓	
CHARM	ADA	52	RR	✓	✓
FORTIFY	RKZ	52	RR	✓[a]	✓
GEMINI 2	VDZ	46	RR	✓[a]	✓
IM UNITI	UST	44	RR	✓	✓
SEAVUE	UST/ADA	44	TT	✓	
U-ENDURE	UPA	52	RR	✓[a]	✓
VISIBLE 2	VDZ	46	RR	✓[a]	✓
VIVID-1	UST/MIRI	40	TT	✓	✓

Watanabe 2020	VDZ	46	RR	✓[a]	✓

Footnotes: [a] Studies not included in base case analysis as disconnected from network with MIRI
Abbreviations: ADA: adalimumab; BF: biologic failure; CCF: conventional care failure; Clin REM: clinical remission; Clin RES: enhanced clinical response; disc.: discontinuation; Endo REM: endoscopic remission; Endo RES: endoscopic response; IFX: infliximab; MIRI: mirikizumab; RKZ: risankizumab; RR: re-randomised; TT: treat-through; TNF: tumour necrosis factor; UST: ustekinumab; VED: vedolizumab.

Excluded studies

As described in Section B.3.9.1, the SLR identified 95 unique studies; including the VIVID-1 trial, 96 studies were considered for inclusion in the NMA. Following the NMA feasibility assessment, 60 studies were excluded due to outcome, treatment or dosage not being of interest. Six further studies were excluded following the similarity assessment, due to differences in patient characteristics, study characteristics and design, and outcomes measure, as the identified respective differences were thought to violate the similarity assumptions which are necessary to perform an NMA. In addition, four studies which evaluated FDA-only approved dosing regimen were excluded. A list of excluded studies, including further details of reasons for exclusion by study, is presented in Table 39 in Appendix D.1.5.

B.3.9.3 Methodology

All NMAs were conducted under a Bayesian framework in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2, using binomial models with logit link for all outcomes.[106] For each analysis (summarised in Table 33) both fixed effects and random-effects models were considered, and models with and without baseline risk adjustment were fitted in recognition of differences in placebo response observed across trials. Results from the best fitting model (according to pre-defined model performance criteria) are reported for each outcome, population and timepoint combination. The selection of the main model presented was based on the inspection of model fit statistics, convergence diagnostics, and assessment of model performance. In several models, where model selection criteria were ambiguous and inconsistent with direct evidence, such as active treatments no longer differentiating from placebo, or were uninterpretable, such as presenting with very large credible intervals, another model was preferred.

Full descriptions of the statistical methods employed in the NMA, including the fixed and random effects models considered, the multinomial and binomial statistical models employed, and discussion of model convergence and selection, are presented in Appendix D.1.10.

Table 33: NMA models used in the base case analysis

Population	Timepoint	Outcome	Statistical model
CCF	Induction	Enhanced clinical response[a]	Fixed effects **with** baseline risk adjustment
		Clinical remission	Fixed effects **with** baseline risk adjustment
		Endoscopic response	Fixed effects **without** baseline risk adjustment
		Endoscopic remission	Fixed effects **without** baseline risk adjustment
	Maintenance	Clinical remission	Fixed effects **without** baseline risk adjustment

BF	Induction	Enhanced clinical response	Fixed effects **without** baseline risk adjustment
		Clinical remission	Fixed effects **without** baseline risk adjustment
		Endoscopic response	Fixed effects **with** baseline risk adjustment
		Endoscopic remission	Fixed effects **without** baseline risk adjustment
	Maintenance	Clinical remission	Fixed effects **without** baseline risk adjustment
Overall/mixed population	Induction	SAEs	Random effects **without** baseline risk adjustment
		All-cause discontinuations	Random effects **without** baseline risk adjustment

Footnotes: Reported definitions "No biologic failure", "tumour necrosis factor (TNF) naïve", "biologic naïve" were grouped under CCF; "TNF experienced" and "TNF failure" were grouped under BF; overall population with regards to prior medication. Note that base case NMAs will include only EMA-approved treatment regimens.
[a] Studies of infliximab do not report enhanced clinical response (CDAI decrease ≥100) data. Hence, the base case will include reweighted infliximab data for CDAI decrease ≥70 using the average relative difference from CDAI 100 observed for other comparators, as described in the risankizumab National Institute for Health and Care Excellence (NICE) submission.[1]
Abbreviations: BF: biologic failure; CCF: conventional care failure; NMAs: network meta-analyses; SAEs: serious adverse events.

B.3.9.3.1 Subgroup analyses

Where the evidence base allowed, efficacy analyses were performed for induction and maintenance timepoints separately for the two populations of interest: conventional care failure (CCF) and biologic failure (BF). These subgroups were defined as follows:

- Conventional care failure (CCF): Patients who have had an inadequate response, loss of response or intolerance to conventional care. This could be the overall trial population (if trial eligibility specified) or a subgroup of the overall trial population.
- Biologic failure (BF): Patients who had previously received at least one biologic and had an inadequate response, loss of response or intolerance to biologics. This could be the overall trial population (if trial eligibility specified) or a subgroup of the overall trial population.

NMAs of safety outcomes were performed for the overall mixed population regardless of prior exposure to biologic therapy due to limitations in reporting by prior therapy as per CONSORT[99] recommendations and at the end of the induction period only, due to heterogeneity in the definition of the 'placebo' safety population within maintenance trials.

B.3.9.4 Results

The results of the NMAs are presented by timepoint (induction or maintenance) and by efficacy outcome. In each subsection, pairwise odds ratios (ORs) and 95% credible intervals (CrIs) are presented. A network diagram, input data tables, summary of model fit statistics and forest plots of ORs and 95% CrIs versus placebo are presented in Appendix D.1.10.1 (efficacy outcomes, conventional care-failed population), D.1.10.2 (efficacy outcomes, biologic-failed population) and D.1.10.3 (safety outcomes, overall population). Further stand-alone scenario and sensitivity analyses may be available from Eli Lilly upon request.

B.3.9.4.1 Summary of efficacy outcomes: mirikizumab versus risankizumab

As risankizumab is the primary comparator for mirikizumab presented in this submission, a summary of the efficacy and safety outcomes for mirikizumab and risankizumab from the NMA is presented below in Table 34. No statistically significant differences between the two treatments were identified for any of the outcomes or populations considered.

Table 34: Summary of efficacy outcomes from the NMA in the CCF and BF populations

	Mirikizumab vs. risankizumab[a], pairwise OR (95% CrI)	
	CCF	BF
Induction period		
Enhanced clinical response (decrease CDAI ≥100)	0.90 (0.57, 1.40)	0.79 (0.48, 1.33)
Clinical remission (CDAI <150)	0.68 (0.38, 1.29)	0.71 (0.40, 1.23)
Endoscopic response	0.46 (0.18, 1.17)	0.85 (0.49, 1.51)
Endoscopic remission	0.73 (0.27, 2.00)	1.63 (0.39, 11.4)
Serious adverse events	2.36 (0.92, 6.67)	
All-cause discontinuation	1.63 (0.52, 5.74)	
Maintenance period		
Clinical remission (CDAI <150)	2.29 (0.63, 8.29)	1.68 (0.56, 5.07)

[a] Risankizumab 600 mg for induction; 360 mg for maintenance.
Abbreviations: BF: biologic failed; CF: conventional care failed; CDAI: Crohn's disease activity index; NMA: network meta-analysis.

B.3.9.4.2 Efficacy outcomes (conventional care-failed population)

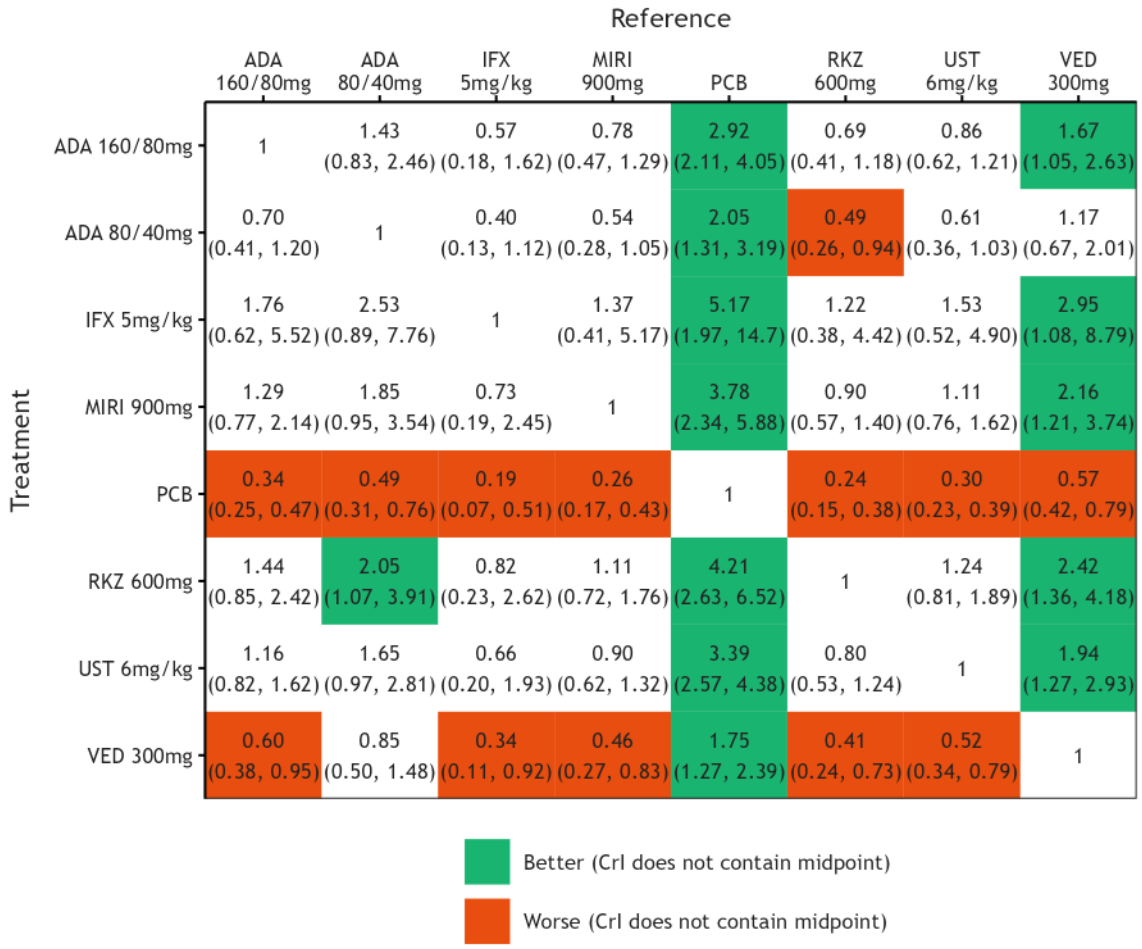
Induction

Enhanced clinical response (decrease in CDAI ≥100)

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for enhanced clinical response during the induction period for the CCF population are presented in Appendix D.1.10.1.1. Results for enhanced clinical response during the induction period for the CCF population described in this section were derived from a fixed effect model with baseline risk adjustment.

All interventions presented statistically significant improvements in the rate of clinical response over placebo. Furthermore, mirikizumab achieved a statistically significant benefit compared to vedolizumab and was not statistically significantly different to all other active comparators (Figure 21).

Figure 21: All pairwise odds ratios versus placebo for the fixed treatment effect model with baseline risk adjustment: Enhanced Clinical Response, Induction, CCF Population



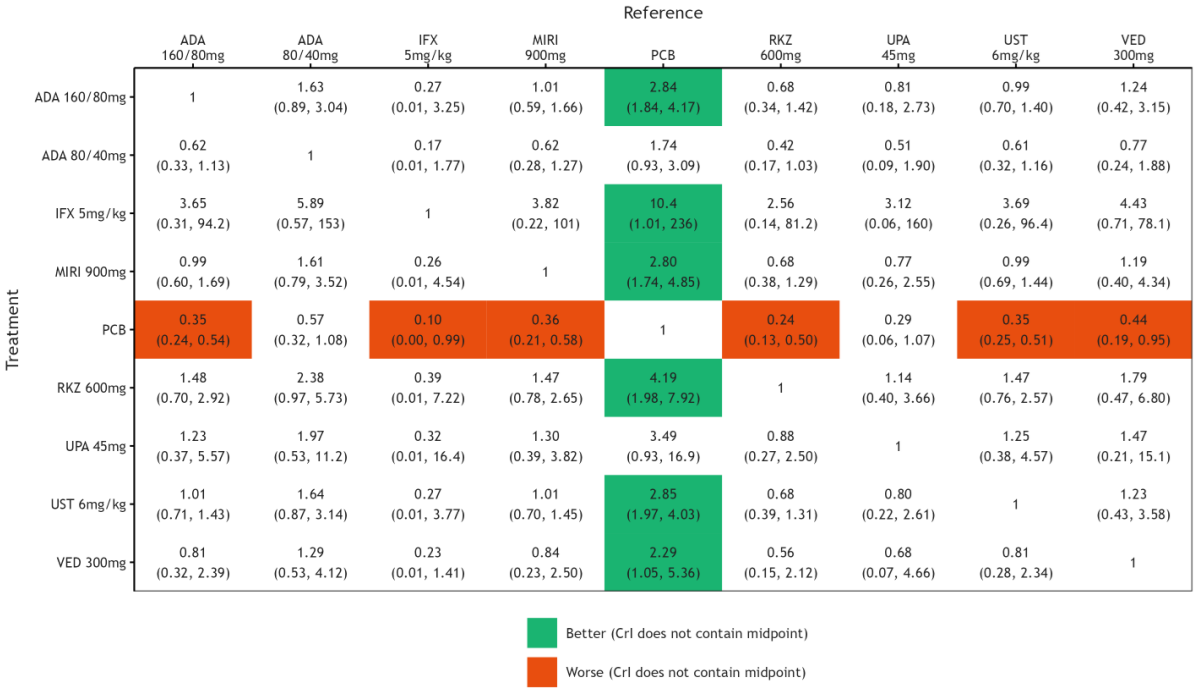
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; IFX: infliximab; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UST: ustekinumab; VED: vedolizumab.

Clinical remission (CDAI <150)

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical remission during the induction period for the CCF population are presented in Appendix D.1.10.1.2. As described further in Appendix D. 1.10.1.2, results for clinical remission during the induction period for the CCF population described in this section were derived from the fixed effect model with baseline risk adjustment.

All interventions except for upadacitinib 45mg and adalimumab 80/40mg offered significant improvements in the rate of clinical remission over placebo (Figure 22). There were no statistically significant differences between any of the active treatments.

Figure 22: All pairwise odds ratios for the fixed treatment effect model with baseline risk adjustment: Clinical Remission, Induction, CCF Population



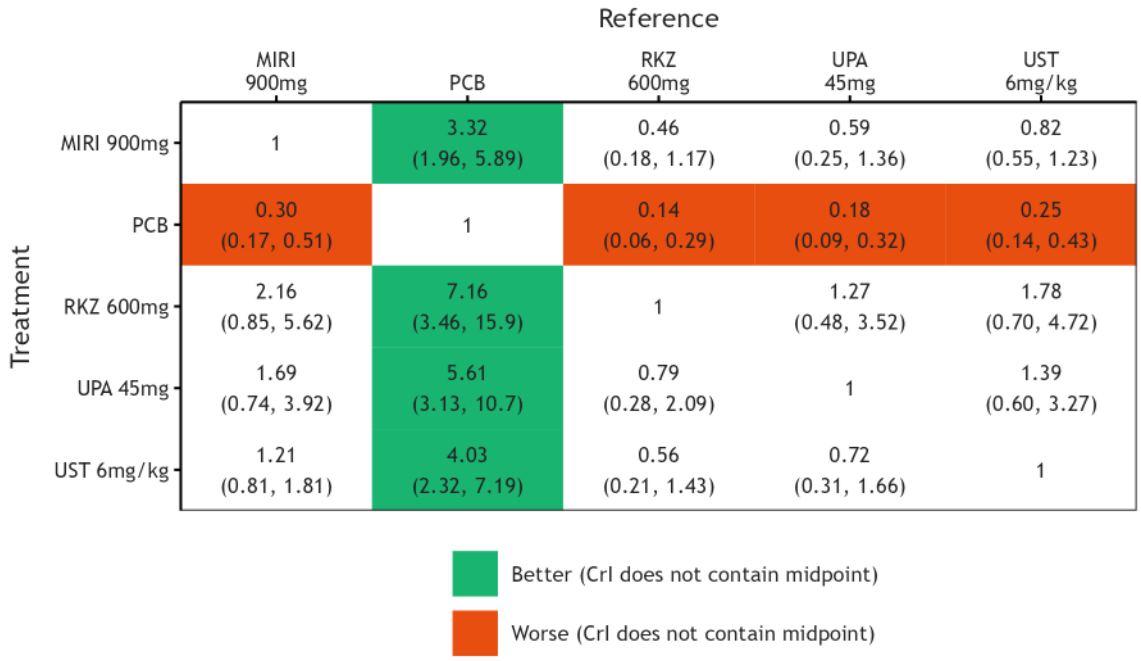
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; IFX: infliximab; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Endoscopic response

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for endoscopic response during the induction period of the CCF population are presented in Appendix D.1.10.1.3. As described further in Appendix D.1.10.1.3, results for endoscopic response during the induction period for the CCF population described in this section were derived from the fixed effect model without baseline risk adjustment.

All interventions offered significant improvements in the rate of endoscopic response over placebo (Figure 23). No statistically significant differences between the active treatments were observed. It should be noted that the low number of placebo responders (n=3) in the GALAXI 1 trial likely complicated the estimation of the ustekinumab OR, and therefore a high level of uncertainty is observed.

Figure 23: All pairwise odds ratios for the fixed treatment effect model: Endoscopic Response, Induction, CCF Population



ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.

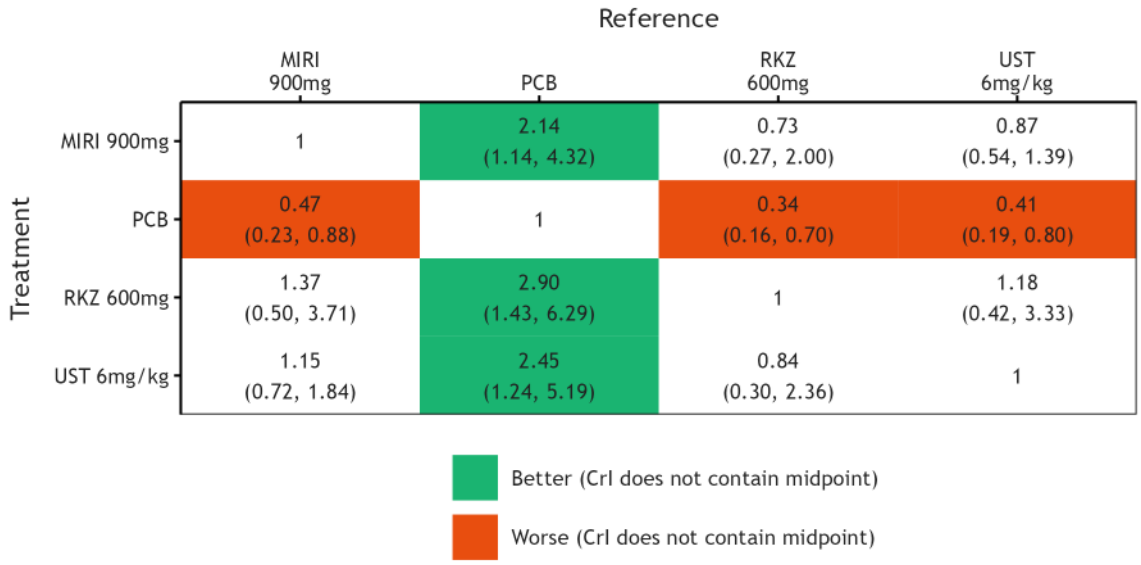
Abbreviations: MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab.

Endoscopic remission

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for endoscopic remission during the induction period of the CCF population are presented in Appendix D.1.10.1.4. As described further in Appendix D.1.10.1.4, results for endoscopic remission during the induction period for the CCF population described in this section were derived from the fixed effect model without baseline risk adjustment.

All interventions offered significant improvements in the rate of endoscopic remission over placebo (Figure 24). No statistically significant differences between the active treatments were observed.

Figure 24: All pairwise odds ratios for the fixed treatment effect model: Endoscopic Remission, Induction, CCF Population



ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UST: ustekinumab.

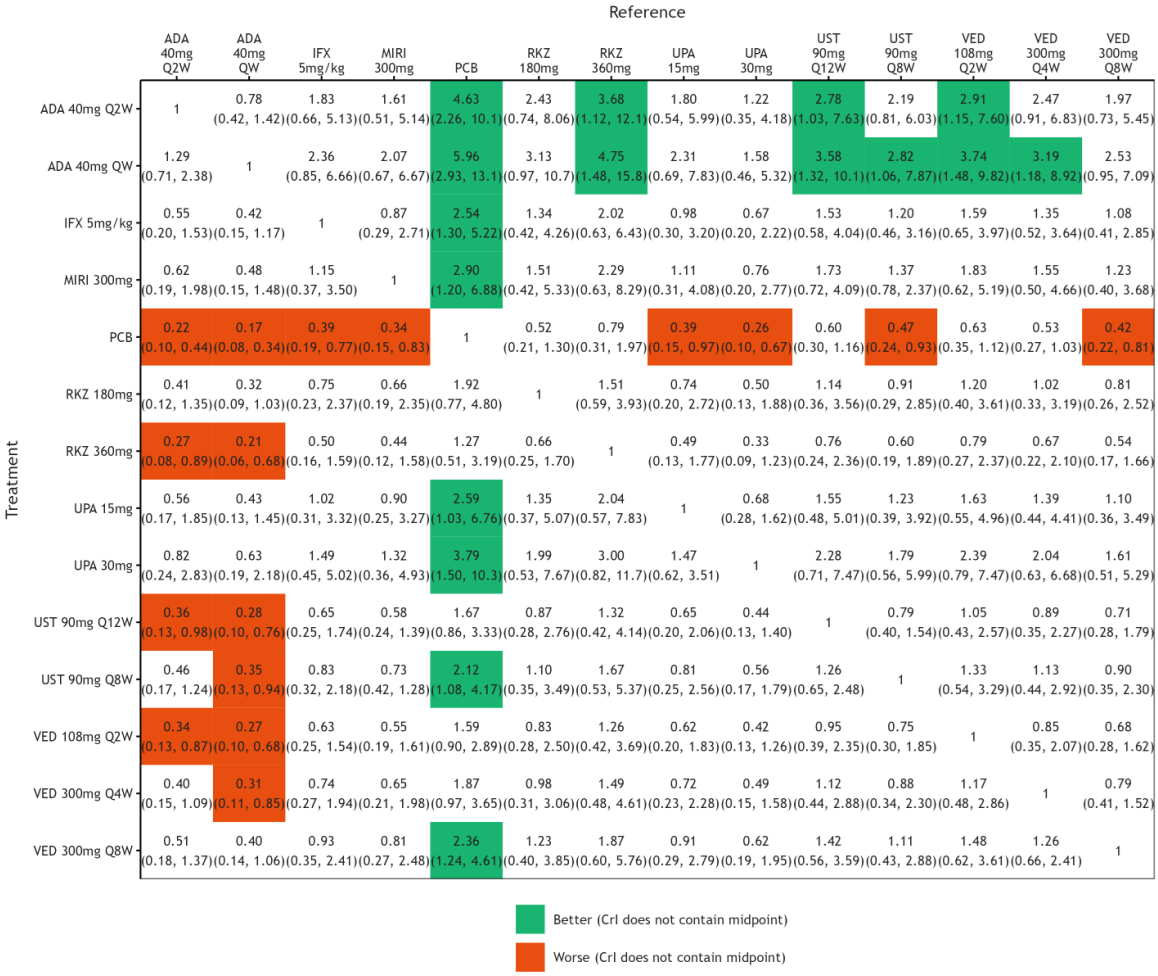
Maintenance

Clinical remission (CDAI <150)

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical remission during the maintenance period of the CCF population are presented in Appendix D.1.10.1.5. As described further in Appendix D.1.10.1.5, results for clinical remission during the maintenance period for the CCF population described in this section were derived from the fixed effect model without baseline risk adjustment.

Most interventions except for risankizumab 180mg and 360mg, vedolizumab 300mg Q4W and 108mg Q2W, and ustekinumab 90mg Q12W offered statistically significant improvements in the rate of clinical remission over placebo. Adalimumab 40mg Q2W and QW performed statistically significantly better than risankizumab 360mg, ustekinumab 90 mg Q12W and vedolizumab 108mg Q2W; in addition, adalimumab 40 mg QW also performed statistically significantly better than ustekinumab 90 mg Q8W and vedolizumab 108mg Q4W. No other statistically significant differences between active treatments were observed (Figure 25).

Figure 25: All pairwise odds ratios for the fixed treatment effect model: Clinical Remission, Maintenance, CCF Population



ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; IFX: infliximab; MIRI: mirikizumab; PCB: placebo; RKZ: Risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

B.3.9.4.3 Efficacy outcomes (biologic failure population)

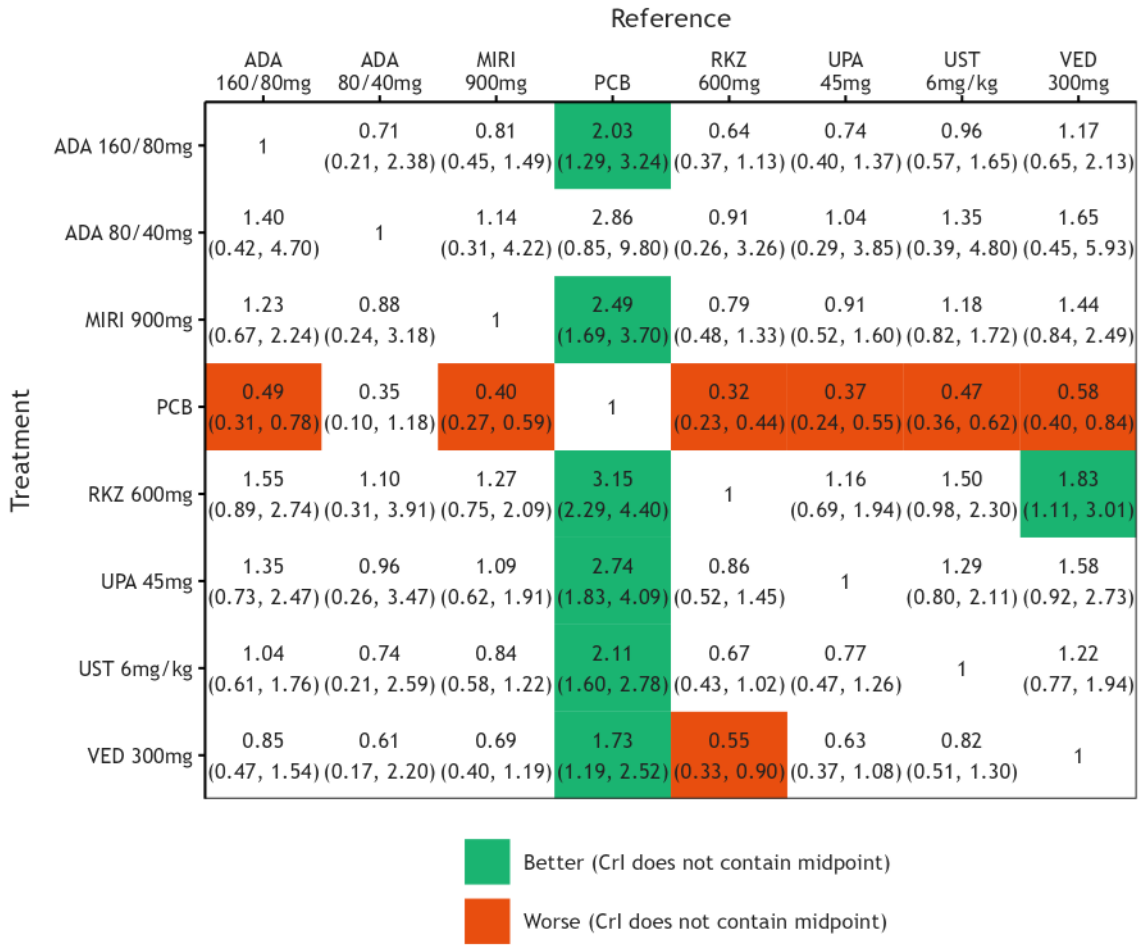
Induction

Enhanced clinical response (decrease in CDAI ≥100)

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for enhanced clinical response during the induction period of the BF population are presented in Appendix D.1.10.2.1. As described further in Appendix D.1.10.2.1, results for enhanced clinical response during the induction period for the BF population described in this section were derived from the fixed effect model.

All interventions except for adalimumab 80/40mg offered statistically significant improvements in the rate of enhanced clinical response over placebo (Figure 26). There were no statistically significant differences between mirikizumab and any of the active treatments.

Figure 26: All pairwise odds ratios for the fixed treatment effect model: Enhanced Clinical Response, Induction, BF Population



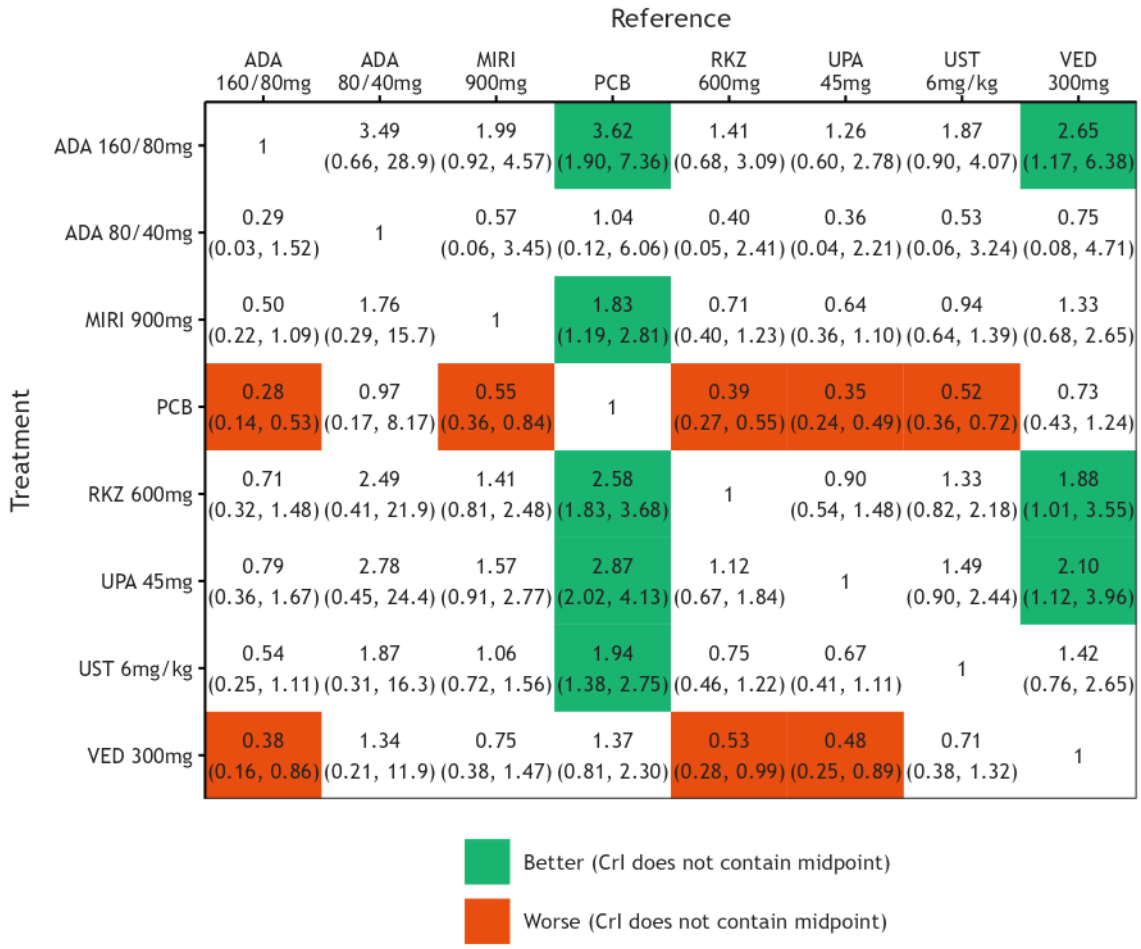
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Clinical remission (CDAI <150)

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical remission during the induction period of the BF population are presented in Appendix D.1.10.2.2. As described further in Appendix D.1.10.2.2, results for clinical remission during the induction period for the BF population described in this section were derived from the fixed effect model.

All interventions except for adalimumab 80/40mg and vedolizumab 300mg offered statistically significant improvements in the rate of clinical remission over placebo (Figure 27). There were no statistically significant differences between mirikizumab and any of the active treatments.

Figure 27: All pairwise odds ratios for the fixed treatment effect model: Clinical Remission, Induction, BF Population



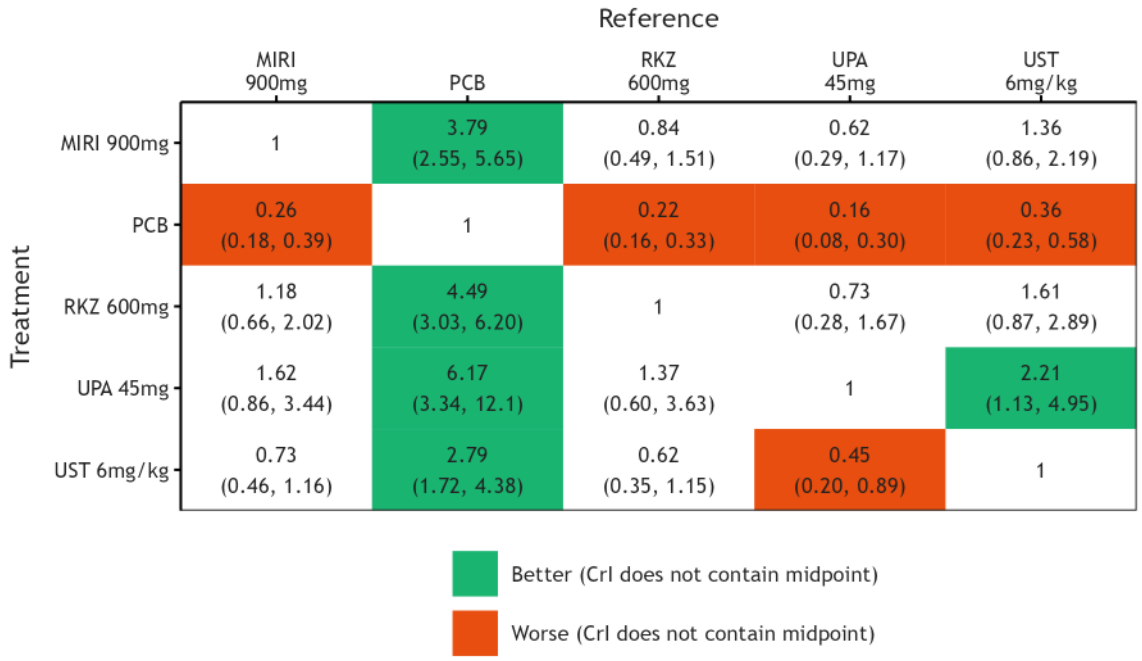
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Endoscopic response

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for endoscopic response during the induction period of the BF population are presented in Appendix D.1.10.2.3. As described further in Appendix D.1.10.2.3, results for endoscopic response during the induction period for the BF population described in this section were derived from the fixed effect model with baseline risk adjustment.

All interventions offered statistically significant improvements in the rate of endoscopic response over placebo (Figure 28). There were no statistically significant differences between mirikizumab and any of the active treatments.

Figure 28: All pairwise odds ratios for the fixed treatment effect model with baseline risk adjustment: Endoscopic Response, Induction, BF Population



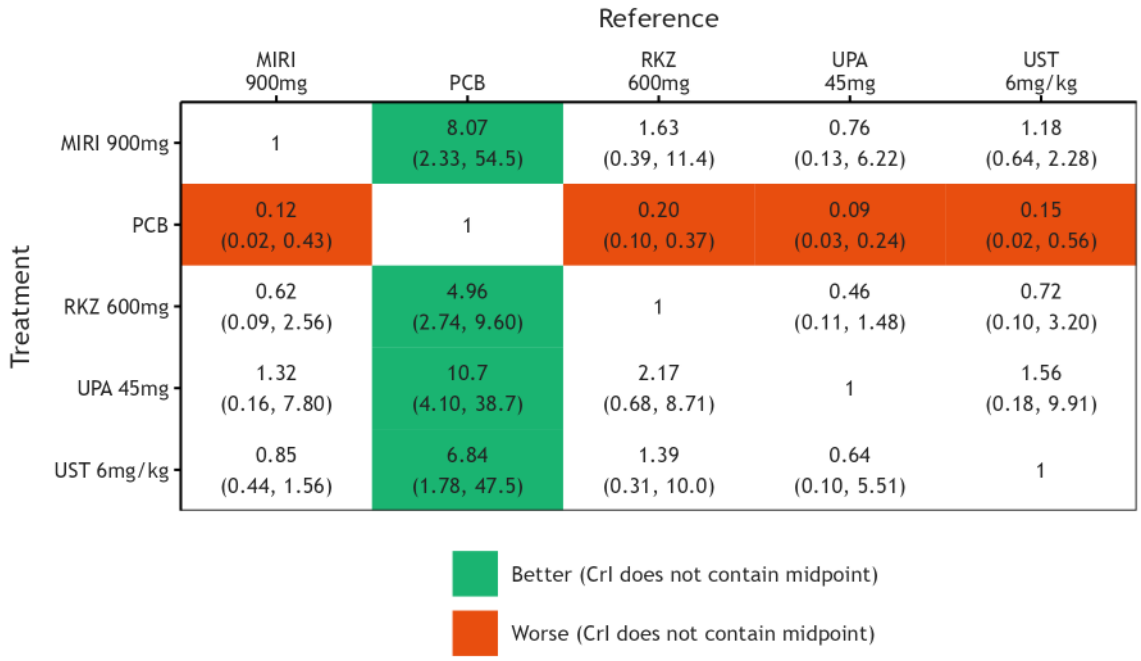
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab.

Endoscopic remission

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for endoscopic remission during the induction period of the BF population are presented in Appendix D.1.10.2.4. As described further in Appendix D.1.10.2.4, results for endoscopic remission during the induction period for the BF population described in this section were derived from the fixed effect model.

All interventions offered statistically significant improvements in the rate of endoscopic remission over placebo (Figure 29). There were no statistically significant differences between any of the active treatments.

Figure 29: All pairwise odds ratios for the fixed treatment effect model: Endoscopic Remission, Induction, BF Population



ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab.

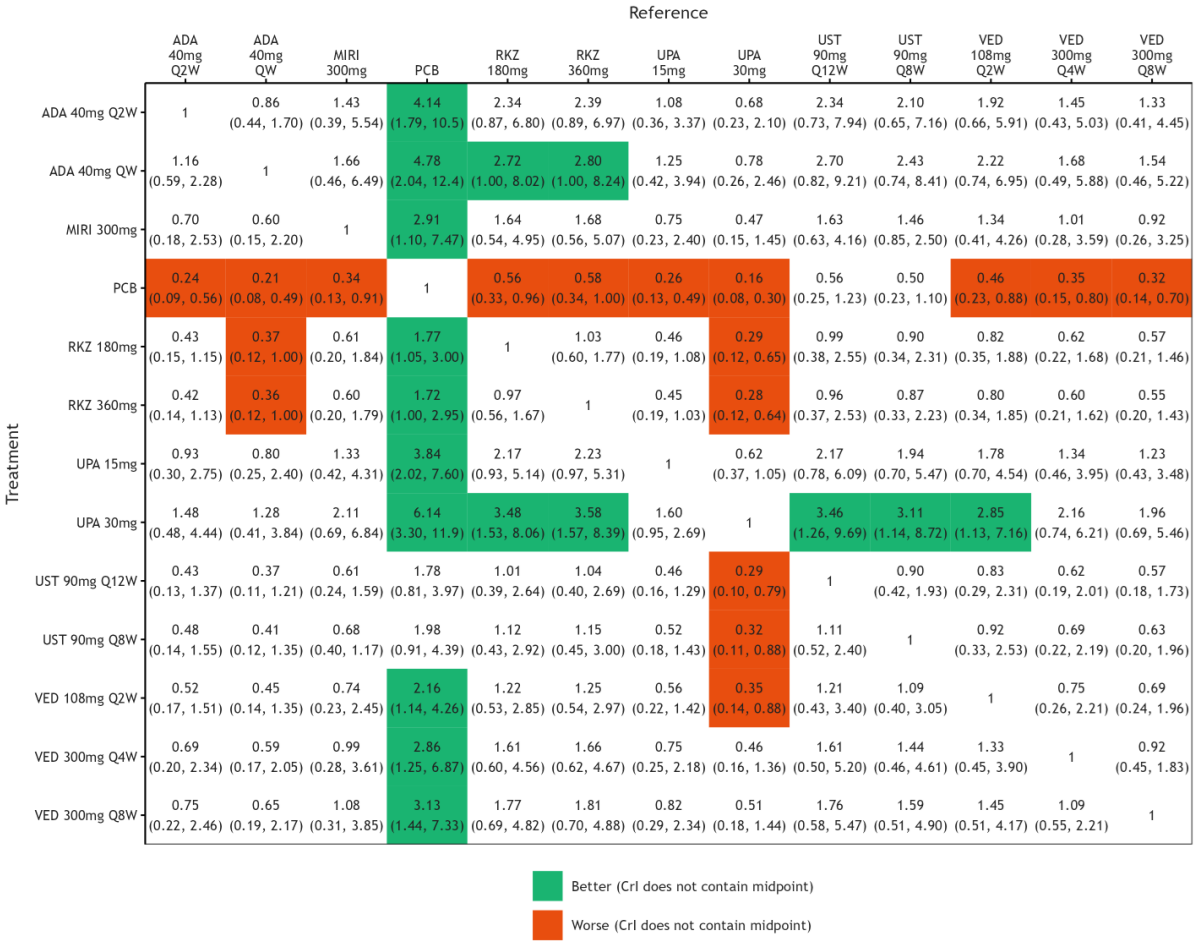
Maintenance

Clinical remission (CDAI <150)

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical remission during the maintenance period of the BF population are presented in Appendix D.1.10.2.5. As described further in Appendix D.1.10.2.5, results for clinical remission during the maintenance period for the BF population described in this section were derived from the fixed effect model without baseline risk adjustment.

All interventions except for ustekinumab 90mg Q8W and Q12W offered statistically significant improvements in the rate of clinical remission over placebo (Figure 30). Adalimumab 40mg QW performed statistically significantly better than risankizumab 180mg and 360mg, and upadacitinib 30mg performed statistically significantly better than risankizumab 180mg, risankizumab 360mg, ustekinumab 90mg Q12W, ustekinumab 90mg Q8W, and vedolizumab 108mg Q2W. All other differences between the active treatments were non-significant (Figure 30).

Figure 30: All pairwise odds ratios for the fixed treatment effect model: Clinical Remission, Maintenance, BF Population



ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

B.3.9.4.4 Safety outcomes (overall mixed population)

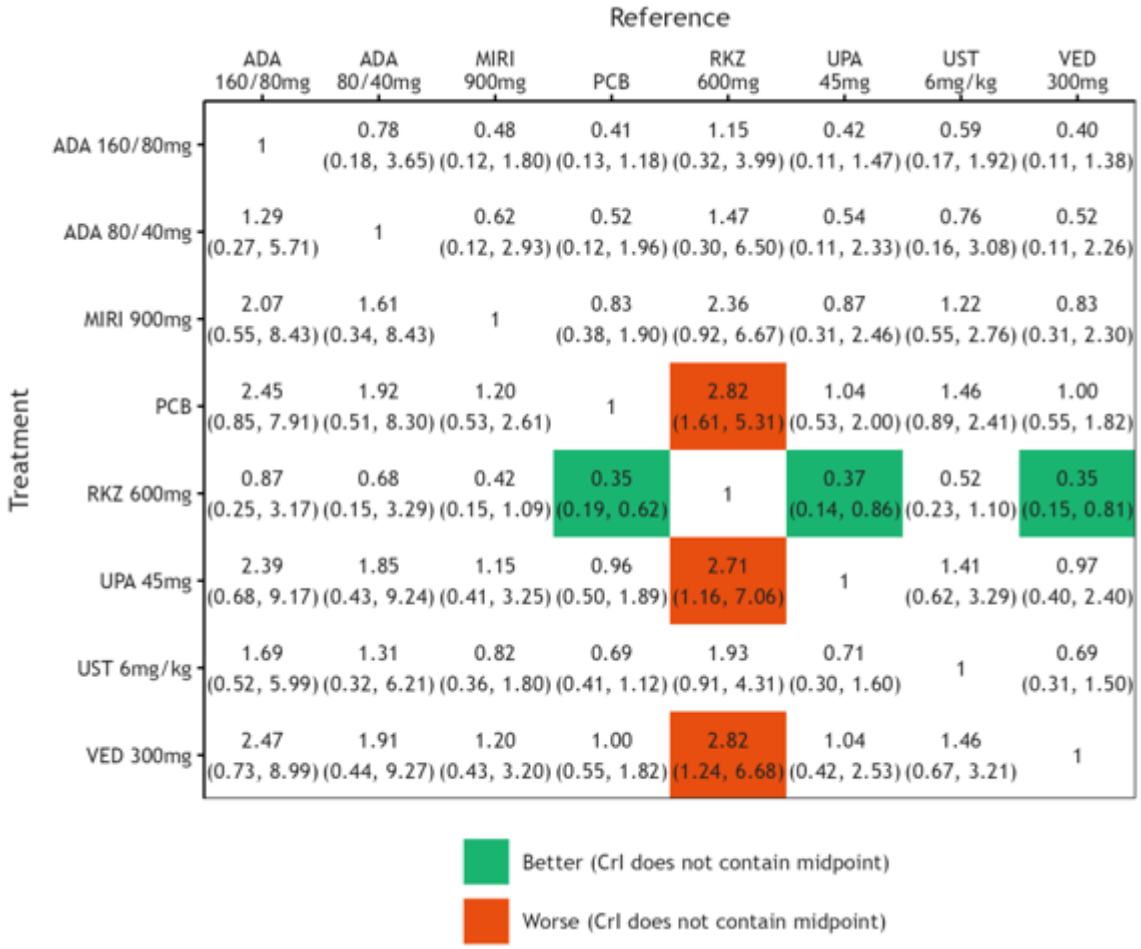
Induction

Serious adverse events

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for SAEs during the induction period of the overall population are presented in Appendix D.1.10.3.1. As described further in Appendix D.1.10.3.1, results for SAEs during the induction period for the overall population described in this section were derived from the random effect model without baseline risk adjustment.

Most treatments did not show statistically significant differences in terms of SAEs over placebo with the exception of risankizumab (Figure 31). Only risankizumab performed significantly better than active treatments upadacitinib 45 mg and vedolizumab 300 mg (Figure 31).

Figure 31: All pairwise odds ratios for the random treatment effect model: SAEs, Induction, Mixed Population



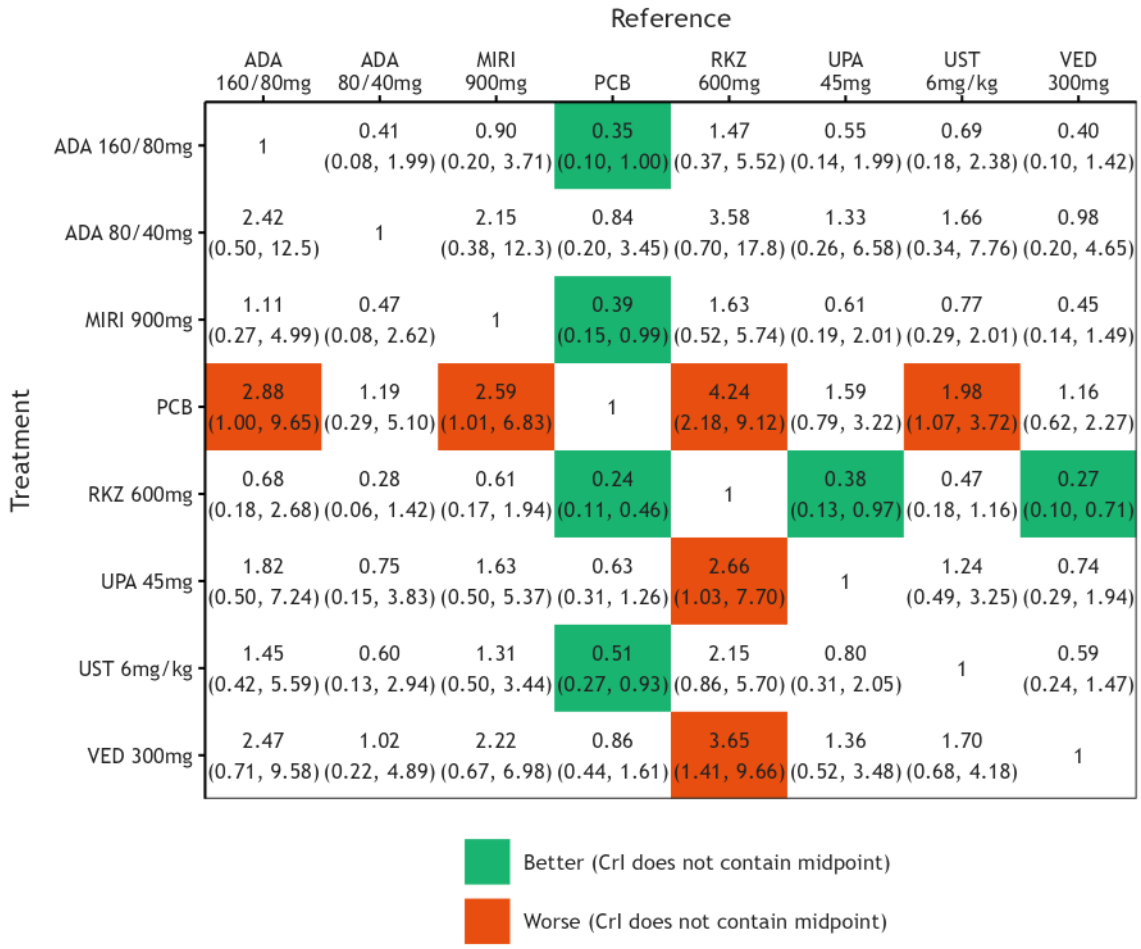
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

All-cause discontinuation

The network diagram, model fit statistics, input data and ORs for all active treatments, including mirikizumab, versus placebo for all-cause discontinuation during the induction period of the overall population are presented in Appendix D.1.10.3.2. As described further in Appendix D.1.10.3.2, results for all-cause discontinuation during the induction period for the overall population described in this section were derived from the random effects model.

Adalimumab 80/40mg, upadacitinib 45 mg and vedolizumab 300 mg did not show statistically significant differences in terms of all-cause discontinuation compared to placebo, while adalimumab 160/80mg, mirikizumab 900 mg, risankizumab 600 mg and ustekinumab 6 mg/kg showed statistically significant differences for all-cause discontinuation compared to placebo (Figure 32). Most of the active treatments did not show a statistically significant difference compared to each other, except for risankizumab 600 mg, which performed better compared to upadacitinib 45 mg and vedolizumab 300 mg (Figure 32).

Figure 32: All pairwise odds ratios for the random treatment effects model: All-cause Discontinuation, Induction, Mixed Population



ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment. CrI not containing midpoint corresponds to a >95% probability of statistical significance.
Abbreviations: ADA: adalimumab; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons

There were several limitations of note to the analyses reported in the sections above. The primary challenge relates to the included studies having one of two distinct trial designs: treat-through or re-randomised. Generally, the interpretation of a maintenance network including studies with different study designs is challenging, due to the various data adjustments that are required to allow for statistical comparison between the different types of studies, but also as the underlying trial designs aim to answer different research questions. Therefore, the interpretation of results of such analyses should be made with caution, ensuring that the underlying differences are carefully considered.

In re-randomised studies, generally only induction responders continue to maintenance, while in treat-through trials both responders and non-responders proceed to maintenance. Therefore the populations in the maintenance phase differ between these trial designs.

To allow for comparison, maintenance data of treat-through studies needed to be adjusted to mimic a re-randomised trial design; this approach has previously been followed and accepted by HTA bodies, for example in UC.[107] The implemented method to combine results from re-randomised and treat-through study designs adapted maintenance outcomes among induction responders. While during this adaptation randomisation was broken, the propensity score matching required individual patient data that were available only for VIVID-1 data, not allowing an analysis of all relevant comparators.

Additional NMAs were conducted for treat-through studies only (see Appendix D.1.10.1.6) in attempt to explore the uncertainty associated with adjusting across study designs. The results from these networks were reflective of the base case analyses for both induction and maintenance periods. The subsequent networks were very small (two studies) and all models (fixed and random effects) were associated with wide CrI. As such, while no significant differences were observed between the analysed interventions in these treat-through NMAs, any results from these analyses should be interpreted with caution.

An additional challenge for the composition of maintenance networks was the absence of a comparable placebo arm in the maintenance phase in VIVID-1, since only induction responders were allowed to continue on placebo into maintenance. Connection to networks was therefore limited to common ustekinumab arms, considerably limiting the feasible networks in the maintenance NMAs.

Limitations were further introduced by the underlying evidence base and despite a comprehensive preparation, not all assumptions could be explored ahead of the analyses. As there were a limited number of clinical studies available per treatment, results in the NMA may have been driven by studies or study arms with low patient numbers or high placebo rates. Additionally, in the induction networks for the BF population for enhanced clinical response and remission, odds ratios for adalimumab 80/40mg showed high uncertainty with very wide CrI, and did not differentiate from placebo; presumably driven by small patient numbers and the low number of events in the placebo arm in the trial reported in Watanabe (2011). In the induction safety networks for the overall population, the results observed for risankizumab may be driven by the ratio of patient numbers in the active compared to the placebo arm and the related relative event numbers (see input data in Tables 73 and 75 in Appendix D.1.10.3).

Despite these sources of heterogeneity, the thorough feasibility assessment performed, and methodological approach adopted as part of this analysis are considered to be strengths of the NMA. A rigorous SLR was performed and updated on a regular basis to ensure the most up to date and relevant comparators, studies, and outcomes were captured, and all results were assessed in separate networks for CCF and BF patients, to reduce heterogeneity in the networks of evidence. Additionally, as outlined in Section B.3.9.3, model selection was based on model fit statistics, convergence diagnostics, and assessment of model performance, and all analyses were performed with and without a baseline risk adjusted meta-regression approach following the methodology recommend by NICE.[108] Evaluating the models under different assumptions and statistical approaches reinforced the results of the network.

B.3.9.6 Conclusions

Overall, the results of the NMA broadly indicate similar performance across advanced therapies available for the treatment of moderately to severely active CD and showed their superiority compared to placebo. Mirikizumab demonstrated comparable performance to the other advanced

treatments across all endpoints in both CCF and BF population at both induction and maintenance. In the absence of head-to-head studies for most active treatments, these results provide supportive evidence to inform the relative efficacy of mirikizumab versus relevant comparators and support the assumption that mirikizumab offers a clinical benefit that is comparable to that of currently available comparators, including risankizumab, ustekinumab and vedolizumab, in both the induction and maintenance phases of treatment.

B.3.10 Adverse reactions

Summary of key safety outcomes from the VIVID-1 trial

- The frequencies of treatment-emergent adverse events (TEAEs) in the mirikizumab-treated patients of VIVID-1 were similar to those for patients receiving placebo or ustekinumab across both the induction period and the treatment regimen period.
- The majority of TEAEs observed being mild to moderate in nature in all treatment arms in both the induction period and the treatment regimen period.
- Frequencies of serious adverse events (SAEs) were similar for both mirikizumab and ustekinumab, but there was a higher frequency of SAEs observed in the placebo group across both the induction period and the treatment regimen period.
- Treatment discontinuation due to an AE were similar for both mirikizumab and ustekinumab, but there was a higher frequency of discontinuations due to an AE observed in the placebo group across both the induction and treatment regimen period.
- [redacted] deaths occurred throughout the study: [redacted] deaths in the placebo arm ([redacted] in the induction period and [redacted] in the maintenance period) and [redacted] in the ustekinumab arm (in [redacted] in the treatment regimen period).

Induction period

- During the induction period (Week 0–12), the frequencies of AEs were higher in the placebo group than in the mirikizumab group.
- The proportion of patients experiencing one or more TEAE was [redacted]% in the placebo arm, compared to [redacted]% in the mirikizumab arm and [redacted]% in the ustekinumab arm, with the majority of TEAEs being mild to moderate in nature.
- There was a higher proportion of patients in the placebo group who experienced a SAE ([redacted]%) compared to the mirikizumab group ([redacted]%) and ustekinumab group ([redacted]%).
- Few patients discontinued treatment due to an AE with similar proportions of patients discontinuing the study due to AEs between mirikizumab and ustekinumab arms (mirikizumab: [redacted]%; ustekinumab: [redacted]%) and with a numerically higher proportion observed in the placebo arm ([redacted]%).

Treatment regimen period

- The proportion of patients experiencing one or more TEAE or a SAE during the treatment regimen period was higher than during the induction period.
- The proportion of patients experiencing one or more TEAE was 73.0% in the placebo arm, compared to 78.6% in the mirikizumab arm and [redacted]% in the ustekinumab arm, with the majority of TEAEs being mild to moderate in nature.[91]
- There was a higher proportion of patients in the placebo group who experienced a SAE (17.1%) compared to the mirikizumab group (10.3%) and ustekinumab group ([redacted]%).[91]
- Few patients discontinued treatment due to an AE with similar proportions of patients discontinuing the study due to AEs between the mirikizumab and ustekinumab arms (mirikizumab: 5.1%; ustekinumab: [redacted]%) and with a slightly greater proportion of discontinuations observed in the placebo arm (9.5%).[91] However, approximately double the proportion of patients discontinued the study due to AEs in each study arm compared to the induction period.

VIVID-1 trial results relating to adverse events in this submission are presented for the safety population, which included all randomised participants who received at least one dose of a study intervention. Further details regarding the safety population can be found in Section B.3.4. Extended safety data are available in the VIVID-1 CSR.[93]

B.3.10.1 Overview of adverse events

As shown in Table 35, the frequencies of adverse events (AEs) during the induction and treatment regimen periods were lower in the mirikizumab-treated patients compared to those receiving placebo. The overall frequencies of AEs were higher in the placebo group, when compared to the mirikizumab group in the induction period. Furthermore, the overall exposure-adjusted incidence rate (EAIR) for TEAEs was higher in the placebo group when compared to the mirikizumab group in the treatment regimen period. The frequencies of AEs were similar between the patients treated with mirikizumab and those treated ustekinumab.

The proportion of patients receiving placebo who experienced one or more treatment emergent adverse event (TEAE) was [redacted] during the induction period (Weeks 0–12), as compared with [redacted] of those receiving mirikizumab, and [redacted] of those receiving ustekinumab (Table 35). The majority of TEAEs were mild to moderate in nature in all treatment arms. The frequency of serious adverse events (SAEs) wase higher in the placebo arm, compared to the mirikizumab arm, in both the induction and maintenance periods (SAEs in the placebo arm: [redacted] induction, 17.1% maintenance, SAEs in the mirikizumab arm: [redacted] induction, 10.3% maintenance).[91] Additionally, the frequency of patient treatment discontinuation due to AEs in the placebo arm was higher in both the induction and treatment regimen periods ([redacted] respectively) compared to the frequency of patient treatment discontinuation due to AE in the mirikizumab arm in the induction and treatment regimen periods (2.4%, 5.1%, respectively).[91] [redacted] occurred during VIVID-1; [redacted] occurred during the induction period in the placebo group, whilst [redacted] occurred during the treatment regimen period in the placebo and ustekinumab groups respectively.

Table 35: Overview of adverse events in the VIVID-1 trial (safety population)

Adverse event	Induction Period, n (%) [EAIR]			Treatment Regimen Period, n (%) [EAIR]		
	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])	PBOa (N=211)	Miri (N=630)	Uste (N=[redacted])
Patients with ≥1 TEAE[b]	[redacted]	[redacted]	[redacted]	154 (73.0) [291.8]	495 (78.6) [201.9]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation due to AE[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]For participants who were randomised to placebo, only the exposure period to placebo is included. [b]Participants with multiple occurrences of the same event were counted under the highest severity. [c]One death in the placebo non-responder participant that switched to mirikizumab after Week 12 is not presented in this table. [d]Including death. [e]Two participants in the placebo group and two in the mirikizumab group reported AEs during the induction period but were not discontinued until the treatment regimen period.
Abbreviations: AE: adverse event; EAIR: exposure adjusted incidence rate; Miri: mirikizumab; PBO: placebo; TEAE: treatment emergent adverse event; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.5.22 (page 110).[93] Ferrante et al. (2024).[91]

B.3.10.2 Treatment-emergent adverse events

TEAEs occurring in ≥2% of patients in the safety population of the VIVID-1 trial during the treatment regimen period are presented in Table 36. COVID-19 was the most frequently reported TEAE across all treatment arms (placebo: 13.7%, mirikizumab: 16.5%, ustekinumab: [redacted]).[91] Other commonly reported TEAEs across groups included anaemia, arthralgia, and headache.

Table 36: TEAEs occurring in ≥2% of patients in the safety population of the VIVID-1 trial

TEAE, n (%) [EAIR][a]	Treatment Regimen Period		
	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])
Patients with ≥1 TEAE	154 (73.0) [291.8]	495 (78.6) [201.9]	[redacted]
COVID-19	29 (13.7) [26.4]	104 (16.5) [19.3]	[redacted]
Anaemia	14 (6.6) [12.2]	42 (6.7) [7.4]	[redacted]
Arthralgia	11 (5.2) [9.6]	41 (6.5) [7.2]	[redacted]
Headache	9 (4.3) [7.8]	41 (6.5) [7.2]	[redacted]
Upper respiratory tract infection	9 (4.3) [7.8]	38 (6.0) [6.7]	[redacted]
Nasopharyngitis	9 (4.3) [7.7]	36 (5.7) [6.3]	[redacted]
Diarrhoea	10 (4.7) [8.6]	35 (5.6) [6.1]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Crohn's disease	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]

Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]

Footnotes: [a]EAIR is presented as IR per 100 patient years of exposure.
Abbreviations: COVID-19: coronavirus disease 2019; EAIR: exposure adjusted incidence rate; miri: mirikizumab; PBO: placebo; TEAE: treatment emergent adverse event; uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.5.23 (page 113).[93] Ferrante et al. (2024).[91]

B.3.10.3 Serious adverse events

Serious adverse events (SAEs) for the safety population in VIVID-1 are presented in Table 37. The SAEs reported by more than 1% of the safety population in the induction and treatment regimen periods were gastrointestinal disorders and infections and infestations. No clinically significant differences in SAE incidences were noted between the treatment arms.

Table 37: SAEs in patients in the safety population in VIVID-1

System organ class	Induction Period, n (%) [EAIR][a]			Treatment Regimen Period, n (%) [EAIR][a]		
	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])
Patients with ≥1 SAE	[redacted]	[redacted]	[redacted]	36 (17.1) [32.5]	65 (10.3) [11.5]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	-	-	-	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-	-	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	-	-	-	[redacted]	[redacted]	[redacted]
Psychiatric disorders	-	-	-	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	-	-	-	[redacted]	[redacted]	[redacted]
Congenital, familial and genetic disorders	-	-	-	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	-	-	-	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	-	-	-	[redacted]	[redacted]	[redacted]

Footnotes: - represents a system organ class for which the results are not reported. [a]EAIR is presented as incidence rate per 100 patient years of exposure.
Abbreviations: EAIR: exposure adjusted incidence rate; miri: mirikizumab; PBO: placebo; SAE: serious adverse event; uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.5.25, AMAM.5.26 (pages 120–121), AMAM.8.132 (pages 4349–4359) and AMAM.8.133 (pages 4361–4382).[93] Ferrante et al. (2024).[91]

B.3.10.4 Adverse events of special interest

Seven adverse events were predetermined as adverse events of special interest (AESI) in the VIVID-1 safety population: hepatic safety, malignancies, depression and suicidal ideation or behaviour, hypersensitivity reactions, infusion and injection site reactions, infections (including opportunistic and serious infections), and cerebro-cardiovascular events. Table 38 describes the incidence of AESIs in the VIVID-1 safety population.

Table 38: AESIs in patients in the safety population in VIVID-1

AESI, n (%)	Induction Period			Treatment Regimen Period		
	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])

Hepatic TEAEs	[redacted]	[redacted]	[redacted]	9 (4.3)	39 (6.2)	[redacted]
Malignancies	[redacted]	[redacted]	[redacted]	1 (0.5)	2 (0.3)	[redacted]
Depression and suicidal ideation or behaviour (QIDS SR-16)						
Any worsening in depression severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase from No or Mild depression to Moderate, Severe or Very Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase from Mild or Moderate depression to Severe or Very Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity reactions						
Immediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-immediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion site reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections						
All treatment-emergent infections and infestations	[redacted]	[redacted]	[redacted]	73 (34.6)	261 (41.4)	[redacted]
Opportunistic infections	[redacted]	[redacted]	[redacted]	0	7 (1.1)	[redacted]
Serious infections	[redacted]	[redacted]	[redacted]	6 (2.8)	14 (2.2)	[redacted]
Cerebro-cardiovascular events						
Cerebro-cardiovascular events	[redacted]	[redacted]	[redacted]	2 (0.9)	3 (0.5)	[redacted]

Abbreviations: AESI: adverse event of special interest; miri: mirikizumab; PBO: placebo; QIDS SR-16: Quick Inventory of Depressive Symptomatology – Self Report (16 items); TEAE: treatment emergent adverse event; uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.8.125–8.179 (pages 2285–*5208)*.[93] Ferrante et al. (2024).[91]

B.3.10.5 Discontinuations due to adverse events

Adverse events which led to treatment discontinuation in the safety population of the VIVID-1 trial are presented in Table 39. Overall, a higher proportion of treatment discontinuations due to AEs occurred in patients receiving placebo as compared with patients receiving mirikizumab treatment in both the induction ([redacted] versus [redacted], respectively) and treatment regimen periods (9.5% versus 5.1%, respectively).[91]

Table 39: Discontinuations due to AEs in the safety population in VIVID-1

Adverse event, n (%)	Induction Period			Treatment Regimen Period		
	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])	PBO (N=211)	Miri (N=630)	Uste (N=[redacted])
Treatment discontinuation due to AE	[redacted]	[redacted]	[redacted]	**20 (9.5)**	**32 (5.1)**	[redacted]
Abdominal abscess	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Anaphylactic reaction						
Angina pectoris						
Anorectal disorder						
Arthralgia						
Bile duct stone						
Breast cancer						
Colectomy						
Crohn’s disease						
Depression						
Dyspnoea						
Enterocolonic fistula						
Fatigue						
Haematuria						
Headache						
Hepatitis B DNA assay positive						
Hepatitis cholestatic						
Herpes zoster						
Hypersensitivity						
Ileectomy						
Infusion-related hypersensitivity reaction						
Injection site pain						
Interstitial lung disease						
Intestinal abscess						
Large intestine perforation						
Large intestine polyp						
Non-alcoholic fatty liver						
Pulmonary embolism						
Sepsis						
Septic shock						
Small intestinal obstruction						
Urosepsis						
Urticaria						
Weight decreased						

Abbreviations: AE: adverse event; miri: mirikizumab; PBO: placebo; uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.8.136 and AMAM.8.137 (pages 4943–4948).[93] Ferrante et al. (2024).[91]

B.3.11 Conclusions about comparable health benefits and safety

Mirikizumab has demonstrated clinical efficacy and tolerability in patients with moderately to severely active CD. Results from the VIVID-1 trial showed mirikizumab to be statistically significantly superior to placebo for the key outcomes of clinical remission, clinical response, endoscopic remission, bowel urgency and fatigue. In addition, the efficacy of mirikizumab was demonstrated across both BF and CCF subgroups, which is highly clinically relevant given that patients in UK clinical practice commonly switch or cycle through treatments in order to induce or maintain remission.

The direct evidence available from VIVID-1 shows mirikizumab to be an effective and tolerable treatment for inducing clinical response and clinical remission in patients with moderately to severely active CD, in both subgroups of interest. Furthermore, mirikizumab treatment was associated with significant improvements in the burdensome and commonly-reported symptom of bowel urgency, addressing a key unmet need for these patients.

Indirect efficacy estimates obtained from NMAs evidenced that at induction, mirikizumab offered similar efficacy to most treatments, regardless of biologic exposure. Similar results were observed at maintenance, irrespective of prior biologic therapy or conventional-care exposure, versus all other comparators in the NMAs, including the comparators of relevance in the decision problem; risankizumab, ustekinumab and vedolizumab. In the absence of head-to-head studies for most active treatments, these results provide supportive evidence to inform the relative efficacy of mirikizumab versus relevant comparators and demonstrate the value of mirikizumab in the current treatment pathway.

The clinical evidence presented therefore supports the cost comparison analysis focused on risankizumab, as outlined in Section B.1.1, and suggest that mirikizumab would provide a valuable new treatment option for patients with CD in the UK.

B.3.12 Ongoing studies

The VIVID-2 study (NCT04232553) is an open-label long-term extension study designed to determine the long-term efficacy and safety of mirikizumab in moderately to severely active CD. Patients who completed the VIVID-1 trial could enrol in VIVID-2 which is currently ongoing. Results are expected to become available in [redacted].

B.4 Cost-comparison analysis

As described in Section B.1.1, mirikizumab is positioned for use as an alternative to risankizumab. As such, the cost-comparison analysis presented herein focuses on the comparison of cost outcomes associated with mirikizumab and risankizumab. Additionally, due to the rationale outlined in Section B.1.1 further comparisons against ustekinumab and vedolizumab have also been presented for completeness.

In the model, mirikizumab is compared against risankizumab, ustekinumab and vedolizumab in the target BF and CCF sub-populations (see Section B.3.4.1 for subgroup definitions), as these are the populations in which mirikizumab is expected to displace these treatments. These populations were modelled identically other than minor differences in their baseline characteristics (see Section B.4.2.1), so costs related to treatment acquisition and administration (see Section B.4.2) were very similar across the BF and CCF subgroups. Therefore, results for the BF population of patients with moderately to severely active CD only are presented in this submission, given that results for the CCF population are in very close alignment.

B.4.1 Changes in service provision and management

Mirikizumab is administered IV at Weeks 0, 4 and 8 during the induction period, followed by a SC injection [redacted] (the maintenance period). It is anticipated that the initial subcutaneous dose and all IV dosing will be administered in the secondary care setting, supported by NHS resource. After training in the SC injection technique, patients will self-inject all subsequent maintenance doses of mirikizumab at home. Therefore, the expected costs to the NHS associated with mirikizumab relate to the induction period and the initial subcutaneous dose.

Since risankizumab, ustekinumab and vedolizumab share a similar method of administration to mirikizumab (IV in induction, SC in maintenance), it is not anticipated that the introduction of mirikizumab to clinical practice would require any changes to current service provision or management.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A cost-comparison analysis was conducted to evaluate the expected costs of mirikizumab in UK clinical practice as compared to risankizumab under the assumption that the treatments have the same efficacy and safety. Cost comparison analyses were also conducted against ustekinumab and vedolizumab. The cost-comparison model was developed in Microsoft Excel with a structure consistent with models developed for other recent NICE appraisals in moderately to severely active CD (risankizumab [TA888] and upadacitinib [TA905]).[1, 3]

As further outlined in Section B.1.1, the target population considered in the model is narrower than the anticipated licence population and is in line with the decision problem: adult patients with moderately to severely active CD, *only if*:

- The disease has not responded well enough or lost response to a previous biological treatment, *or*

- A previous biological treatment was not tolerated, *or*
- TNF-α inhibitors are not suitable.

The efficacy of all treatments was assumed to be equal to the efficacy of mirikizumab, as evidenced in Section B.3.9, and is not considered further under this cost-comparison approach.

The base case model time horizon was set as 3 years. This is in line with clinical expert opinion provided to the NICE Committee in TA888 that median duration of treatment persistence with biologic therapies is approximately 2–3 years.[3] Alternate time horizons of 2 years and 5 years were tested in scenario analyses, based on the reported time horizons of models identified in the SLR described in Appendix I.

Discounting was not applied in the model, as recommended by NICE in the user guide applicable to cost-comparison models.[2] The model was populated with UK data, and the analysis was based on the UK National Health Service and the Personal Social Services (NHS & PSS) perspective.

B.4.2.1.1 Model structure

A cost-comparison model was developed, consistent with the models reported in TA888 and TA905.[1, 3] In line with the design of the VIVID-1 trial, the model was designed to capture all relevant costs to treatment during the treatment induction period and the maintenance period. Separate induction and maintenance periods were modelled due to differences in treatment formulations and dosing regimens, and the resulting differences in costs for treating patients in the induction and maintenance periods.

B.4.2.1.2 Dose escalation

In clinical practice, patients who lose response to certain treatments may be treated with increased doses or increased frequency of administration ("dose escalation", see "dose adjustments" in Table 41) instead of immediately discontinuing treatment. Efficacy and safety data at escalated doses of mirikizumab are not available, and dose escalation will not be included in the marketing authorisation for mirikizumab. Therefore, dose escalation was not considered for mirikizumab in the cost-comparison model. Similarly, dose escalation is not included in the licence for risankizumab, and as such was not considered in the cost-comparison model.

However, to reflect clinical practice for treatment with other advanced therapies where escalated doses are commonplace, dose escalation was included in the model for ustekinumab and vedolizumab. The proportion of patients who required an escalated dose was informed by past appraisals in CD (see Table 43).[1, 3]

B.4.2.1.3 Baseline characteristics

Patient baseline characteristics informing the model were informed by the VIVID-1 trial, stratified based on prior treatment failure, are presented in Table 40 below. As outlined in Section B.4, results for the BF population of patients with moderately to severely active CD only are presented in this submission, given that results for the CCF population are in very close alignment.

Table 40: Patient baseline weight characteristics used in the cost comparison model

Characteristic	CCF	BF

Mean weight, kg (SE)	[redacted]	[redacted]
Weight ≤55 kg, %	[redacted]	[redacted]
Weight >55 kg and ≤85 kg, %	[redacted]	[redacted]
Weight >85 kg, %	[redacted]	[redacted]

Abbreviations: BF: biologic-failed; CCF: conventional care failed; SE: standard error.

B.4.2.2 Intervention and comparators' acquisition costs

Drug acquisition costs were estimated for the induction and maintenance phases. Where escalated dosage was modelled (see Section B.4.2.1.2 and Section B.4.2.3.1), drug acquisition costs during the maintenance phase accounted for distribution of patients on standard and escalated doses. Additionally, dosing regimens were used to calculate the total drug use and were based on the relevant SmPCs for risankizumab[109], ustekinumab[110] and vedolizumab.[111] All drug acquisition unit costs were sourced from the Monthly Index of Medical Specialities (MIMS) and the British National Formulary (BNF).[112, 113]

The drug acquisition costs per patient were calculated by determining the number of vials needed to provide the required dose multiplied by the unit price of the vial; as ustekinumab is a weight-based drug, the characteristics presented in Section B.4.2.1.3 were used to derive a weighted average dose and treatment cost. In the base case, it was assumed that any leftover drug not used by a specific patient would be discarded i.e., vial wastage. Vial wastage was based on the selected vial size that provides the lowest acquisition cost for each dose. Vial sharing, where any leftover drug was modelled to be used for another patient such that costs are accrued only for the actual amount of medication administered, was explored in a scenario analysis.

The key inputs, assumptions and acquisition costs included for mirikizumab, risankizumab, ustekinumab and vedolizumab are presented Table 41. Total induction and total annual maintenance costs are presented in Table 42 and Table 43, respectively.

Table 41: Acquisition costs of the intervention and comparator technologies

	Mirikizumab	Risankizumab	Ustekinumab	Vedolizumab
Pharmaceutical formulation	**Induction**: Mirikizumab 900 mg (three 300 mg vials) is available as a concentrate for solution for infusion **Maintenance**: A full maintenance dose consists of [redacted]	**Induction**: Risankizumab 600 mg (10 mL vial; 60 mg risankizumab per mL) is available as a concentrate for solution for infusion **Maintenance**: A full maintenance dose consists of 360 mg (2.4 mL vial; 150 mg risankizumab per mL) risankizumab delivered via on-body device	**Induction**: Ustekinumab 130 mg is available as a solution for infusion (26 mL, 5 mg per mL) **Maintenance**: Ustekinumab 90 mg is available as a pre-filled syringe (1 mL)	**Induction**: Vedolizumab 300 mg is available as a powder for concentrate for solution for infusion **Maintenance**: Vedolizumab 108 mg is available as a solution for injection in pre-filled syringe
(Anticipated) care setting	Secondary care			
Acquisition cost (excluding VAT)	Induction dose (300 mg for IV infusion) list price: £2,056.56 Maintenance dose [redacted]	600 mg/10 mL solution list price: £3,326.09 360 mg/2.4mL on-body device cartridge list price: £3,326.09	130 mg/26mL solution list price: £2,147.00 90 mg/mL pre-filled syringe list price: £2,147.00	300 mg powder list price: £2,050.00 108 mg/0.68 mL list price: £512.50
Method of administration	• **Induction**: IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC *or* IV. As per TA888, it is assumed within the model that during maintenance, 50% of patients receive vedolizumab IV and 50% receive vedolizumab SC.[1]
Doses	• **Induction**: 900 mg IV mirikizumab per administration (three 300 mg vials) • **Maintenance**: [redacted]	• **Induction**: 600 mg IV risankizumab per administration • **Maintenance**: 360 mg SC mirikizumab per administration (one 2.4	IV dose at Week 0 is based on body weight (recommended dose: 6 mg/kg): • ≤55 kg: 260 mg • >56 to ≤85 kg: 390	• **Induction**: 300 mg IV vedolizumab per administration • **Maintenance**: 300 mg IV vedolizumab or 108 mg SC vedolizumab

	[redacted]	mL cartridge)	• mg • >85 kg: 520 mg At Week 8, 90 mg SC ustekinumab, followed by 90 mg ustekinumab every 12 weeks	
Dosing frequency	• **Induction**: Weeks 0, 4 and 8 • **Maintenance**: [redacted]	• **Induction**: Weeks 0, 4 and 8 • **Maintenance**: Week 12 and then every 8 weeks	• **Induction:** Week 0 • **Maintenance**: Week 8 and then every 12 weeks	• **Induction**: Weeks 0, 2, and 6 • **Maintenance**: Every 8 weeks (IV) or every 2 weeks (SC)
Dose adjustments	No dose adjustments were considered for mirikizumab in the model.	No dose adjustments were considered for risankizumab in the model.	• Delayed response was not modelled for ustekinumab. • However, patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks • Therefore, 92.5% of patients receiving ustekinumab are modelled to receive the escalated dose. This value was based on clinical expert opinion received by the Committee in TA888[1] • Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment	• Delayed response was not modelled for vedolizumab • However, patients receiving 300 mg IV vedolizumab every 8 weeks may be considered to receive treatment every 4 weeks if there is a decrease in response • Therefore, 30% of patients receiving IV vedolizumab are modelled to receive the escalated dose. This value was based on clinical expert opinion received by the Committee in TA888[1] • No dose adjustment is modelled for patients receiving 108 mg SC vedolizumab maintenance therapy

Average length of a course of treatment	As these treatments are for a chronic disease, treatment is long-term or until the patient's clinician determines the treatment should be discontinued. In the model, patients remain on treatment throughout the model time horizon.
Average cost of a course of treatment (acquisition costs only)	
(Anticipated) average interval between courses of treatment	
(Anticipated) number of repeat courses of treatment	

Abbreviations: IV: intravenous; SC: subcutaneous.

Table 42: Drug acquisition costs for mirikizumab and comparators during the induction phase

Treatment	Duration (weeks)	Total doses (mg)	Total treatment cost
Mirikizumab (IV)	12	2,700	£18,995
Risankizumab (IV)	12	1,800	£10,464
Ustekinumab (IV/SC)	8	390	£6,603
Vedolizumab (IV)	10	900	£6,636
Vedolizumab (IV/SC)	10	900	£6,636

Abbreviations: IV: intravenous; PAS: patient access scheme; SC: subcutaneous.

Table 43: Drug acquisition costs for mirikizumab and comparators during the maintenance phase

Treatment	% Escalated dose	Total doses per year (mg)		Total maintenance treatment cost per year	
		First year	Subsequent years	First year	Subsequent years
Mirikizumab (SC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab (SC)	NA	1,808	2,348	£16,751	£21,694
Ustekinumab (IV/SC)	92.5%	485	572	£11,563	£13,653
Vedolizumab (IV)	30.0%	2,056	2,544	£15,161	£18,756
Vedolizumab (IV/SC)	0%	2,278	2,818	£10,854	£13,371

Abbreviations: IV: intravenous; NA: not applicable; PAS: patient access scheme; SC: subcutaneous.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

B.4.2.3.1 Administration costs

IV treatments were assumed to be administered in an outpatient setting and were therefore costed as an outpatient visit. The costs for IV administration were set as the cost of one non-consultant led single professional first appointment (code WF01B) at £162.00.[114] The unit costs were taken from the 2023/2024 National Tariffs Payment System(see Table 44).[114]

Consistent with the approach taken in the appraisals of risankizumab (TA888)[1] and upadacitinib (TA905),[3] it was assumed that all patients self-inject subcutaneous treatment apart from the initial injection for which patients would receive training by a nurse. Therefore, the model included a cost for the first SC injection, based on the cost per working hour of a Band 5 nurse; costs were taken from the Unit costs of Health and Social Care from the Personal Social Services Research Unit (PSSRU) 2022 (see Table 45).[115]

The number of administrations for mirikizumab and the comparators during the induction and maintenance phase are presented in Table 46.

Table 44: Unit cost of treatment administration for IV therapies

	Cost	Source
First administration	£162.00	WF01B, non-consultant led, first attendance, single professional, 301 (Gastroenterology Service). National Tariff Payment System 2023/24[114]
Subsequent administrations		

Abbreviations: IV: intravenous.

Table 45: Unit cost of treatment administration for SC therapies

	Cost	Source
First administration	£46.00	Cost per working hour of band 5 Nurse. PSSRU 2022.[115]
Subsequent administrations	£0.00	N/A

Abbreviations: N/A: not applicable; PSSRU: Personal Social Services Research Unit; SC: subcutaneous.

Table 46: Drug administrations for mirikizumab and the comparators during the induction and maintenance phase

Treatment	Induction		Maintenance	
	Duration (weeks)	Total admins	First year	Subsequent years
Mirikizumab (IV/SC)	12	IV: 3	[redacted]	[redacted]
Risankizumab (IV/SC)	12	IV: 3	SC: 5	SC: 7
Ustekinumab (IV/SC)	8	IV: 1	SC: 5	SC: 6
Vedolizumab (IV)	10	3	7	8
Vedolizumab (IV/SC)	10	IV: 3	SC: 21	SC: 26

Abbreviations: IV: intravenous; SC: subcutaneous.

B.4.2.3.2 Disease management costs

Given that efficacy is assumed to be the same for all treatments, the health state distribution during maintenance treatment is expected to be the same for all comparators, and therefore disease management costs are not modelled explicitly. Similarly, costs for monitoring and tests during the induction period were not modelled as these were expected to be the same for all treatments.

B.4.2.4 Adverse reaction unit costs and resource use

Adverse events related to treatment were not included in the analysis, based on the NMA data (Section B.3.9) which demonstrated that the safety profiles of mirikizumab and the comparators of interest were broadly similar. Furthermore, the assumption of similar adverse event incidence across all treatments is in line with the assumption of similar efficacy.

B.4.2.5 Miscellaneous unit costs and resource use

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

B.4.2.6 Model validation

The model design was informed by previous economic analyses in CD (TA888, TA905), as identified by the economic SLR, and was aligned with the Committee preferences from these appraisals.[1, 3] The model and report underwent structured internal peer-review at the agency that developed it. In addition, an external agency not involved in its development further validated the model using a structured black-box approach, to confirm the validity of model function, and a structured white-box approach, to quality control check all formulae.

B.4.2.7 Uncertainties in the inputs and assumptions

Settings and values used in the base case analysis are presented in Table 47, with key assumptions of the cost-comparison model presented in Table 48.

Table 47: Settings and values used in the base case analysis

Item	Base-case setting	Reference
Perspective	UK NHS	Section B.4.2.1
Time horizon	3 years	Section B.4.2.1
Weight in kg, mean	BF: [redacted]	Section B.4.2.1.3
Delayed response	No	Section B.4.2.7 (Table 48)
Dose escalation for comparators	Yes	Section B.4.2.1.2 and Section B.4.2.3.1
Cost discount rate	Not applied	Section B.4.2.1

Abbreviations: BF: biologic-failed; NHS: National Health Service; UK: United Kingdom.

Table 48: Key model assumptions

Assumption	Justification
No treatment discontinuation was assumed	As a simplifying assumption, treatment discontinuation was not modelled in the cost comparison analysis; all patients are modelled to remain on treatment throughout the entire model time horizon. This is in line with previous cost comparison appraisals in CD.[1, 3]
All modelled treatments have the same efficacy	Given the results of the NMA (Section B.3.9), mirikizumab is associated with a similar relative efficacy as risankizumab, ustekinumab and vedolizumab.
No delayed response assessment and/or delayed induction therapy is modelled for any treatments	• **Mirikizumab:** As per the dosing regimen used in the VIVID-1 trial, patients who do not respond to IV mirikizumab induction after 12 weeks of induction therapy may be considered for a delayed response assessment (extended induction). [redacted] However, given that the frequency and dosing of mirikizumab is the same during extended induction and maintenance, no cost impact is expected for patients who receive extended induction therapy. • **Risankizumab:** Delayed response assessment or extended

Assumption	Justification
	induction are not included in the risankizumab licence. • **Ustekinumab:** Simplification assumption. While a proportion of patients receiving ustekinumab in clinical practice may move to receive subcutaneous treatment, the anticipated cost impact of this within the model is minor.
Dose escalation modelled for relevant comparators	Patients who lose response to ustekinumab and vedolizumab IV may be treated with increased frequency of administration: 90 mg SC Q12W to Q8W and 300 mg IV Q8W to Q4W, respectively. Proportions of patients modelled to receive these escalated doses were informed by clinical expert opinion received during previous appraisals in moderately to severely active CD (TA888 and TA911): 92.5% and 30% of patients receiving ustekinumab and vedolizumab (IV), respectively.[1, 3] In line with the license wording for risankizumab and the anticipated licence wording for mirikizumab, dose escalation was not modelled for mirikizumab or risankizumab.[1, 109, 116]
No disease management, monitoring or adverse event costs	Disease management and monitoring costs largely reflect disease severity and should therefore be very similar across all modelled treatments. Adverse events were not included in the model due to the NMA results demonstrating broadly similar safety outcomes for mirikizumab, risankizumab, ustekinumab and vedolizumab
Normal population mortality	Consistent with previous models. Does not introduce mortality benefits that have not been demonstrated in RCTs

Abbreviations: CD: Crohn's disease; IV: intravenous; NMA: network meta-analysis; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; RCT: randomised controlled trial; SC: subcutaneous.

B.4.3 Base-case results

Base case results for a 3-year time horizon with mirikizumab (at list price) are presented in Table 49. Confidential PAS discounts for comparators are not included in the analysis as these are not publicly known. These results indicate that at its list price, mirikizumab is more expensive than risankizumab, ustekinumab and vedolizumab (IV and IV/SC) at their list prices. However, a PAS is planned for mirikizumab. It is anticipated that at the PAS price, mirikizumab will be a cost-saving treatment option versus the risankizumab, ustekinumab and vedolizumab (IV/SC), at their list prices.

Table 49: Base case results for a 3-year time horizon at mirikizumab list price

Treatment	Per patient costs			Incremental costs
	Induction costs	Maintenance costs	Total treatment costs	
Mirikizumab	[redacted]	[redacted]	[redacted]	-
Risankizumab	£10,464	£60,138	£70,603	[redacted]
Ustekinumab	£6,603	£38,870	£45,473	[redacted]
Vedolizumab IV/SC	£6,636	£45,134	£51,770	[redacted]

Abbreviations: PAS: patient access scheme.

B.4.4 Scenario analyses

The scenario analyses detailed in Table 50 were explored in the model. Results for these scenario analyses are presented in Table 51. These results show that at list price, mirikizumab remains a the more costly option versus all comparators presented. However, as discussed earlier, following confirmation of the PAS price, it is assumed that mirikizumab will remain cost-effective versus all compared treatments, in these scenario analyses. This suggests that the model is reasonably robust to uncertainty.

Table 50: Scenario analyses

#	Scenario	Base case	Scenario value(s)
1	Model horizon	3 years	2 years
2			5 years
3	Drug wastage	No vial sharing	Vial sharing assumed
4	Administration costs	Treatment administration and acquisition costs considered	Only treatment acquisition costs considered

Table 51: Scenario analyses results at mirikizumab list price

Scenario	Incremental costs (list price)		
	RIS	UST	VED
Base case	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]

Abbreviations: IV: intravenous; PAS: patient access scheme; RIS: risankizumab; SC: subcutaneous; UST: ustekinumab; VED: vedolizumab.

B.4.5 Subgroup analysis

As outlined in Section B.4, economic analysis results are presented for the BF population of patients with moderately to severely active CD only, given that results for the CCF population are in very close alignment. No other subgroups were considered.

B.4.6 Interpretation and conclusions of economic evidence

As outlined in Section B.1.1, risankizumab represents the most relevant comparator used in clinical practice in this restricted population, and thus should form the basis for decision making. This analysis aimed to evaluate the expected costs of mirikizumab in clinical practice as compared to risankizumab in relevant patient subgroups under the assumption that the treatments have the same efficacy. Comparisons against ustekinumab and vedolizumab were also presented for completeness.

Overall, mirikizumab at its list price was found to be more costly than these comparators of relevance at their list prices. Mirikizumab is associated with additional incremental costs of

£22,750 versus risankizumab, £47,879 versus ustekinumab and £41,583 versus vedolizumab IV/SC. These base-case results were also corroborated in a series of scenario analyses. However, it is anticipated that following the confirmation of the PAS, and if it were to be approved, mirikizumab would offer patients with CD a valuable new treatment option, that is a well-tolerated and efficacious with a convenient maintenance dosing schedule, while offering a cost-saving, or at least budget neutrality, to the NHS.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

Summary of Information for Patients (SIP)

June 2024

File name	Version	Contains confidential information	Date
ID6244_Mirikizumab in CD_SIP	Final	No	21st June 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections or documents are highlighted in **orange**.

SECTION 1: Submission summary

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

Generic name: Mirikizumab; **Brand name**: Omvoh®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population being considered for this medicine is adults with **moderate to severely active Crohn's disease (CD)** *only if*:

- The disease has not responded well enough or lost response to a previous biologic therapy, *or*
- A previous biologic therapy was not tolerated, *or*
- **Tumour necrosis factor alpha (TNF-α) inhibitors** are not suitable.

This means that a patient may be eligible for mirikizumab if they have had:

- A **biologic therapy** (see Section 2c) before that didn't work well enough for them (termed "**biologic-failed**"), *or*
- Previous **conventional care therapies** (see Section 2c) which didn't work well enough for them *and* they are not suitable to receive a TNF-α inhibitor (termed "**conventional care-failed**").

This patient population being considered for this medicine is a subset of the wider population expected to be included in the regulatory license for mirikizumab in the United Kingdom (UK), known as its **marketing authorisation** (MA) (see Section 1c).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **Medicines and Healthcare products Regulatory Agency (MHRA)** is reviewing whether mirikizumab should be approved and granted MA as a treatment for patients with moderately to severely active CD in the UK. The MA for mirikizumab is therefore still pending. Please refer to Section B.1.2 of Document B of the company evidence submission for further details on the anticipated dates and wording of the paperwork.

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

The table below shows support from Eli Lilly to relevant patient advocacy groups in the UK, and how the company engages or supports these charities and/or patients who use them.

Patient group:	Engagement/activity with each group:	Financial support provided:
Crohn's & Colitis UK	2-year Corporate Membership from December 2022–December 2024	£20,000, paid and reported in 2023
	Sponsorship of Crohn's & Colitis Early Diagnosis Campaign	£40,000, paid in February 2024
IBD Relief	For services provided to develop, attend, and facilitate UK Ulcerative Colitis Patient Experience Workshop	£3,000, paid and reported in 2023
	For services provided for participation in filming patient experience of Living with Ulcerative Colitis	£1,950, paid and reported in 2023

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

The condition that mirikizumab is being planned to treat is **Crohn's disease** (referred to as **CD** throughout). Along with ulcerative colitis (UC), CD is classified as one of the **inflammatory bowel diseases (IBD)**.

What is Crohn's disease?

CD is a long-term, lifelong condition, where parts of the **gastrointestinal tract** (or gut), which is the passageway from the mouth to the anus, become **inflamed**. The **inflammation** occurs because the body's **immune system**, which usually protects against sickness, becomes too highly activated and causes small sores, known as **ulcers,** to develop on the inside walls of the gut, which can bleed and produce pus.(1)

The gut is the part of the body responsible for transporting food taken in when eating through the stomach and bowels, before ultimately passing out of the anus as **stool** (poo). In CD, the inflammation can affect any part of the gut, but it usually affects the small and/or large bowels.(1)

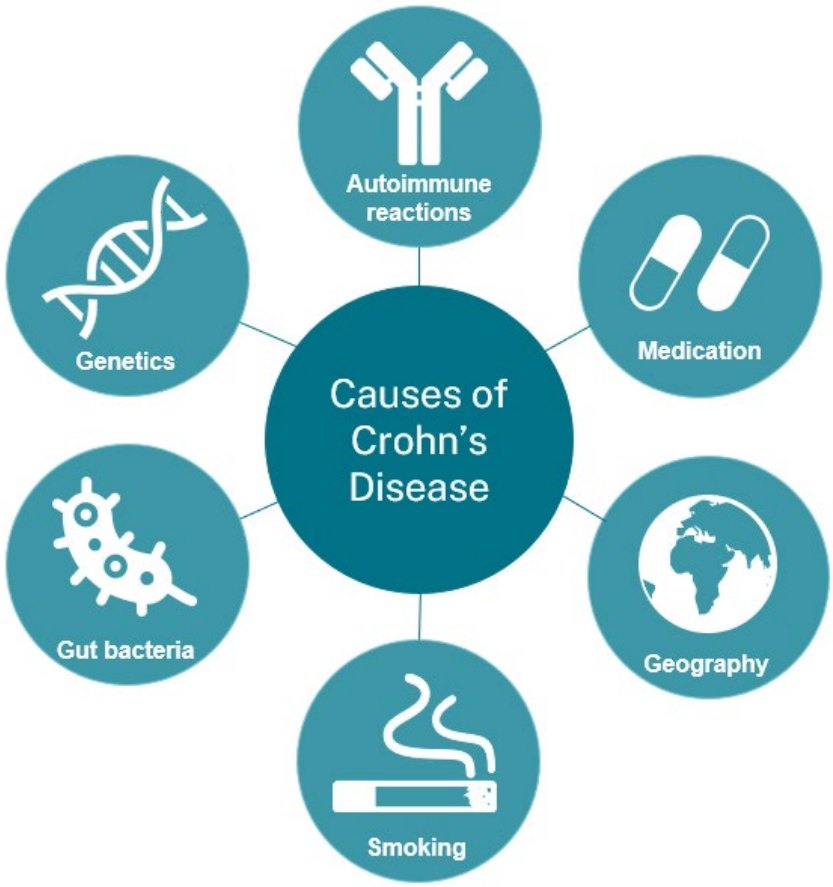
How many people have CD?

CD is a **common** condition. In the UK, it is estimated that around **1 in 323** people have this condition. That means there are around **208,000 people** living with it in the UK.(1) However, based on observed trends, it is expected that the number of adults and children living with CD will increase worldwide in the coming years.(2, 3)

What are the causes of CD?

The exact cause of CD is **unknown**. Usually, the immune system protects against harmful substances and infections, but CD occurs when the immune system starts attacking the gut instead. Scientists are unsure exactly why this happens, but it is thought that it may be due to a mix of **genes**, bacteria in the gut, and a range of factors in your environment (**Figure 1**).(1) People with any immediate family members who have previously been diagnosed with IBD, or who have a history of smoking, may be at a greater risk of CD.(4-6)

Figure 1: Possible causes of CD (1, 4-6)



What are the main symptoms of CD?

People with CD report that the disease is changeable and unpredictable. Patients typically experience periods where they feel worse and have more symptoms (**flare-ups**) and other periods where they have fewer symptoms and feel better (**remission**).(1) Symptoms of CD commonly reported by patients include diarrhoea (which may contain blood, pus or mucus), **bowel urgency** (a sudden and urgent need to go to the toilet), tummy pain, extreme tiredness, loss of appetite, and weight loss.(1) These symptoms are usually experienced during a flare-up when the disease is more active. Flare-ups can also affect other parts of the body causing pain in the joints, mouth ulcers, **nausea** (the urge to vomit), skin rashes, or swelling in the eyes.(1)

Staging CD

Remission or response to treatment can be assessed by healthcare professionals using a rating scale called the **Crohn's Disease Activity Index (CDAI)**.(7) The CDAI measures various domains of CD, such as the number of times a patient needs to go to the toilet (stool frequency), how much stomach pain (abdominal pain) is experienced and any bleeding through the anus (rectal bleeding). The CDAI is used to divide

patients into 4 categories:

- Patients in remission – CDAI score less than 150
- Patients with mild to moderate CD – CDAI score between 150 and 220
- Patients with moderate to severe CD – CDAI score between 220 and 450
- Patients with severe CD – CDAI score above 450

Some doctors may also use the **Harvey-Bradshaw Index (HBI)**, to classify disease activity. The HBI is a simpler version of the CDAI, and is more widely used in clinical practice due to its relative speed and ease of use.(8)

Healthcare professionals can also use the **Simple Endoscopic Score for Crohn's disease (SES-CD)** to group people with CD into 4 categories according to the results of **endoscopy**: inactive CD, mild CD, moderate CD and severe CD.(9)

What is the impact of CD (disease burden)?

The impact of disease on the **quality of life** of individuals is known as **health-related quality of life (HRQoL)**. Scientists usually compare the HRQoL of patients with a disease (such as CD) with the HRQoL of patients without the disease, to get an idea of the impact a disease has on daily living, and to examine which factors improve or worsen quality of life.

Due to the long-term and unpredictable nature of CD, and the range and severity of the symptoms experienced during flare-ups, people with CD often report a worsening in HRQoL and daily living compared to people without CD. This includes a negative impact on their ability to work, study, or attend social events.(10, 11) For further details on the patient-reported impact of CD on HRQoL, see Section 2d.

As well as the symptoms directly related to CD, people with CD often report having other medical conditions occur at the same time. Mental health disorders, such as stress, anxiety and depression, are more common in people with CD compared to people without CD.(10) Other diseases that affect the immune system may also occur more commonly in people with CD. For example, **psoriasis** affects around 10% of people with CD, compared to 2% of people without CD.(12, 13) People with CD are also more likely to develop problems with their heart, or metabolism, compared to people who do not have CD.(14)

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

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is CD diagnosed?

Although no 'gold standard' method exists to diagnose CD, your doctor will aim to make a diagnosis using a **multifaceted approach.** This will usually begin with examinations to

check your pulse and blood pressure, as well as a manual examination of your abdomen. The signs and symptoms of disease (clinical factors) and the results of any prescribed medical tests (laboratory factors) will be considered. A visual inspection may take place via a small tube with a camera inside being inserted into the gut via the mouth or anus (endoscopic imaging). A doctor may also ask you a few questions to rule out other potential diseases which can show similar symptoms to CD, such as **infectious colitis** or **irritable bowel syndrome (IBS)**.(15)

2c) Current treatment options:

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

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for CD?

In England and Wales, the management of CD is guided by advice from the National Institute for Health and Care Excellence (NICE) (NG129),(16) and guidelines from the British Society of Gastroenterology and the European Crohn's and Colitis Organisation.(17, 18)

Unfortunately, there is currently no known cure for CD, therefore doctors will aim to manage the symptoms as best as possible with the available treatments options. The ultimate goal is the achievement and maintenance of **clinical remission**: a state where the disease is controlled and the debilitating symptoms of CD are not experienced. However, at a minimum, doctors will try to reduce the frequency of flare-ups, and limit the severity of the symptoms (defined as **clinical response**).(16, 17)

In general, CD is treated in a stepwise manner, and a doctor may change the medicine prescribed if it doesn't work well enough (**inadequate response**), stops working (**loss of response**), or if it doesn't work at all (**non-response**).

Initially, moderate to severely active CD is treated with medicines which change the functioning of the immune system as a whole, rather than specifically targeting the underlying inflammation of CD. These treatments, known as **immunomodulators** and **corticosteroids**, are often referred to as "**conventional care therapies**". Although given as the first option for all patients who are suitable to receive them, many people find that these medicines are not able to control their CD symptoms effectively.(19-21) If this happens, patients may be '**switched**' to receive stronger medicines which have specific targets within

the immune system. These are also the medicines that a patient would receive if they are unsuitable to receive any conventional care therapies at all.

These stronger medicines are often grouped under the term "**advanced therapies**". By targeting, and blocking, the specific **molecules** that are involved in the inflammation pathway, advanced therapies directly reduce the inflammation that occurs with CD. Treatment options currently available for people with CD in the UK are:

- **Conventional care therapies:**
  - Corticosteroids, such as prednisolone and budesonide
  - Immunomodulators, such as azathioprine and mercaptopurine
- **Advanced therapies:**
  - Biologic therapies:
    - TNF-α inhibitors: infliximab and adalimumab
    - Other biologics: ustekinumab, vedolizumab and risankizumab
  - Small molecule inhibitors:
    - Upadacitinib

Throughout the rest of this document, the term "biologic therapies" is used to encompass all advanced therapies including upadacitinib. This is in line with the terminology used in the key clinical trial of mirikizumab in Crohn's disease (the VIVID-1 trial, see Section 3d).

Over the course of a patients' illness, a doctor may prescribe one or more of these treatments in order to find one(s) that are most effective. An alternative for people who continue to have poorly controlled disease despite trying some of these medicines, or those who choose to have it, is surgery. This usually involves the removal of part of the gut.(22) However, this is typically reserved as a last resort, due to the possibility of complications.(23)

Limitations of current treatment options and unmet needs

While doctors are currently able to select from a range of different treatment options, like all treatments, these are associated with limitations. Conventional care therapies are associated with problems such as limited response, low rates of maintained remission and both short- and long-term **side effects**.(19, 20, 24) Furthermore, due to the non-targeted nature of conventional care therapies, they do not help the intestinal wall to heal, meaning that the underlying cause of CD symptoms are not addressed.(25)

Biologic options considered after treatment failure with conventional care therapies are also associated with limitations and side effects. Drugs that **inhibit** the inflammatory chemical known as TNF-α are often used as the first biologic option after conventional care therapy. However, a study showed that approximately one-third of patients showed no initial response to TNF-α inhibitor induction therapy (termed "primary non-response"), while nearly half (46%) of patients who do initially respond go on to lose that response over time (termed "secondary non-response").(26-28)

Potential solutions to overcome non-response to a TNF-α inhibitor may include switching to a treatment that works in a different way, or using other biologic therapies such as vedolizumab, ustekinumab or risankizumab.(29) However, these treatments are also

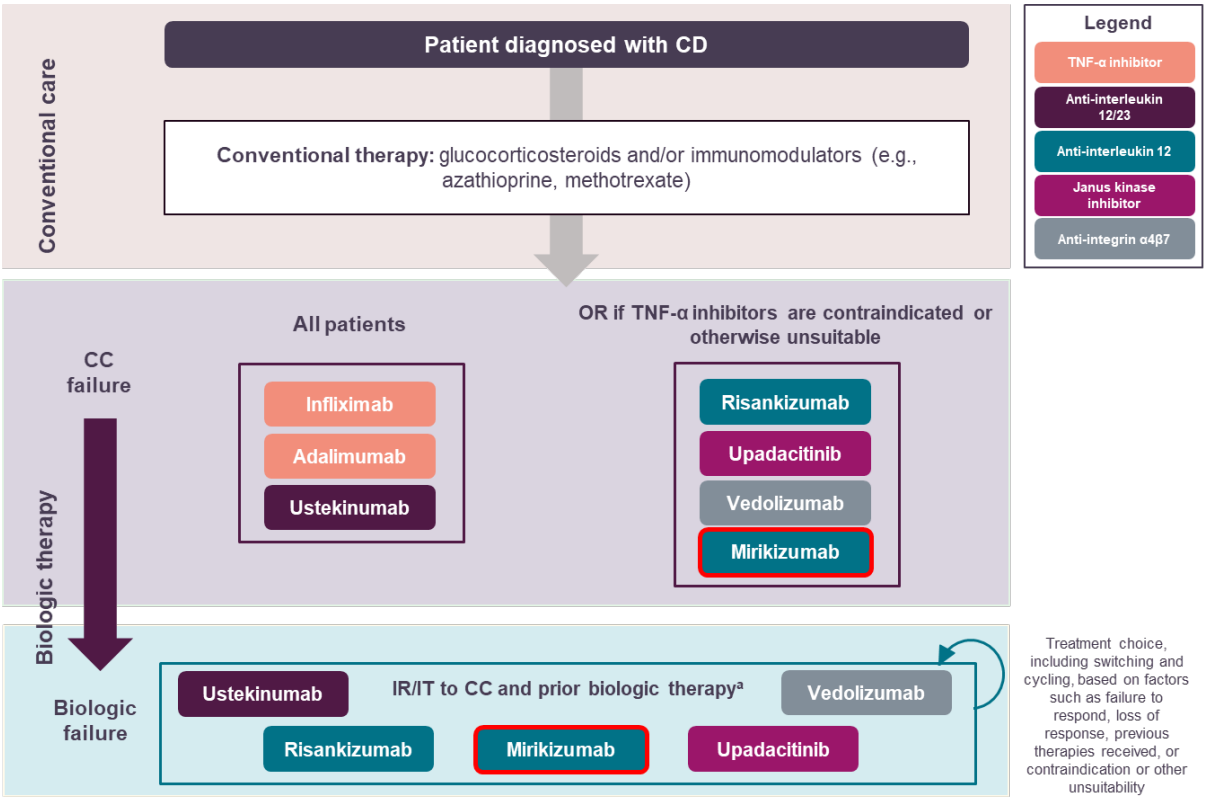
associated with certain disadvantages, including the common prospect of losing response over time and the continued experience of debilitating CD symptoms, despite ongoing treatment.(30, 31)

As such, despite several options being available, there remains an unmet need in the UK for a new treatment for people with moderate to severely active CD that both works well and has a tolerable **safety** profile.

Where does mirikizumab fit in the treatment pathway?

As described in Section 1b, mirikizumab is being assessed for use in adults with moderate to severely active CD in the UK for whom conventional treatment cannot be tolerated or is not working well enough and other biologic therapies are not suitable, *or* for whom biologic therapy cannot be tolerated or is not working well enough. This is presented in **Figure 2**.

Figure 2: Anticipated place of mirikizumab in the UK clinical care pathway



Footnotes: [a]Following relapse on biologic therapies, patients are switched onto an alternative biologic therapy that has not been used previously.
Abbreviations: CD: Crohn's disease; CT: conventional therapy; IR: inadequate response; IT: intolerant; TNF-α: tumour necrosis factor-alpha

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

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden

and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

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

As mentioned in Section 2a, the symptoms of CD have a significant impact on patients and several studies have been conducted to try to assess or quantify that impact. Some of these studies are outlined below, but in summary, they consistently show that CD has a considerable negative impact on patients' lives which is reflected by reductions in their overall quality of life.

The impact of CD, as reported by patients

Numerous studies have been carried out to assess how patients feel they are affected by having CD. During a focus group of people with CD, many reported that having CD "changed who they were" and almost all participants reported experiencing fear and embarrassment due to their condition.(32) Another study found that 68% of people with CD feel that having CD affects their ability to work.(33) Additionally, patients report that CD negatively impacts their self-esteem, autonomy and ability to form relationships.(34)

The quality of life of people with CD

Studies investigating the impact of a disease or condition on patients' quality of life typically make the use of surveys, the answers from which are translated into a scoring system which permits the impact to be quantified numerically. A study conducted in 2022 made use of one of these surveys, the **European Quality of Life 5-Dimension 5 Level (EQ-5D-5L)**, to investigate the effect of CD in 853 people with the condition across the USA and Europe.(35, 36) The study found that patients with moderate to severe CD had a quality of life score that was between 20–25% lower than patients with mild CD or those in remission.(35)

Impact of current treatments on patients

In the UK, corticosteroids are commonly used for people with moderate to severely active CD, but for some people they do not work.(20) This was observed in a study of 173 people with CD who were treated with corticosteroids, which reported that, although 58% achieved remission, 16% did not respond at all.(20) Additionally, many people who initially responded to corticosteroid treatment lost their response over time: after one year, only half of all patients who had initially achieved remission in the study had maintained it, while over one-third (38%) relapsed back to active disease.(20) HRQoL in these patients was reduced, and while symptom relapse was thought to be a factor in this, common side effects of corticosteroids such as weight gain and acne may have also contributed.(20)

On the other hand, biologic therapies have been shown to have a positive impact on HRQoL, particularly when they are able to improve symptoms in the short term.(37, 38) Despite this, further understanding of the long-term **efficacy** and safety of these

treatments may be necessary to determine the long-term impact on HRQoL for people with CD, particularly if loss of response occurs.(37, 38)

Patient preferences for treatment objectives

A patient preference study carried out in 2020 found that people with CD identified the most important treatment objectives as improving quality of life (40.2%) and completely resolving symptoms (33.3%). Furthermore, one of the symptoms that patients considered to be most important when prioritising their control was bowel urgency (17.1%).(39)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How does mirikizumab work?

Monoclonal antibodies are proteins that recognise and bind specifically to certain other proteins in the body. Mirikizumab is a type of monoclonal antibody that recognises and binds specifically to a protein called **interleukin-23 (IL-23)**. IL-23 plays an important role in the inflammation of the lining of the gut in CD. Mirikizumab works by binding to IL-23 (known as **"**inhibiting" it), which in turn prevents IL-23 from interacting with cells that are a key source of inflammation-causing molecules (**cytokines**), as it normally would.(40-44) Therefore, by blocking the action of IL-23, mirikizumab can reduce the inflammation in the gut that underlies CD, and therefore help to reduce the severity and frequency of symptoms experienced by patients.

Innovation in patient care

As outlined in **Section 2c**, several biologic therapy options are available for patients with CD and switching between them in order to try to maintain control of the disease is common. However, once a person with CD has failed a biologic therapy, they may be switched to other treatments as a potential way to overcome resistance to the previous therapy. The introduction of mirikizumab would expand the potential treatment options available to people in the UK with CD following a failure or intolerance to other currently available therapies.(27)

Additionally, mirikizumab has been shown to reduce bowel urgency, which people with CD have identified as a particularly important unmet need, affecting 70% of people with CD and contributing to reduced wellbeing (see **Section 2d** for more information).(39, 45) As such, the approval for the use of mirikizumab for people with moderately to severely active CD, would potentially provide these people with a treatment that significantly reduces the burden caused by a having to constantly worry about needing to use the toilet.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No – mirikizumab is anticipated to be used as a standalone therapy. However, it may be used alongside concomitant conventional therapies.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is mirikizumab taken?

The way in which mirikizumab would be taken by patients is split into two parts: the **induction dose** which is received when patients first start to receive mirikizumab, and the **maintenance dose** which is given longer term to maintain disease control:

- **Induction dose**: the first dose of 900 mg will be given by a healthcare professional through a drip in a vein of the patient's arm (**intravenous [IV] infusion**). This will take place over at least 30 minutes. Four weeks after the first dose, patients will receive the next dose of mirikizumab 900 mg in the same way, and again after an additional four weeks (at Week 0, Week 4 and Week 8).
- **Maintenance dose**: four weeks after the last IV infusion. The maintenance dose is currently going through regulatory approval and is confidential. Maintenance treatment must be started with a specialist giving the medicine, but after proper training by a doctor or nurse on how to perform the subcutaneous injections, patients with CD can do it themselves if they feel comfortable to do so.

The induction dosing takes place over 12 weeks. After this point, a doctor assesses the patient's clinical response to the induction treatment (**post-induction assessment**), and all patients transition to receive the SC maintenance dosing. If patients are concluded not to have shown an adequate response at this post-induction assessment point, a second response assessment is carried out by the doctor after 12 weeks of the maintenance dosing. For patients who do not show any evidence of getting a clinical benefit to mirikizumab by this point, mirikizumab treatment should be stopped.

How does this compare with other treatments?

Other treatments for CD are given in a variety of ways. For example, some have induction doses given via SC injection, followed by SC injections of maintenance doses, whereas other treatments involve IV induction doses followed by IV or SC maintenance doses. A number of current treatment options are taken orally for all doses.

Unlike mirikizumab, the regulatory license for some treatment options, such as adalimumab, infliximab, ustekinumab and vedolizumab, states that the maintenance dose should be increased (known as "dose escalation") if patients lose response whilst receiving maintenance therapy, with no time limit on this escalation.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size,

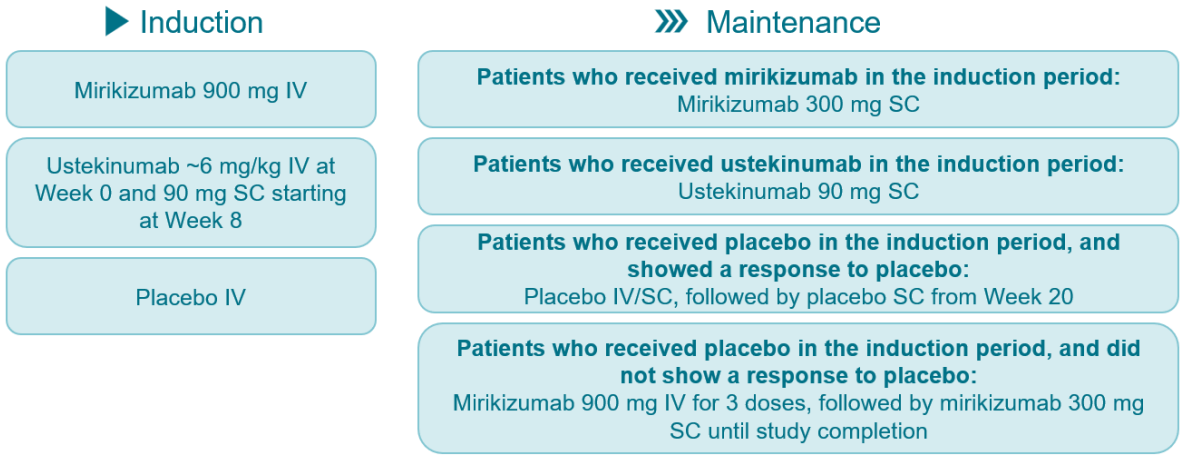
comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The effectiveness and safety of mirikizumab in the treatment of people with moderately to severely active CD, was studied in the **VIVID-1 trial**.

VIVID-1 was a **Phase 3 trial**. This means it looked at how well mirikizumab worked to treat moderately to severely active CD (its efficacy) and how safe the medicine is as compared with a standard treatment. The trial also looked at the impact of mirikizumab on patients' **quality of life**.

In **VIVID-1**, mirikizumab was compared to a '**dummy treatment**', **placebo,** and to the biologic therapy **ustekinumab**. In line with the dosing pattern for mirikizumab described in **Section 3c**, patients in the VIVID-1 trial received different doses of the study treatments based on the trial period they were in i.e., whether they were in induction or the maintenance period of the study (see **Figure 3**).

Figure 3: Study treatments in the VIVID-1 trial, by period of study



Abbreviations: IV: intravenous; SC: subcutaneous

The VIVID-1 trial included people who had moderately to severely active CD. In this study, patients were selected for inclusion if they:

- Were aged above 18 and below 80 years
- Had an established diagnosis of CD at least 3 months prior to baseline
- Have previously had an inadequate response to, loss of response to, or intolerance to conventional or to biologic therapy for CD

A summary of the key information about the VIVID-1 trial is provided in **Table 1**.

Table 1. Summary of the VIVID-1 trial

Trial name and number	Location	Number of patients included	Study period	Study completion date

VIVID-1 (NCT03926130)	International (Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, France, Germany, Hungary, India, Israel, Italy, Japan, Latvia, Lithuania, Mexico, The Netherlands, Poland, Romania, Russian Federation, Serbia, Slovakia, South Korea, Spain, Switzerland, Turkey, Ukraine, **United Kingdom**, and the United States)	1,152	Induction period of 12 weeks, and a maintenance period of 40 weeks, representing a total of 52 weeks of therapy	10th February 2023

Further details on the VIVID-1 trial can be found at Clinicaltrials.gov: https://clinicaltrials.gov/study/NCT03926130

3e) Efficacy

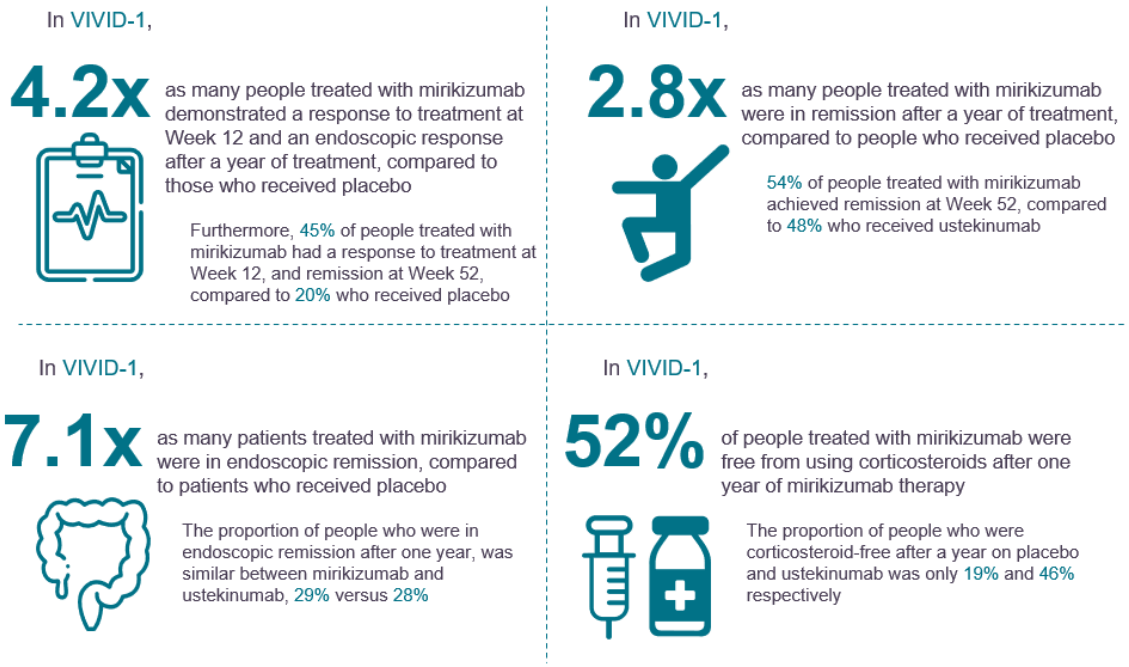
Efficacy is the measure of how well a treatment works in treating a specific condition.

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

Results from the VIVID-1 trial

The results from the VIVID-1 trial after a year of treatment are shown in **Figure 4**. Overall, people who received mirikizumab demonstrated improvements over placebo in clinical response, endoscopic response, and clinical remission.(46, 47) These improvements were statistically significant for all outcomes, meaning they were unlikely to have happened by chance.(46, 47) Mirikizumab demonstrated similar health benefits versus ustekinumab.(46, 47)

Figure 4: Efficacy results from the VIVID-1 trial(46, 47)



Further effectiveness results for the VIVID-1 trial, are presented in Section B.3.6 of Document B of the main Company submission.

Indirect treatment comparison

As discussed in Section 2c, people with moderate to severe CD in the UK currently have access to other active treatment options, with treatment decisions made based on factors such as how well they have responded to other treatments in the past, and whether there are any medical reasons that would make them unsuitable to receive certain options. In order to make a decision about how beneficial mirikizumab would be for these patients in the UK, its efficacy and safety must be compared with the efficacy and safety of these other active treatment options that patients could receive. However, the VIVID-1 trial discussed above provides data for the efficacy and safety of mirikizumab compared with placebo and ustekinumab only, and not every possible treatment for CD; this is typical across previous **clinical trials** in CD, including in studies of **comparators** to mirikizumab. As such, a statistical method called a **network meta-analysis (NMA)** was used to obtain estimates of the necessary safety and efficacy information for mirikizumab compared with these other treatments.

Results from the NMA which compared the VIVID-1 trial with other comparators showed that mirikizumab is likely to be as effective, or more effective, than other currently available treatments in terms of the achievement and maintenance of clinical response and clinical remission. In addition, the NMA which compared safety data concluded mirikizumab to have a similar tolerability to other available treatments.

It should be considered that these analyses are associated with some limitations since the results are estimations only (due to the lack of head-to-head data). In addition, factors such as differences between the patient populations recruited to the trials being indirectly

compared are likely to introduce uncertainty in the estimates produced. Despite this, these results nevertheless suggest that mirikizumab is at least as effective as existing treatments.

Further results for the NMAs, are presented in **Section B.3.9** of **Document B** of the main Company submission.

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

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

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

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

The VIVID-1 trial measured how patient quality of life changed after taking mirikizumab, ustekinumab or placebo. Quality of life was measured using questionnaires completed by patients in the trial, and were completed at Week 12 and Week 52 of the VIVID-1 trial. A range of questionnaires were used, including the EQ-5D-5L and the **Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)**. Overall, the questionnaires asked patients about different aspects of their daily life, their mental health and their levels of tiredness. Patients were asked to quantify the extent to which CD impairs these aspects of daily living.(48, 49)

At Weeks 12 and 52 of the VIVID-1 study, it was found that patients receiving mirikizumab showed greater improvements on the EQ-5D-5L and FACIT-Fatigue scales compared with those receiving placebo. Additionally, after a year of treatment, patients receiving mirikizumab showed improvements in bowel urgency as compared with patients receiving placebo. This is particularly important because patients have placed a high value on improving bowel urgency as a symptom (**see Section 2d**).(39)

Further HRQoL results for the VIVID-1 trial, are presented in **Section B.3.6** of **Document B** of the main Company submission.

3g) Safety of the medicine and side effects

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

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient

readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Safety results from the VIVID-1 trial

As with all medications, mirikizumab can cause side effects, although not everyone will experience them. As well as the effectiveness of mirikizumab, the safety of mirikizumab was also assessed in the VIVID-1 trial and compared against placebo and ustekinumab. After a year of treatment, the proportion of people who experienced a side effect during treatment (a "**treatment emergent adverse event", TEAE**) was similar between those who received mirikizumab and those who received placebo or ustekinumab.(46, 47) Among others, the most common TEAEs observed during the trial were COVID-19, **anaemia**, joint pain, headaches and diarrhoea.(46) These side effects were generally mild or moderate in severity, with only a small proportion of the TEAEs observed in the mirikizumab arm of the VIVID-1 trial reported as being serious.(46) Furthermore, after one year of treatment, the proportion of serious TEAEs was higher in the placebo arm of the trial than in the mirikizumab arm.(46)

Potentially serious side effects

Serious side effects experienced by more than or equal to 1% of patients receiving mirikizumab during the induction period and maintenance period of the VIVID-1 trial are presented in **Table 2**. There was a higher frequency of patients in the placebo group reporting one or more serious side effects than in the mirikizumab group in both the induction period and maintenance period.(50) The frequency of patients who experienced serious side effects was consistently lower in the mirikizumab and ustekinumab groups than in the placebo group in both the induction and the maintenance periods of the trial.(50)

Table 2: Serious side effects experienced by patients in the VIVID-1 trial

	Placebo (N=211)	Mirikizumab (N=630)	Ustekinumab (N=309)
Induction period, n (%)			
Patients with ≥1 serious side effect	19 (9.0)	37 (5.9)	11 (3.6)
Gastrointestinal disorders	14 (6.6)	23 (3.7)	6 (1.9)
Infections and infestations	1 (0.5)	7 (1.1)	3 (1.0)

Induction and Maintenance period, n (%)			
Patients with ≥1 serious side effect	36 (17.1)	65 (10.3)	33 (10.7)
Gastrointestinal disorders	22 (10.4)	34 (5.4)	16 (5.2)
Infections and infestations	6 (2.8)	14 (2.2)	9 (2.9)

The frequency and nature of the side effects experienced by patients with CD receiving treatment with mirikizumab is similar to those experienced by patients receiving mirikizumab to treat UC.(51)

Further safety results for the VIVID-1 trial are presented in **Section B.3.10** of **Document B** of the main Company submission.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Clinical trials have specified primary **endpoints**, which are the main results measured at the end of the study to see how well the treatment worked. The VIVID-1 trial had two co-primary endpoints:

1. To measure how many patients achieve a response to treatment at Week 12, and demonstrate an endoscopic response by Week 52
2. To measure how many patients achieve a response to treatment at Week 12, and are in remission by Week 52

Following one year of treatment in the VIVID-1 trial, mirikizumab:

Results in greater control over CD symptoms as compared with patients receiving placebo

- Mirikizumab helps people achieve greater control of their CD, and helps them achieve symptom-free remission at a significantly greater rate to placebo, while remaining equally as good as, and often better, than ustekinumab

Shows a manageable safety profile

- Mirikizumab is generally well tolerated, with no apparent safety concerns following one year of treatment
- The side effects observed were similar to that observed for ustekinumab, so are likely to be familiar to clinicians and readily managed by the healthcare community

Positively impacts QoL and productivity

- Mirikizumab reduces bowel urgency compared to placebo
- Patients who receive mirikizumab are more productive and are less impaired in their ability to work and perform daily activities than those who receive placebo

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

In the VIVID-1 trial, mirikizumab was associated with some side effects. However, as outlined in **Section 3g**, the proportion of people who experienced a TEAE was similar in the mirikizumab, placebo and ustekinumab groups, and these side effects were generally mild or moderate in severity.

3j) Value and economic considerations

Introduction for patients:

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

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

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**.

What type of model was created?

Since mirikizumab demonstrated in the NMA (see Section 3e) that it can provide similar or greater clinical benefits than existing therapies, a **cost comparison** tool was created with the aim of comparing the costs associated with treatment when using this drug, as compared with using other drugs that are also available in this disease area. Notably, under this approach, the model did not incorporate any clinical data. Instead, it is assumed that all treatments have the same clinical efficacy.

How were the comparators in the model selected?

The model was designed to reflect the usual way that CD is treated within the NHS and compares patients receiving either mirikizumab, risankizumab, vedolizumab or ustekinumab.

Risankizumab was considered the primary comparator against mirikizumab for the model because it is recommended for use in the same adult population for which mirikizumab is being positioned. In addition, risankizumab has the same mechanism of action as mirikizumab.

Vedolizumab and ustekinumab were also included as additional comparators in the cost-comparison tool. Head-to-head data on the efficacy and safety of mirikizumab versus ustekinumab are available from the VIVID-1 trial (see Section 3e). In the trial, mirikizumab showed similar efficacy as ustekinumab in terms of managing moderately to severely active CD, justifying its presentation as a supportive analysis. Importantly, in the previous technology appraisal for risankizumab in moderately to severely active CD (TA888),(52) the NICE committee agreed that risankizumab could be considered the same as ustekinumab in terms of efficacy, lending further credence to the use of risankizumab as the most relevant comparator to mirikizumab in this submission.

Lastly, vedolizumab was included as a supportive comparator as it was considered to be the most relevant comparator to risankizumab in TA888.(52)

How do the costs of treatment differ with mirikizumab?

In the model, the following costs were included:

- Cost of the medicine (including dose escalation for ustekinumab and vedolizumab)
- Cost of giving the treatment to patients (administration costs)

It is planned that mirikizumab will be provided to the NHS at a confidential discounted price, but this discounted price is not yet confirmed so has not been included in the results. It should be noted that confidential discounts may apply to risankizumab, vedolizumab and ustekinumab as well, but these cannot be included in the analysis because they are unknown to Eli Lilly.

Cost-comparison results

When assuming comparable efficacy for mirikizumab, risankizumab, vedolizumab and ustekinumab, Eli Lilly's cost-comparison tool predicted mirikizumab (at its full price) to cost more than risankizumab, vedolizumab and ustekinumab (at their full price). This means that the introduction of mirikizumab to clinical practice would cost NHS England more than it is already spending on current treatment options. However, it is anticipated that following the confirmation of the discounted price, mirikizumab may cost about the same as other treatments, and its introduction to UK clinical practice may even represent a cost-saving for the NHS.

Uncertainty in the model

Some key assumptions were made in the model which introduce some uncertainty, and are detailed in **Section B.4.2.7 of Document B**.

A key assumption of the analysis was that mirikizumab has comparable efficacy to risankizumab, ustekinumab and vedolizumab. This assumption is based on data from an NMA, which is a widely used approach to compare treatments when no head-to-head comparisons are available, but is also sensitive to differences between the participants in the included trials (see **Section 3e** and **Section B.3.9 of Document B** for further details).

Other assumptions included what proportions of patients receive the escalated doses of comparator (ustekinumab and vedolizumab) therapies as compared with the standard dose, and the exclusion of treatment discontinuation and extended induction from the model.

To determine the impact of certain assumptions and inputs used in the model, analyses were conducted which vary the model inputs and assumptions. Based on Eli Lilly's internal analyses, it was found that varying these inputs and assumptions did not change the overall conclusion of the model. Detailed results from these analyses are reported in detail in **Section B.4.4 of Document B**.

Conclusion

Overall, at its list price, the results of the economic analysis showed mirikizumab to be a more costly use of NHS resources as an additional treatment option for patients with CD who have failed, or are not eligible for, prior therapies. This conclusion is based on an analysis in which the efficacy of mirikizumab, risankizumab, vedolizumab and ustekinumab were assumed to be identical, with the difference in costs associated with each treatment representing the only modelled difference between them. However, at the discounted price, it is believed that mirikizumab may cost about the same as other treatments, and its introduction to UK clinical practice may even represent a cost-saving for the NHS, but due to confidential discounts for the comparator treatments this is uncertain.

3k) Innovation

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

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Mirikizumab is an antibody that binds to the IL-23 protein, representing the same mechanism of action as risankizumab, which is already approved in the same adult population as mirikizumab is positioned. The switching of treatments is a potential way to overcome resistance to certain biologic therapies in CD, and the introduction of mirikizumab would expand the potential treatment options that people in the UK with CD may receive following a failure or intolerance to other currently available therapies.(27)

Mirikizumab has also demonstrated significant effectiveness in improving bowel urgency, which was reported as one of the most bothersome symptoms in a patient preference study, with patients identifying it as a significant unmet need.(39)

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

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

SECTION 4: Further information, glossary and references

4a) Further information

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

Further information on NICE and the role of patients**:**

- Crohn's and Colitis UK: https://crohnsandcolitis.org.uk/
- NICE NG129: https://www.nice.org.uk/guidance/ng129
- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment – an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Glossary term	Definition
Anaemia	A condition in which the number of red blood cells or the **haemoglobin** concentration within them is lower than normal
Biologic therapy	A medical therapy manufactured by the **immune system** of living organisms which

	specifically targets parts of patients' **immune system** to manage disease.
Biologic-failed	Patients who have previously received one or more **biologic therapy** but it did not work well enough for them.
Bowel urgency	The urgent need to have a bowel movement/defecate.
Clinical remission	A state where **Crohn's disease** is controlled and the debilitating symptoms of the disease are not experienced.
Clinical response	Where a patient shows a response to a drug, reducing both the frequency of **flare-ups** and the severity of symptoms experienced.
Clinical trial	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Colon	Part of the **gastrointestinal tract** and makes up most of the large intestine. The colon forms faeces from digested food.
Comparators	The standard (for example, another medicine or usual care) against which a medicine is compared in a study. The comparator can be no intervention (for example, best supportive care).
Conventional care/conventional therapy	Widely used and accepted treatments by healthcare professionals. These are the first treatment options used to treat **Crohn's disease** and consist of **immunomodulators** and **corticosteroids**.
Conventional care-failed	Patients who have previously received one or more **conventional care therapy** but it did not work well enough for them.
Corticosteroids	A type of drug which reduces **inflammation**.

Cost comparison	A cost comparison analysis is used to identify and compare the costs associated with the use of two or more different medicines.
Crohn's disease (CD)	A type of inflammatory bowel disease caused by persistent **inflammation** of the **gastrointestinal tract**, causing stomach pain, severe diarrhoea, **fatigue**, weight loss and **malnutrition**.
Crohn's Disease Activity Index (CDAI)	A rating scale used by healthcare professionals to determine the level of severity of a patient's **Crohn's disease**.
Cytokines	A **molecule** released by the **immune system** which helps to regulate **inflammation** and the **immune response**.
Dummy treatment	A treatment that appears real, but that does not treat the disease. It is used in clinical trials to compare treatments to. Also known as a **placebo**.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial.**
Endoscopy	An examination of the **gastrointestinal tract** using a camera attached to a flexible tube which is passed in to the body via the throat.
Endpoint	A targeted outcome of a **clinical trial** which is analysed to determine the **efficacy** or **safety** of the drug being studied.
European Quality of Life 5-Dimension 5 Level (EQ-5D-5L)	A self-report survey used to measure patients' **quality of life** across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
Fatigue	The feeling of tiredness.
Flare-ups	Period where the disease is very bad.

Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)	A self-reported survey used to measure the impact of **fatigue** on patients' daily activities and functioning.
Gastrointestinal tract	The organs that food and liquids travel through when they are swallowed and digested, before leaving the body as faeces. These organs include the mouth, pharynx (throat), oesophagus, stomach, small intestine, large intestine, rectum, and anus. The gastrointestinal tract is part of the digestive system.
Genes	A gene is an inherited part of a cell in a living thing that controls physical characteristics, growth and development.
Haemoglobin	The protein contained in red blood cells that is responsible for delivery of oxygen to the tissues.
Harvey-Bradshaw Index (HBI)	A tool used to measure the severity of a patient's Crohn's disease.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a **clinical trial**.
Health-related quality of life (HRQoL)	The overall impact of a patient's health on their overall enjoyment of life **(quality of life**).
Immune response	Activity of the **immune system** to protect the body from harmful agents.
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
Immunomodulators	Medicines that prevent activity of the immune system.
Inadequate response	When a medicine works but doesn't work well enough for a patient.
Induction dose	The amount of drug needed to give a response at the start of treatment.

Infectious colitis	A condition caused by infection with bacteria, parasites or viruses which leads to **inflammation** of the **colon**.
Inflamed	Swelling of a body part/organ as a result of **inflammation**.
Inflammation	The result of the immune response to injury of tissues including redness, swelling and loss of function.
Inflammatory bowel diseases (IBD)	A long-term health condition caused by **inflammation** of the **gastrointestinal tract**. **Crohn's disease** and **ulcerative colitis** are two types of inflammatory bowel disease.
Inhibit	To prevent a **molecule** from carrying out its usual function.
Interleukin-23 (IL-23)	A type of protein that plays a key role in the immune system.
Intestinal obstruction	A blockage of the intestines (part of he **gastrointestinal tract**).
Intravenous (IV) drip	Some cancer drugs are diluted in a bag of fluid which is connected to a very thin tube and goes into one of your veins.
Intravenous (IV) infusion	This is when you are given medicine through an injection or drip (see '**intravenous drip**') into one of your veins.
Irritable bowel syndrome (IBS)	A common condition that affects the **gastrointestinal tract** and cases symptoms like stomach pain, bloating, diarrhoea and constipation.
Loss of response	When a medicine stops working.
Maintenance dose	The amount of drug given throughout treatment to maintain effective drug concentration in the blood.
Malnutrition	A condition which results from lack of sufficient nutrients in the body.

Marketing authorisation (MA)	The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency (MHRA)	The **regulatory body** that evaluates, approves and supervises medicines throughout the United Kingdom.
Moderately to severely active Crohn's disease	**Crohn's disease** can be categorised as mild, moderate or severe according to the severity of symptoms experienced. Moderate Crohn's disease is associated with symptoms which can **impact quality of life** such as stomach pain and diarrhoea which lead to weight loss and **malnutrition**. Severe Crohn's disease limits day-to-day function and can include complications like **intestinal obstruction**.
Molecule	A group of two or more atoms bonded together.
Multifaceted approach	An approach including multiple different perspectives and views.
Nausea	Sickness in the stomach with an urge to vomit.
Network meta-analysis (NMA)	A technique for comparing the **efficacy** of multiple treatments at the same time in a single analysis.
Non-response	When the medicine doesn't work at all.
Phase 3 trial	This type of **clinical trial** that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer **side effects**.
Placebo	A treatment that appears real, but that does not treat the disease. It is used in clinical trials to compare treatments to.
Psoriasis	A long-term disease of the skin which causes scaly and itchy patches of skin.
Quality of life	The overall enjoyment of life. Many **clinical trials** assess the effects of cancer

	and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Regulatory body	These are legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
Remission	Period of relative disease inactivity.
Safety	The number and severity of **side effects**.
Side effects	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Simple Endoscopic Score for Crohn's disease (SES-CD)	A scale used by healthcare professionals to categorise patients with **Crohn's disease**, based off the results of an **endoscopy**, according to the level of severity of their disease.
Stool	Also known as faeces or poo.
Subcutaneous (SC) injection	A type of injection in which a short needle is used to inject a drug into tissue layer between the skin and the muscle.
Switched	When patients stop taking one medicine to begin treatment with a different medicine.
Treatment emergent adverse event (TEAE)	A **side effect** (also known as adverse event) which first appears or worsens during treatment.
Tumour necrosis factor alpha (TNF-α) inhibitors	Molecules which prevent the usual action of tumour necrosis factor alpha, and therefore prevent **inflammation**.
Ulcerative colitis (UC)	A type of **inflammatory bowel disease** which is characterised by **inflammation** of the large intestine, causing inflammation, **ulcers** and bleeding.
Ulcers	Small sores which produce pus, cause abdominal pain and the urge to frequently have a bowel movement.
Ustekinumab	A type of **biologic therapy** which **inhibits** IL-12 and **IL-23** to reduce **inflammation**

	and is used to treat **Crohn's disease** and **ulcerative colitis**.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

Clarification questions

August 2024

File name	Version	Contains confidential information	Date
ID6244_Mirikizumab in CD_Clarification Questions_05Aug24_(noCON)	1.0	No	5th August 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Baseline characteristics

A1. Priority question. Please provide the baseline characteristics for each trial arm for the conventional-care failed (CCF) and biologic failed (BF) subgroups of VIVID-1 (as provided in Tables 9 and 10 of the company submission for the full PAS population).

Summaries of the demographic characteristics and baseline disease characteristics are presented in Table 1 and Table 2, respectively, for patients included in the conventional care-failed (CCF) and biologic-failed (BF) subgroups of the VIVID-1 trial.

Table 1: Baseline patient demographic characteristics (VIVID-1; BF and CCF subgroups)

Characteristics	BF			CCF		
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region, n (%)						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Central/South America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe/Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF: biologic failed; BMI: body mass index; CCF: conventional care failed; Miri: mirikizumab; PAS: primary analysis set; PBO: placebo; SD: standard deviation; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs. Outputs T_dm_bc_biof_pas and T_dm_bc_nobiof_pas (pages 1–28).[1]

Table 2: Baseline patient disease characteristics and prior therapies (VIVID-1; CCF and BF subgroups)

Characteristics	BF			CCF		
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])
Duration of CD (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease location, n (%)						
Ileal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colonic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ileal-colonic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior surgical bowel resection						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDAI measures						
CDAI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDAI ≥300, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SES-CD measures						
SES-CD, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SES-CD ≥12, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-reported outcomes (PRO)						
AP, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AP average ≥2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF average ≥7, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease biomarkers						

Characteristics	BF			CCF		
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])
CRP (mg/L), median (range: Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Faecal calprotectin (µg/g), median (range: Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AP: abdominal pain; BF: biologic failed; CCF: conventional care failed; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; Miri: mirikizumab; PBO: placebo; PRO: patient-reported outcomes; Q1: quartile 1; Q3: quartile 3; SD: standard deviation; SES-CD: Simple Endoscopic Score-Crohn's disease; SF: stool frequency; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs. Outputs T_dm_bc_biof_pas and T_dm_bc_nobiof_pas (pages 1–28).[1]

A2. Priority question. Please provide baseline prior therapies and concomitant therapies by trial arm for the PAS population, CCF subgroup and BF subgroup of VIVID-1.

The baseline prior therapies and concomitant therapies for the primary analysis set (PAS) population and the CCF and BF subgroups of VIVID-1 are reported in Table 3.

Table 3: Baseline prior therapies and concomitant therapies (VIVID-1; PAS population, CCF subgroup, and BF subgroup)

Characteristics	PAS			BF			CCF		
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])
Prior biologic exposure, n (%)									
Never used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of failed biologic, n (%)									
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-TNF failure, n (%)									
Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-integrin failure, n (%)									
Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior corticosteroid failure, n (%)									
Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior immunomodulator failure, n (%)									
Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ever	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline corticosteroid use, n (%)									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	PAS			BF			CCF		
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])
Baseline budesonide use, n (%)									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline prednisone equivalent dose (mg), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline corticosteroid and immunomodulator use, n (%)									
Corticosteroid only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunomodulator only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neither	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Both	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline use of oral aminosalicylates, n (%)									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline use of methotrexate, n (%)									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline use of thiopurine, n (%)									
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF: biologic failed; CCF: conventional care failed; PAS: primary analysis set; PBO: placebo; Miri: mirikizumab; SD: standard deviation; TNF: tumour necrosis factor; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.18 (page 278–289).[2] Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs. Outputs T_dm_bc_pro_biof_pas and T_dm_bc_pro_nobiof_pas (pages 29–60).[1]

A3. Priority question. Please provide the baseline characteristics for patients who entered the maintenance phase of VIVID-1 by trial arm (including placebo arm) for the PAS population, CCF subgroup and BF subgroup.

The VIVID-1 trial had a treat-through design. As such, the baseline characteristics presented in Table 1, Table 2 and Table 3 above are the baseline characteristics for the patients in the PAS population, CCF subgroup and the BF subgroup who participated in both the induction and the maintenance phase of the VIVID-1 trial.

Whilst some patients in the VIVID-1 trial did not enter the maintenance phase after treatment in the induction phase, this represented a small proportion of enrolled patients. As such, this would have had a negligible impact on the baseline characteristics presented above.

A4. Please provide baseline smoking status by trial arm for the PAS population, CCF subgroup and BF subgroup of VIVID-1.

The baseline smoking status of patients in the placebo, mirikizumab and ustekinumab trial arms in the PAS population is provided in Table 4 below.

Table 4: Baseline smoking status (VIVID-1; PAS population, CCF subgroup, and BF subgroup)

	PAS			BF			CCF		
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])
Never, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF: biologic failed; CCF: conventional care failed; PAS: primary analysis set; PBO: placebo; Miri: mirikizumab; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.8.18 (page 283).[2] VIVID-1 Additional Clinical Study Outputs. Outputs T_dm_bc_pro_biof_pas and T_dm_bc_pro_nobiof_pas (pages 29–60).[1]

A5. Please clarify if patients with perianal Crohn's disease were included in VIVID-1, and if so please provide the number of patients in each trial arm at baseline.

As noted in the VIVID-1 study protocol, patients randomised in VIVID-1 were selected for inclusion following a rigorous screening programme which included an assessment of patient Crohn's disease (CD) status. To be eligible for inclusion, patients were required to have had a diagnosis of CD or fistulising CD, established at least three months prior to enrolment, and confirmed by clinical, endoscopic and histological criteria.

While disease location was recorded at baseline for patients with confirmed CD, this was limited to the location of the disease within the small and large intestines, and was stratified into the following categories: ileal, ileal-colonic and colonic. Patients with perianal disease were not explicitly excluded from inclusion in VIVID-1, but perianal disease involvement was not recorded for patients included in the study.

However, the proportion of patients presenting with cutaneous fistulae was recorded in VIVID-1. This includes patients presenting with rectal fistulae, a hallmark of perianal CD. At study baseline, [redacted] ([redacted]) patients presented with cutaneous fistulae in the PAS population (see Table 5).

Table 5: Baseline cutaneous fistulae presentation (VIVID-1; PAS population)

Characteristic	PAS			
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])	Total (N=[redacted])
Baseline fistulae, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Miri: mirikizumab; PAS: primary analysis set; PBO: placebo; Uste: ustekinumab.
Source: Eli Lilly (Data on File): VIVID-1 Clinical Study Report. Table AMAM.8.19 (page 299).[2]

Outcomes

A6. Priority question. Please clarify if the 10% non-inferiority margin for common risk difference (as stated in Table 13) applies to all secondary endpoints and other secondary endpoints, or if it only applies to CDAI outcomes?

a) If only for CDAI, please confirm what non-inferiority margins were used for other outcomes?

As discussed in Section B.3.3.1 of the original Company submission, the VIVID-1 trial was designed to investigate the clinical effectiveness and safety of mirikizumab compared with placebo and ustekinumab. A major secondary endpoint in VIVID-1 was to evaluate the efficacy of mirikizumab in comparison to ustekinumab at Week 52, as assessed by clinical remission by Crohn's disease activity index (CDAI); a non-inferiority analysis was used for this endpoint. Non-inferiority analyses were also performed for the following other secondary endpoints which evaluated the efficacy and safety of mirikizumab in comparison to ustekinumab:

- Clinical remission by CDAI at Week 12

- Clinical response by CDAI at Week 12
- Clinical response by CDAI at Week 52
- Corticosteroid-free remission by CDAI at Week 52

However, it should be noted that only the co-primary and major secondary endpoints in VIVID-1 were multiplicity-controlled (see VIVID-1 statistical analysis plan included in the reference pack for the original Company submission). As such, clinical remission by CDAI at Week 52 for mirikizumab versus ustekinumab was the only non-inferiority analysis sufficiently powered to identify any statistically significant results.

Beyond those discussed above, no further non-inferiority analyses were conducted in VIVID-1, and therefore no further non-inferiority margins were required or considered for the remaining endpoints in VIVID-1.

b) Please provide references or justification to support the choice of 10% as the non-inferiority margin.

Lilly understand that there is no universally accepted value for what is considered to be a clinically unimportant difference in CDAI remission between two treatments. However, regulatory guidance from the US and Europe indicates that the selection of non-inferiority margins should be based on a combination of statistical and clinical methods.[3, 4]

Calculations to estimate approximate risk differences between ustekinumab and placebo were based on modelling publicly available summary data from two induction studies (UNITI1 and UNITI2) followed by a single maintenance study (IM-UNITI).[5] Prior to VIVID-1 unblinding, it was estimated that in a treat-through design, 39.2% of patients on ustekinumab 6 mg/kg, followed by 90 mg Q8W, would achieve clinical remission by CDAI at Week 52, compared to 12.3% of patients on placebo.[6] This equated to an approximate treatment versus placebo risk difference of 26.9% (95% CI: 19.5, 34.6).[6]

Using the fixed 95%/95% margin method, a 10% non-inferiority margin, as reported in Pouillon *et al.*,[7] represents clinical judgement about the amount of the active control effect that should be retained. Given the assumption that the proportions of patients who were BF or CCF in VIVID-1 were similar to those observed in the UNITI program, and that the constancy assumption held, the proposed non-inferiority margin was expected to preserve 50% of the expected ustekinumab effect in clinical remission by CDAI at Week 52 in a treat-through study. It was estimated that even with a conservative treatment versus placebo risk difference of ~20% (ustekinumab versus placebo), using a 10% non-inferiority margin demonstrated that a substantial portion (50%) of that 20% risk difference was also achieved with mirikizumab.

Further methodological details on the non-inferiority margin are presented in the VIVID-1 statistical analysis plan.[6]

A7. Please provide the rates of surgery and the rates of hospitalisations in the VIVID-1 trial, both for the mirikizumab vs placebo and mirikizumab vs ustekinumab comparisons, including the common risk differences (with 95% confidence intervals) and associated p-values for the PAS population, CCF subgroup and BF subgroup.

The rates of hospitalisations and the rates of surgeries for the PAS population, the BF subgroup and the CCF subgroup are presented in Table 6 and Table 7 respectively.

Table 6: Rates of Crohn's-related hospitalisations in the VIVID-1 trial for the PAS population and the BF and CCF subgroups (Week 52)

Outcome	PBO	Miri	Uste	Miri vs PBO[a], RD (95% CI) [p-value]	Miri vs Uste[a], RD (95% CI) [p-value]
PAS					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalised patients with ≥1 SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BF					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalised patients with ≥1 SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCF					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalised patients with ≥1 SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Cochran-Mantel-Haenszel test adjusted by stratification factors: prior biologic failure (yes/no), baseline SES-CD total score (<12, ≥12), and either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown/no)
Abbreviations: AP: abdominal pain; BF: biologic-failed; CCF: conventional care failed; CD: Crohn's disease; CI: confidence interval; PAS: primary analysis set; PRO: patient-reported outcome; RD: risk difference; SAE: serious adverse event; SES-CD: simple endoscopic score Crohn's disease; SF: stool frequency.
Source: Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs, Output t_crsurg_hosp_a7_pas (page 62), Output t_crsurg_hosp_a7_pasbf (page 64) and Output t_crsurg_hosp_a7_pasnbf (page 66).[1]

Table 7: Rates of Crohn's-related surgeries in the VIVID-1 trial for the PAS population and the BF and CCF subgroups (Week 52)

Outcome	PBO	Miri	Uste	Miri vs PBO[a], RD (95% CI) [p-value]	Miri vs Uste[a], RD (95% CI) [p-value]
PAS					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with ≥1 CD-related surgeries, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CD-related surgeries, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BF					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with ≥1 CD-related surgeries, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CD-related surgeries, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CCF					
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with ≥1 CD-related surgeries, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CD-related surgeries, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Cochran-Mantel-Haenszel test adjusted by stratification factors: prior biologic failure (yes/no), baseline SES-CD total score (<12, ≥12), and either baseline SF ≥7 and/or baseline AP ≥2.5 (yes or unknown/no)
Abbreviations: AP: abdominal pain; BF: biologic-failed; CCF: conventional care failed; CD: Crohn's disease; CI: confidence interval; PAS: primary analysis set; PRO: patient-reported outcome; RD: risk difference; SES-CD: simple endoscopic score Crohn's disease; SF: stool frequency.
Source: Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs, Output t_crsurg_hosp_a7_pas (page 61), Output t_crsurg_hosp_a7_pasbf (page 63) and Output t_crsurg_hosp_a7_pasnbf (page 65).[1]

A8. Priority question. Please provide EQ-5D-5L VAS change from baseline at Week 12 and Week 52 by trial arm for the CCF subgroup and BF subgroups (as provided in Table 29 of the company submission for the full PAS population).

The EQ-5D-5L visual analogue scale (VAS) change from baseline at Week 12 and Week 52 are presented in Table 8 for the comparisons for mirikizumab against placebo and in Table 9 for the comparisons for mirikizumab against ustekinumab.

Table 8: EQ-5D-5L VAS change from baseline (treatment regimen period; PAS population, ANCOVA with mBOCF)

Population	LSM change from baseline (SE)		LSM difference vs placebo (95% CI) [p-value]
	Placebo IV	Miri IV/SC[a]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W.
Abbreviations: ANCOVA: analysis of covariance; BF: biologic-failed; CCF: conventional care-failed; CI: confidence interval; EQ-5D-5L: EuroQol 5 dimension 5 level; IV: intravenous; LSM: least square mean; mBOCF: modified baseline observation carried forward; Miri: mirikizumab; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous; SE: standard error; VAS: visual analogue scale.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.81 (page 1889), and Table AMAM.8.81 (page 1891).[2] Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs, Output t_a_qs_eq5d5l_vas_chg_ancova_a8_pasbf (pages 69 and 71) and Output t_a_qs_eq5d5l_vas_chg_ancova_a8_pasnbf (pages 75 and 77).[1]

Table 9: EQ-5D-5L VAS change from baseline (treatment regimen period; PAS population, ANCOVA with mBOCF)

Population	LSM change from baseline (SE)		LSM difference vs ustekinumab (95% CI) [p-value]
	Ustekinumab IV/SC[a]	Miri IV/SC[b]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Ustekinumab dose regimen is ~6mg/kg IV at Week 0, then 90 mg SC Q8W starting at Week 8. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W. Note: of the [redacted] patients receiving mirikizumab and [redacted] patients receiving ustekinumab in VIVID-1, [redacted] and [redacted] of these patients were used in this analysis for mirikizumab and ustekinumab, respectively.

Abbreviations: ANCOVA: analysis of covariance; BF: biologic-failed; CCF: conventional care-failed; CI: confidence interval; IV: intravenous; LSM: least square mean; mBOCF: modified baseline observation carried forward; Miri: mirikizumab; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous; SE: standard error; VAS: visual analogue scale.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.81 (page 1889, 1891).[2] Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs, Output t_a_qs_eq5d5l_vas_chg_ancova_a8_pasbf (pages 69 and 71) and Output t_a_qs_eq5d5l_vas_chg_ancova_a8_pasnbf (pages 75 and 77).[1]

A9. Priority question. Please provide comparisons between mirikizumab and placebo for endoscopic response at Week 12 and Week 52 (to match those in Table 26 of the company submission for mirikizumab versus ustekinumab) for the PAS population, CCF subgroup and BF subgroup of VIVID-1.

The comparisons between mirikizumab and placebo for endoscopic response at Week 12 and Week 52 for the PAS population and the CCF and BF subgroups of VIVID-1 are presented in Table 10.

Table 10: Endoscopic response by SES-CD at Week 12 and Week 52 (treatment regimen period; PAS, BF and CCF populations, NRI)[a]

Population	Response, n/N (%)		Risk difference[c] vs placebo (CI[d]) [p-value]
	Placebo	Miri IV/SC[b]	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Footnotes: [a] Endocscopic response is defined as ≥50 reduction from baseline in SES-CD score. [b] Mirikizumab dose regimen is 900 mg IV Q4W for 3 doses, then 300 mg SC Q4W [c] Risk differences are reported as common risk differences for the PAS population, and unadjusted risk differences for the BF and CCF subgroups. [d] 99.5% CI for Week 12 PAS population, 95% CI for all other risk differences presented
Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PAS: primary analysis set; Q4W: every 4 weeks; SC: subcutaneous; SES-CD: Simple Endoscopic Score-Crohn's disease.
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Tables AMAM.5.3 (page 84), AMAM.8.24 (page 318) and AMAM.8.33 (pages 540 and 542).[2]

A10. Please provide the equivalent of Figure 39: Summary of patient disposition in VIVID-1 (PAS population), for the CCF and BF subgroups of VIVID-1.

Patient disposition diagrams for the BF and CCF subgroups from VIVID-1 are presented in Figure 1 and Figure 2, respectively.

Figure 1: Summary of patient disposition in VIVID-1 (BF subgroup)

Abbreviations: BF: biologic-failed; IV: intravenous; Miri: mirikizumab, Q4W: every 4 weeks; Q8W: every 8 weeks; SC: subcutaneous; Uste: ustekinumab.
Source: Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs, Output t_trtdsp_p1_pasbf and Output t_trtdsp_p2_pasbf (pages 79 and 82).[1]

Figure 2: Summary of patient disposition in VIVID-1 (CCF subgroup)

Abbreviations: CCF: conventional care-failed; IV: intravenous; Miri: mirikizumab, Q4W: every 4 weeks; Q8W: every 8 weeks; SC: subcutaneous; Uste: ustekinumab
Source: Eli Lilly (Data on File). VIVID-1 Additional Clinical Study Outputs, Output t_trtdsp_p1_pasnbf and Output t_trtdsp_p2_pasnbf (pages 80, 81 and 83).[1]

Adverse events

A11. Priority question. Grade 3 and above adverse events were not presented in the company submission.

a) **Please clarify why Grade 3 and above adverse events were not presented.**
b) **Please provide the number of patients with Grade 3 or above adverse events for each trial arm in VIVID-1 and a breakdown of the type of adverse events.**

Adverse event (AE) data collected from VIVID-1 were not stratified by Grade as per the Common Terminology Criteria for Adverse Events (CTCAE). AEs were instead reported as mild, moderate or severe only. This is in alignment with other recently published NICE appraisals in CD (TA888 and TA905) which reported only the number of patients with "Severe" treatment emergent adverse events (TEAEs) rather than AEs by grade.[8, 9]

In the absence of reported Grade 3+ AE data from VIVID-1, an overview of the TEAEs with a maximum reported severity of "Severe" (as assessed by the investigator) for each System Organ Class is presented in Table 11. Lilly believe that the presented data should satisfy the request by the EAG.

Full details of TEAEs by maximum severity categorised by MedDRA Preferred Terms are reported in Table AMAM.8.128 of the VIVID-1 Clinical Study Report.[2]

Table 11: Overview of severe TEAEs per System Organ Class in the VIVID-1 trial (safety population)

System Organ Class	Treatment Regimen Period, n (%)		
	PBO (N=[redacted])	Miri (N=[redacted])	Uste (N=[redacted])
Patients with ≥1 severe TEAE	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]

Metabolism and nutrition disorders			
Respiratory, thoracic and mediastinal disorders			
Vascular disorders			
Renal and urinary disorders			
Psychiatric disorders			
Surgical and medical procedures			
Hepatobiliary disorders			
Reproductive system and breast disorders			
Immune system disorders			
Cardiac disorders			
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Ear and labyrinth disorders			
Congenital, familial and genetic disorders			
Pregnancy, puerperium and perinatal conditions			

Abbreviations: Miri: mirikizumab; PBO: placebo; TEAE: treatment emergent adverse event; Uste: ustekinumab
Source: Eli Lilly (Data on File). VIVID-1 Clinical Study Report, Table AMAM.8.128 (pages 3071 – 4009).[2]

NMAs

A12. Priority question: The EAG considers that based on the odds ratios from the company's NMA, many of the results favour risankizumab (see table below, reproduced based on Table 34 of the CS). Please justify how clinical similarity has been demonstrated (beyond a non-significant result) for mirikizumab compared to risankizumab.

As noted in the main Company submission, head-to-head data between mirikizumab and ustekinumab in the treatment of patients with moderately to severely active CD are available from the VIVID-1 trial. These data demonstrate clinical non-inferiority between mirikizumab and ustekinumab. Similar conclusions of clinical equivalence were established between risankizumab and ustekinumab in TA888.[9] Based on conclusions of clinical similarity between mirikizumab and ustekinumab, and between ustekinumab and risankizumab, it follows that mirikizumab may be considered to have similar efficacy to risankizumab in the same patient population. This is supported by mirikizumab having the same mechanism of action (anti-IL23p19) and a similar method of administration (intravenous [IV] induction, subcutaneous [SC] maintenance) as risankizumab.

Nevertheless, network meta-analyses (NMAs) were performed in the original Company submission to explore the clinical efficacy of mirikizumab versus risankizumab. A standard method to determine clinical equivalence in an NMA involves analysing if the confidence or

credible intervals of the relative treatment effects encompass the value of '1'. When these intervals include 1, it is indicative of an absence of statistically significant differences between the compared treatments, suggesting potential clinical similarity.

Additional Considerations for Clinical Equivalence

- Effect Modifiers Distribution: Effect modifiers, which are specific patient or study characteristics influencing the comparative treatment effect, must be accounted for in any NMAs. In the performed NMA, adjustments were made for the various effect modifiers by conducting separate subgroup analyses for the CCF and BF populations, modifying baseline risks as needed, and omitting outlier trials, based on the most reliable information available. In addition to prior anti-tumour necrosis factor (anti-TNF) treatment experience, heterogeneity in baseline characteristics was assessed for the following potential effect-modifiers: Age, Sex, Weight, Asian population, Time since CD diagnosis, Site of disease, Behaviour of disease, Concomitant medications and Baseline CDAI score. ADVANCE and MOTIVATE were not considered to be outlier studies.
- Study Design Consistency: The uniformity of trial methodologies can imply clinical similarity. Nevertheless, this is not uniformly applicable in the Crohn's disease space, particularly for maintenance studies. For instance, the VIVID-1 trial employed a treat-through design, contrasting with the re-randomised approach of other studies. To enhance comparability, data from the VIVID-1 trial were recalibrated to align with the re-randomised trial format in the maintenance phase, thus promoting clinical similarity and enabling more precise comparisons.

To mitigate potential biases from clinical dissimilarity, Lilly has outlined the primary distinctions between trials and identified any potential sources of bias within the NMA. Sensitivity analyses were also performed to gauge the influence of potential effect modifiers.

In addition, any variations in effect modifiers and study designs have also been evaluated. All trials incorporated into the analysis underwent clinical validation. Additionally, extensive sensitivity analyses were executed to affirm the robustness of the results against pivotal decisions that could impact the NMA. As presented in the original Company submission, Lilly found that the results of the NMA remained unaffected by these analyses. Clinical experts concur that the data supports the conclusion that there is no substantiated basis for clinical dissimilarity between risankizumab and mirikizumab. This conclusion of clinical similarity between mirikizumab and risankizumab remains unchanged based on the results of the updated induction analyses presented below in response to Questions A13 and A14.

A13. Priority question: Due to the network created by the included treatments, doses and studies informing them, the EAG is concerned that the current network meta-analyses (NMAs) are based on an overly complicated network that does not provide additional information on the main comparator of interest (risankizumab). The use of a more complicated network adds unnecessary complexity and heterogeneity. The EAG therefore considers a simplified network of trials focussing only on risankizumab would provide

more precise estimates for the outcomes of interest and could form a more robust basis for an assessment of clinical similarity.

Please conduct indirect treatment comparisons (ITCs) to enable comparison between mirikizumab and risankizumab (via placebo) in the induction period using only the VIVID-1 mirikizumab and placebo arms, and:

a) **the risankizumab and placebo arms from ADVANCE for the CCF population;**

b) **the risankizumab and placebo arms from ADVANCE and from MOTIVATE for the BF population;**

c) **the risankizumab and placebo arms from ADVANCE and from MOTIVATE for the ITT population.**

For each population please provide results for the following outcomes without baseline risk adjustment:

a) **enhanced clinical response;**

b) **clinical remission;**

c) **endoscopic response; and**

d) **endoscopic remission.**

Lilly has conducted Bucher indirect treatment comparisons (ITCs) to evaluate the differences between risankizumab and mirikizumab. All requested analyses have been completed, with the exception of combining the CCF and BF populations.

Regarding the intent-to-treat (ITT) requests, such analyses were not observed in previous submissions. It is expected that the value of these estimates would be negligible, as the combination of the BF and CCF populations would result in a varied distribution of effect modifiers, leading to biased outcomes. Table 12 below displays the patients in each subgroup in the trials included in the Bucher ITC.

If ITT efficacy analyses were to be conducted, efficacy estimates comparing mirikizumab with a [redacted] distribution of CCF and BF patients, respectively, would need to be obtained. For risankizumab, the distribution would be 27%/73%. Lilly believe this significant imbalance would greatly impact the results, and therefore, these comparisons should be discouraged.

Table 12: Number of patients in the CCF and BF subgroups of the trials in the Bucher ITCs

Trial	Subgroup	Mirikizumab	Placebo

		N	%	N	%
VIVID-1	CCF	[redacted]	[redacted]	[redacted]	[redacted]
	BF	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]		[redacted]	
		Risankizumab		**Placebo**	
ADVANCE	CCF	141	42%	78	45%
	BF	195	58%	97	55%
	Total	**336**		**175**	
MOTIVATE	CCF	0	0%	0	0%
	BF	191	100%	187	100%
	Total	**191**		**187**	
ADVANCE+MOTIVATE	CCF	141	27%	78	22%
	BF	386	73%	284	78%
	Total	**527**		**362**	

Abbreviations: BF: biologic-failed; CCF: conventional care-failed; ITC: indirect treatment comparisons.

CCF population

The summary of the results from the Bucher ITC of enhanced clinical response in the CCF population is presented in Table 13. The initial NMA presented in the original Company submission yielded an odds-ratio (OR) of 0.9 (0.57−1.40) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model with baseline risk adjustment. While the OR underwent a numerical alteration upon analysis using the Bucher ITC method, still no statistically significant difference was observed between the two treatments.

Table 13: Summary of results of the enhanced clinical response outcome – CCF population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	87/141 (61.70%)	31/78 (39.7%)	0.409 (0.232, 0.721)
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	0.657 (0.318, 1.356)

Abbreviations: CCF: conventional care-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

The summary of the results from the Bucher ITC of clinical remission in the CCF population is presented in Table 14. The initial NMA presented in the original Company submission yielded an OR of 0.68 (0.38−1.29) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model with baseline risk adjustment. While the OR underwent a numerical alteration upon analysis using the Bucher ITC method, still no statistically significant difference is observed between the two treatments.

Table 14: Summary of results of the clinical remission outcome – CCF population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	69/141 (48.94%)	18/78 (23.08%)	0.313 (0.168, 0.583)
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	0.600 (0.270, 1.334)

Abbreviations: CCF: conventional care-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

The summary of the results from the Bucher ITC of endoscopic response in the CCF population is presented in Table 15. The initial NMA presented in the original Company submission yielded an OR of 0.46 (0.18−1.17) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model. While the OR underwent a numerical alteration upon analysis using the Bucher ITC method, no statistically significant difference is observed between the two treatments.

Table 15: Summary of results of the endoscopic response outcome – CCF population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	71/141 (50.35%)	10/78 (12.82%)	0.145 (0.069, 0.304)
Indirect estimate of effect for Mirikizumab vs Risankizumab	FE	-	-	0.443 (0.1737, 1.129)

Abbreviations: CCF: conventional care-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

The summary of the results from the Bucher ITC of endoscopic remission in the CCF population is presented in Table 16. The initial NMA presented in the original Company submission yielded an OR of 0.73 (0.27-2.00) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model. While the OR underwent a minimal numerical alteration upon analysis using the Bucher ITC method, still no statistically significant difference is observed between the two treatments.

Table 16: Summary of results of the endoscopic remission outcome – CCF population

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	45/141 (37.9%)	11/78 (14.10%)	0.350 (0.169, 0.726)

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Indirect estimate of effect for mirikizumab vs risankizumab	FE			0.733 (0.274, 1.963)

Abbreviations: CCF: conventional care-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

BF population

The summary of the results from the Bucher ITC of enhanced clinical response in the BF population is presented in Table 17. The initial NMA presented in the original Company submission yielded an OR of 0.79 (0.48-1.33) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model. While the OR underwent a minimal numerical alteration upon analysis using the Bucher ITC method, still no statistically significant difference is observed between the two treatments.

Table 17: Summary of results of the enhanced clinical response outcome – BF population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	114/195 (58.46%)	33/97 (34.02%)	0.366 (0.221, 0.609)
	MOTIVATE	114/191 (59.69%)	56/187 (29.94%)	0.289 (0.189, 0.442)
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	0.8906 (0.499, 1.590)

Abbreviations: BF: biologic-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

The summary of the results from the Bucher ITC of clinical remission in the BF population is presented in Table 18. The initial NMA presented in the original Company submission yielded an OR of 0.71(0.40-1.23) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model. While the OR underwent a minimal numerical alteration upon analysis using the Bucher ITC method, no statistically significant difference is observed between the two treatments.

Table 18: Summary of results of the clinical remission outcome – BF population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	83/195 (42.56%)	25/97 (25.77%)	0.469 (0.274, 0.801)
	MOTIVATE	80/191 (41.88%)	37/187 (19.79%)	0.342 (0.216, 0.542)

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	0.657 (0.351, 1.231)

Abbreviations: BF: biologic-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

The summary of the results from the Bucher ITC of endoscopic response in the BF population is presented in Table 19. The initial NMA presented in the original Company submission yielded an OR of 0.84 (0.49-1.51) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model with baseline risk adjustment. While the OR underwent a minimal numerical alteration upon analysis using the Bucher ITC method, still no statistically significant difference is observed between the two treatments.

Table 19: Summary of results of the endoscopic response outcome – BF population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	64/195 (32.82%)	11/97 (11.34%)	0.262 (0.131, 0.525)
	MOTIVATE	55/191 (28.80%)	21/187 (11.23%)	0.313 (0.180, 0.543)
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	1.183 (0.489, 2.861)

Abbreviations: BF: biologic-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

The summary of the results from the Bucher ITC of endoscopic remission in the BF population is presented in Table 20. The initial NMA presented in the original Company submission yielded an OR of 1.63 (0.39-11.4) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a fixed-effect model. While the OR underwent a minimal numerical alteration upon analysis using the Bucher ITC method, no statistically significant difference is observed between the two treatments.

Table 20: Summary of results of the endoscopic remission outcome – BF population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	36/195 (18.46%)	5/97 (5.15%)	0.240 (0.091, 0.633)
	MOTIVATE	37/191 (19.37%)	8/187 (4.29%)	0.186 (0.084, 0.412)

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	1.484 (0.309, 7.119)

Abbreviations: BF: biologic-failed; CI: confidence intervals; FE: fixed effect; OR: odds ratio.

Conclusion

Lilly acknowledge the complexity of the network, however, highlight this was necessary to encompass all comparators pertinent to the initial scope of the decision problem. When examining the comparison involving risankizumab, it is necessary to understand the network geometry to assess the influence of other comparators and placebo. Risankizumab is linked within the network exclusively through placebo, indicating that other input data exert a minimal impact on the outcomes for the fixed-effect models that do not adjust for baseline risk. Consequently, the FE models are expected to yield results aligned with those of the Bucher method.

In summary, none of the newly-performed Bucher ITCs provided evidence contrary to the conclusion that there is no statistically significant difference in the clinical efficacy of mirikizumab and risankizumab in the induction period.

A14. Priority question: Please conduct ITCs to enable comparison between mirikizumab and risankizumab (via placebo) in the induction period using only the mirikizumab and placebo arms from VIVID-1, and the risankizumab and placebo arms from ADVANCE, MOTIVATE and Feagan 2017 for the following outcomes:

a) **all-cause discontinuations;**

b) **discontinuations due to AEs;**

c) **serious adverse events (SAEs); and**

d) **treatment-emergent adverse events (TEAEs)**

Due to the absence of data on discontinuations caused by AEs or TEAEs for the VIVID-1 study, the requested analyses could not be conducted. However, the Bucher ITCs for all-cause discontinuations and serious adverse events (SAEs) have been completed.

A summary of the results from the Bucher ITC of all-cause discontinuation in the overall population is presented in Table 21. The initial NMA presented in the original Company submission yielded an OR of 1.63 (0.52-5.74) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a random effects model. While the OR underwent a numerical alteration upon analysis using the Bucher ITC method, still no statistically significant difference is observed between the two treatments.

Table 21: Summary of results of the all-cause discontinuation outcome – overall population

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	16/336 (4.76%)	25/175 (14.26%)	-
	MOTIVATE	6/191 (3.14%)	26/187 (13.90%)	-
	Feagan 2017	6/39 (15.28%)	1/41 (2.44%)	-
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	1.5081 (0.6395, 3.5567)

Abbreviations: CI: confidence intervals; FE: fixed effect; OR: odds ratio.

The summary of the results from the Bucher ITC of SAEs in the overall population is presented in Table 22. The initial NMA presented in the original Company submission yielded an OR of 2.36 (0.92, 6.67) for mirikizumab compared to risankizumab. These results stem from the selected model, which was a random effects model. While the OR underwent a numerical alteration upon analysis using the Bucher ITC method, still no statistically significant difference is observed between the two treatments.

Table 22: Summary of results of the SAEs outcome – overall population, induction

Trial type or estimate	Trial ID	Intervention, n/N (%)	Placebo, n/N (%)	OR (95% CI)
Mirikizumab vs. placebo trials	VIVID-1	[redacted]	[redacted]	[redacted]
Risankizumab vs. placebo trials	ADVANCE	27/373 (7.24%)	28/186 (15.05%)	-
	MOTIVATE	10/206 (4.85%)	26/207 (12.56%)	-
	Feagan 2017	6/39 (15.28%)	1/41 (2.44%)	-
Indirect estimate of effect for mirikizumab vs risankizumab	FE	-	-	1.6783 (0.8186, 3.4410)

Abbreviations: CI: confidence intervals; FE: fixed effect; OR: odds ratio; SAE: serious adverse event.

A15. Priority question: The EAG notes that the placebo data from the randomised population of FORTIFY comprises of patients who have received prior risankizumab. The EAG therefore does not consider these data suitable for inclusion in a network meta-analysis with the placebo data from VIVID-1.

Please conduct an unanchored Matching-Adjusted Indirect Comparison (MAIC) between mirikizumab and risankizumab in the maintenance period using only the VIVID-1 mirikizumab arm, and the FORTIFY risankizumab 360mg arm for the outcomes of:

- **enhanced clinical response;**
- **clinical remission;**
- **endoscopic remission; and**
- **endoscopic response**

in the following populations:

a) **CCF population;**
b) **BF population;**
c) **overall population.**

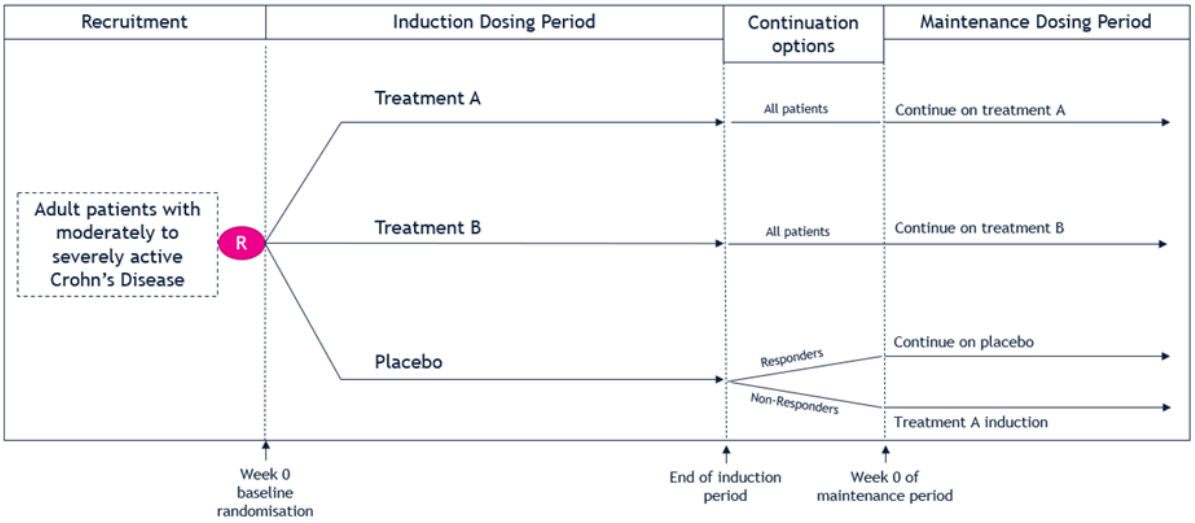
Please provide baseline characteristics before and after matching along with the results for each outcome and accompanying 95% confidence interval.

As requested, Lilly have conducted unanchored matching adjusted indirect comparisons (MAICs) in the maintenance period using data from the mirikizumab arm of VIVID-1 and the risankizumab 360 mg arm of FORTIFY. However, due to differences in trial design, as discussed below, unanchored MAICs have been conducted for the overall population only (i.e., combining the CCF and BF subgroups). Unanchored MAICs were conducted for all requested outcomes in clarification question A15.

MAIC data sources and feasibility

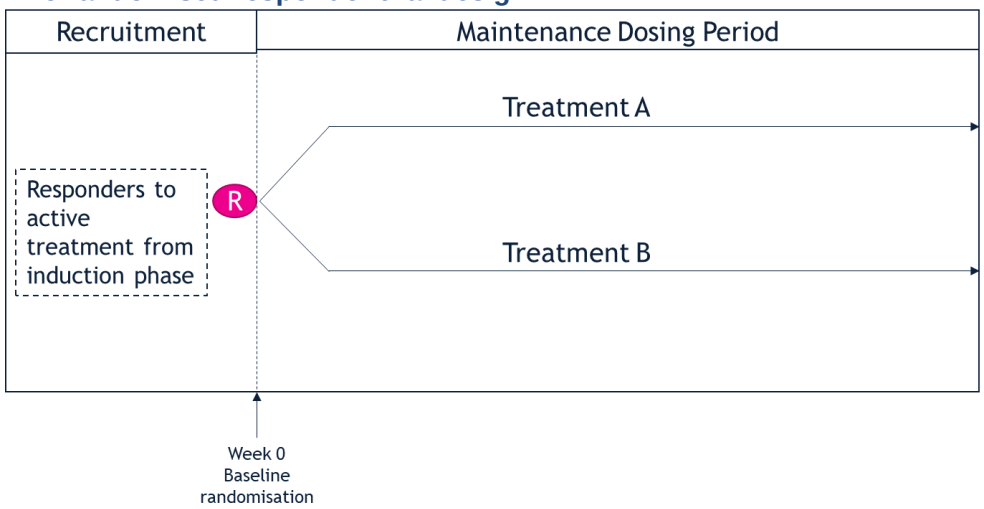
Figure 3 depicts the treat-through trial design for VIVID-1. Patients in treat-through trials are randomised at baseline to either the study drug or a comparator (either another active treatment or placebo), and outcomes are measured multiple times thereafter.

Figure 3: Treat-through trial design



FORTIFY is the maintenance period trial from a re-randomised responder trial design (Figure 4), whereby patients were enrolled following completion from either induction studies ADVANCE or MOTIVATE. Responders on the risankizumab treatment arms from the induction studies were re-randomised at the start of the FORTIFY trial (maintenance period) to continue either risankizumab or placebo. It therefore follows that patients assigned to placebo arms in re-randomised trials present different treatment histories as they responded to different induction treatments.

Figure 4: Re-randomised responder trial design



Footnote: Patients in re-randomised responder trials are either randomised at the start of induction to either study drug or placebo, or all receive induction therapy with the study drug of interest. Following induction, responders who received the study drug are re-randomised at the start of the maintenance period to either continue or discontinue active treatment.

Patients entering the maintenance phase are systematically different in treat-through trials compared to re-randomised responder trials. Therefore, combining the reported maintenance phase outcomes from these divergent trial designs violates the similarity and homogeneity assumptions necessary for an NMA. Additionally, patients in FORTIFY's re-randomised trials may experience a "carry-over" effect from their active treatment during the induction period, and a heightened level of response at maintenance, which may vary by induction treatment given and introduce an unknown degree of heterogeneity between re-randomised trials.

Consequently, an unanchored MAIC to compare the efficacy of mirikizumab and risankizumab was recommended to address these challenges.

In these analyses, only patients that entered the maintenance phase with either mirikizumab (from VIVID-1) and risankizumab (from FORTIFY), and were responders at the end of induction, were included. Individual patient-level data (IPD) from the VIVID-1 trial were considered in the MAIC and included pooled CCF and BF data for patients who received mirikizumab in VIVID-1.[2] Data for risankizumab were sourced from the FORTIFY trial, and included both CCF and BF patients who were treated with risankizumab 360 mg. IPD for FORTIFY were not available for this comparison and therefore only aggregated-level data from the FORTIFY trial was used.[10]

Determination of prognostic factors and effect modifiers

Treatment effect modifiers (TEM) are defined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 as *"a covariate that alters the effect of treatment on outcomes, so that the treatment is more or less effective in different subgroups formed by levels of the effect modifier."*[11]

Parameters considered relevant for matching due to their classification as treatment effect modifiers or prognostic factors were identified based on a literature search and discussed with a clinical expert. Potential TEMs identified were disease duration, CDAI score, previous biologic failure and number of failed biologics, as well as corticosteroids and immunosuppressant use at baseline.[12] Colonic disease was also considered a potential treatment effect modifier but no evidence was available from either study.[12] Colonic disease, age and concomitant medication were considered prognostic factors.[9, 13-18] Additionally, the distributions of ileal disease involvement, weight, sex and Asian race, were assessed given these parameters were included in previous heterogeneity assessments in CD.[9, 19, 20]

These factors were combined in the base case MAIC, and a sensitivity analysis was conducted to test the robustness of the results. Comparing VIVID-1 and FORTIFY, most characteristics were comparable. Differences were seen for 'time since CD diagnosis' (higher in FORTIFY), CDAI scores (higher in VIVID-1), the proportion of Asian patients (higher in VIVID-1) and the proportion of patients with prior biologic treatment (higher in FORTIFY). A summary of the baseline characteristics of patients included in the unanchored MAIC are presented in Table 23. Baseline characteristics of patients from the mirikizumab arm of VIVID-1 are presented both before and after matching to the risankizumab 360 mg arm of patients from FORTIFY.

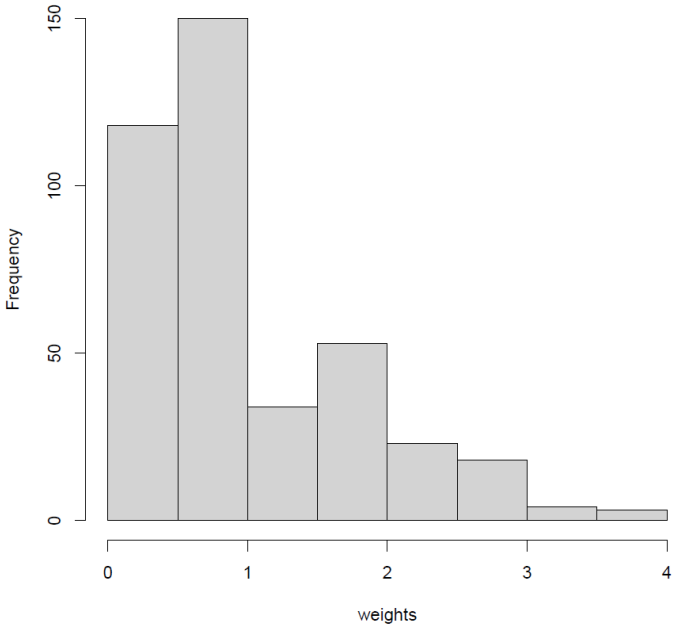
Table 23: Summary of baseline characteristics of patients included in the unanchored MAIC

	Base Case Analysis			Sensitivity Analysis		
	Before matching	After matching	Target	Before matching	After matching	Target
Baseline covariates	VIVID-1 (IPD)	VIVID-1 (IPD)	FORTIFY RIS 360 mg	VIVID-1 (IPD)	VIVID-1 (IPD)	FORTIFY RIS 360 mg
Age (years), mean (SD)	[redacted]	37 (12.8)	37 (12.8)	[redacted]	37 (12.8)	37 (12.8)
Male, %	[redacted]	57.4	57.4	[redacted]	57.4	57.4
Asian, %	[redacted]	14.2	14.2	[redacted]	14.2	14.2
Time since CD diagnosis (years), mean (SD)	[redacted]	9.3 (8.1)	9.3 (8.1)	[redacted]	9.3 (8.1)	9.3 (8.1)
Baseline CDAI, mean (SD)	[redacted]	137.2 (67.8)	137.2 (67.7)	[redacted]	137.2 (67.8)	137.2 (67.7)
Corticosteroids, %	[redacted]	29.8	29.8	[redacted]	29.8	29.8
Immunosuppressants, %	[redacted]	28.4	28.4	[redacted]	28.4	28.4
Prior biologics treatment, %	[redacted]	72.3	72.3	[redacted]	72.3	72.3
ESS	[redacted]	254	141	[redacted]	254	141
Weight (kg), mean (SD)[a]				[redacted]	70.4 (17.5)	70.4 (17.5)
Disease location, %[a]						
Ileal				[redacted]	10.6	10.6
Colonic				[redacted]	41.8	41.8

Footnotes: [a]Indicated covariates were matched for the sensitivity analysis only.
Abbreviations: CD: Crohn's disease; CDAI: Crohn's disease activity index; ESS: effective sample size; IPD: individual patient data; MAIC: matching-adjusted indirect comparison; RIS: risankizumab; SD: standard deviation.
Source: Eli Lilly (Data on File). Population-Adjusted Indirect Treatment Comparisons for Mirikizumab versus Risankizumab in Crohn's disease: Results.[21]

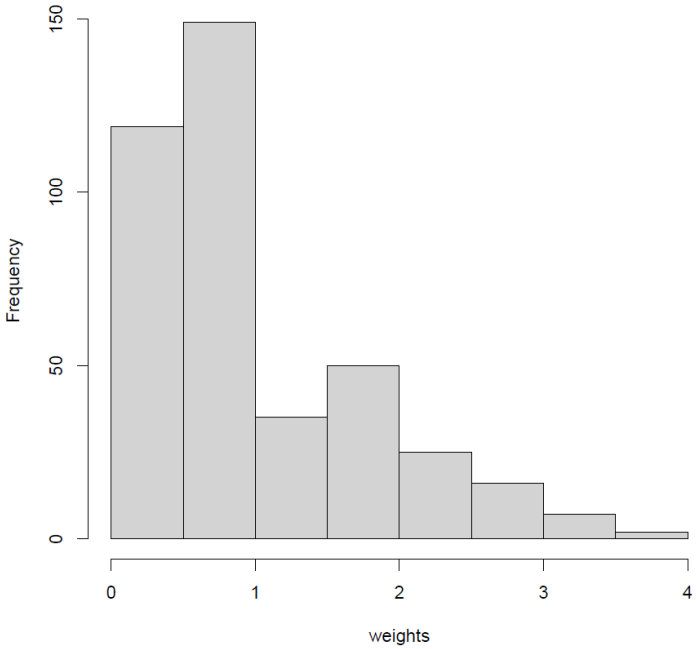
Histograms of the rescaled weights for VIVID-1, based on the covariates noted above, are presented for the base case unanchored MAIC and the sensitivity analysis in Figure 5 and Figure 6, respectively.

Figure 5: Histogram of the rescaled weights for VIVID-1 for the base case MAIC



Abbreviations: MAIC: matching-adjusted indirect comparison.
Source: Eli Lilly (Data on File). Population-Adjusted Indirect Treatment Comparisons for Mirikizumab versus Risankizumab in Crohn's disease: Results.[21]

Figure 6: Histogram of the rescales weights for VIVID-1 for the sensitivity analysis MAIC



Abbreviations: MAIC: matching-adjusted indirect comparison.
Source: Eli Lilly (Data on File). Population-Adjusted Indirect Treatment Comparisons for Mirikizumab versus Risankizumab in Crohn's disease: Results.[21]

MAIC methodology

The unanchored MAIC was conducted in line with the recommendations detailed in the NICE DSU TSD 18,[11] based on the methods originally described by Signorovitch *et al.* (2012).[22] The matching methodology was designed to statistically construct trial patient populations that were like one another so that the outcomes from the trials could be meaningfully compared. Population adjustment was made using the IPD from one or more studies, in this case the VIVID-1 study, and aggregated level data from the comparator studies. The unanchored matching adjusted indirect comparisons were performed using the R package MAIC[1] under R4.3.2.

Results

Base case results from the unanchored MAIC between mirikizumab and risankizumab for efficacy outcomes are presented in Table 24 below. Mirikizumab demonstrated a statistically significantly higher clinical response rate than risankizumab (OR: 2.803 [1.757,4.470], p<0.001). No statistically significant differences between the two treatments were identified for clinical remission, endoscopic remission or endoscopic response. Results of the sensitivity analyses were very similar to those of the base case analysis (Table 25), demonstrating the robustness of the analysis.

Table 24: Efficacy results of the unanchored MAIC between mirikizumab and risankizumab (base case)

Endpoint	Responses, n (%) [N]		OR (95% CI)	SE (log OR)	p-value
	Risankizumab	Mirikizumab			
Clinical remission					
Unadjusted	74 (52.5) [141]	263 (65.3) [403]	1.701 (1.153, 2.510)	0.198	0.007
uMAIC	74 (52.5) [141]	205 (66.1) [310]	1.777 (1.162, 2.716)	0.216	0.008
Clinical response					
Unadjusted	84 (59.6) [141]	330 (81.9) [403]	3.068 (2.013, 4.674)	0.215	<0.001
uMAIC	84 (59.6) [141]	249 (80.3) [310]	2.803 (1.757, 4.470)	0.238	<0.001
Endoscopic remission					
Unadjusted	55 (39.0) [141]	136 (33.7) [403]	0.796 (0.536, 1.184)	0.202	0.261
uMAIC	55 (39.0) [141]	103 (33.2) [310]	0.779 (0.506, 1.198)	0.220	0.255
Endoscopic response					
Unadjusted	66 (46.8) [141]	220 (54.6) [403]	1.366 (0.930, 2.007)	0.196	0.112
uMAIC	66 (46.8) [141]	169 (54.5) [310]	1.365 (0.900, 2.069)	0.212	0.143

Abbreviations: uMAIC: unanchored matching-adjusted indirect comparison; OR: odds ratio; SE: standard error;
Source: Eli Lilly (Data on File). Population-Adjusted Indirect Treatment Comparisons for Mirikizumab versus Risankizumab in Crohn's disease: Results.[21]

Table 25: Efficacy results of the unanchored MAIC between mirikizumab and risankizumab (sensitivity analysis)

Endpoint	Responses, n (%) [N]		OR (95% CI)	SE (log OR)	p-value
	Risankizumab	Mirikizumab			
Clinical remission					
Unadjusted	74 (52.5) [141]	263 (65.3) [403]	1.701 (1.153, 2.510)	0.198	0.007

[1] https://roche.github.io/MAIC/articles/MAIC.html

Endpoint	Responses, n (%) [N]		OR (95% CI)	SE (log OR)	p-value
	Risankizumab	Mirikizumab			
uMAIC	74 (52.5) [141]	205 (66.1) [310]	1.775 (1.161, 2.714)	0.217	0.008
Clinical response					
Unadjusted	84 (59.6) [141]	330 (81.9) [403]	3.068 (2.013, 4.674)	0.215	<0.001
uMAIC	84 (59.6) [141]	249 (80.3) [310]	2.804 (1.757, 4.475)	0.239	<0.001
Endoscopic remission					
Unadjusted	55 (39.0) [141]	136 (33.7) [403]	0.796 (0.536, 1.184)	0.202	0.261
uMAIC	55 (39.0) [141]	103 (33.2) [310]	0.778 (0.505, 1.196)	0.220	0.252
Endoscopic response					
Unadjusted	66 (46.8) [141]	220 (54.6) [403]	1.366 (0.930, 2.007)	0.196	0.112
uMAIC	66 (46.8) [141]	169 (54.5) [310]	1.361 (0.898, 2.063)	0.212	0.146

Abbreviations: uMAIC: unanchored matching-adjusted indirect comparison; OR: odds ratio; SE: standard error.
Source: Eli Lilly (Data on File). Population-Adjusted Indirect Treatment Comparisons for Mirikizumab versus Risankizumab in Crohn's disease: Results.[21]

A16. Priority question: Please conduct an unanchored MAIC between mirikizumab and risankizumab in the maintenance period using only the VIVID-1 mirikizumab arm, and the FORTIFY risankizumab 360mg arm for the following outcomes:

a) all-cause discontinuations;

b) discontinuations due to AEs;

c) serious adverse events (SAEs); and

d) treatment-emergent adverse events (TEAEs)

Please provide baseline characteristics before and after matching along with the results for each outcome and accompanying 95% confidence interval.

Unanchored MAICs for safety outcomes were only conducted for AEs leading to treatment discontinuation, due to the unavailability of comparable data between the VIVID-1 IPD, and the aggregate-level data from FORTIFY.

The baseline characteristics for patients in the unanchored MAIC for safety outcomes were assumed to be equal to those in the efficacy analysis population (see Table 23).

Results

Safety results of the base case unanchored MAIC between mirikizumab and risankizumab are presented in Table 26 below. No statistically significant differences in discontinuation due to AEs were identified between the two treatments (OR: 0.815 [0.281,2.367], p=0.707). Results of the sensitivity analyses were very similar to those of the base case analysis (Table 27), demonstrating the robustness of the analysis.

Table 26: Safety results of the unanchored MAIC between mirikizumab and risankizumab (base case)

Endpoint	Responses, n (%) [N]		OR (95% CI)	SE (log OR)	p-value
	Risankizumab	Mirikizumab			
Discontinuation due to AEs[a]					
Unadjusted	6 (3.4) [179]	13 (3.2) [403]	0.961 (0.359, 2.571)	0.502	0.937
uMAIC	6 (3.4) [179]	9 (2.9) [310]	0.815 (0.281, 2.367)	0.544	0.707

Footnotes: [a]The baseline characteristics for patients in the safety population were assumed to be equal to those in the efficacy analysis population.
Abbreviations: AE: adverse event; uMAIC: unanchored matching-adjusted indirect comparison; OR: odds ratio; SE: standard error.
Source: Eli Lilly (Data on File). Population-Adjusted Indirect Treatment Comparisons for Mirikizumab versus Risankizumab in Crohn's disease: Results.[21]

Table 27: Safety results of unanchored MAIC between mirikizumab and risankizumab (sensitivity analysis)

Endpoint	Responses, n (%) [N]		OR (95% CI)	SE (log OR)	p-value
	Risankizumab	Mirikizumab			
Discontinuation due to AEs[a]					
Unadjusted	6 (3.4) [179]	13 (3.2) [403]	0.961 (0.359, 2.571)	0.502	0.937
uMAIC	6 (3.4) [179]	9 (2.9) [310]	0.815 (0.280, 2.369)	0.544	0.707

Footnotes: [a]The baseline characteristics for patients in the safety population were assumed to be equal to those in the efficacy analysis population.
Abbreviations: AE: adverse event; uMAIC: unanchored matching-adjusted indirect comparison; OR: odds ratio; SE: standard error.
Source: Eli Lilly (Data on File). Population-Adjusted Indirect Treatment Comparisons for Mirikizumab versus Risankizumab in Crohn's disease: Results.[21]

A17. If sufficient data are available and the company considers that adjustments are warranted, please conduct the ITCs requested in Question A13 with baseline risk adjustment.

In NMAs utilising only aggregate data, such as that performed in this submission, the baseline risk adjustment coefficient is derived from the estimated baseline risks across all contributing trials. However, if the data set is limited to merely two or three trials, it is insufficient for the model to produce a credible posterior distribution of the beta coefficient (i.e., the coefficient for placebo adjustments). Therefore, for the Bucher ITCs conducted, baseline risk adjustment was not feasible.

A18. For each of the ITCs in questions A13 to A16, please confirm the outcome definitions used by each of the studies.

Efficacy outcomes of interest in the CCF and BF populations for the included studies:

- Enhanced clinical response (decrease in CDAI≥100)
- Clinical remission (CDAI<150)
- Endoscopic response was defined by all studies reporting it as a decrease in Simple Endoscopic Score–Crohn's disease (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.

- Endoscopic remission was described by almost all studies reporting it 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. Only one study defined it as an SES-CD total score ≤2 (FORTIFY).

Safety outcomes of interest in the overall population:

- Serious adverse events (SAEs)
- All cause discontinuations

A19. Priority question. The number of adverse events for placebo, mirikizumab and ustekinumab are provided in the overview of adverse events for the VIVID-1 trial (Tables 35 and 36 in Document B).

a) Please provide similar data for the risankizumab trials (ADVANCE, MOTIVATE, FORTIFY and Feagan 2017) as included in Tables 35 and 36;

Safety data for the Feagan 2017 (Table 28), ADVANCE (Table 29), MOTIVATE (Table 29) and FORTIFY (Table 30) studies for risankizumab are presented below.

Table 28: Safety data for Feagan 2017

Adverse event	PBO (N=39)	RIS 200 mg (N=41)	RIS 600 mg (N=41)
Any adverse event, n (%)	32 (82)	32 (78)	31 (76)
Severe	9 (23)	6 (15)	3 (7)
Drug-related	8 (21)	10 (24)	5 (12)
Leading to discontinuation	6 (15)	5 (12)	1(2)
Serious adverse event[a], n (%)	12 (31)	9 (22)	3 (7)
Common adverse events[b], n (%)			
Nausea	4 (10)	8 (20)	3 (7)
Worsening of CD	6 (15)	2 (5)	0 (0)
Abdominal pain	4 (10)	6 (15)	3 (7)
Arthralgia	3 (8)	6 (15)	6 (15)
Anaemia	4 (10)	0 (0)	2 (5)
Headache	4 (10)	6 (15)	4 (10)
Vomiting	4 (10)	3 (7)	2 (5)

Footnotes: [a]A serious adverse event was defined as any that results in death, is immediately life-threatening, results in persistent or significant disability or incapacity, requires or prolongs patient hospital stay, is a congenital anomaly or birth defect, or is an important medical event, based upon appropriate medical judgment that might jeopardise the patient and might require medical or surgical intervention. [b]Common adverse events were those reported in at least 10% of patients in any study arm.
Abbreviations: CD: Crohn's disease; PBO: placebo; RIS: risankizumab.
Source: Feagan et al. 2017.[23]

Table 29: Safety data for the ADVANCE and MOTIVATE studies

Adverse event	ADVANCE			MOTIVATE		
	PBO IV (n=186)	RIS 600 mg IV (n=373)	RIS 1200 mg IV (n=372)	PBO IV (n=207)	RIS 600 mg IV (n=206)	RIS 1200 mg IV (n=205)
Any adverse event, n (%)	105 (56)	210 (56)	191 (51)	137 (66)	98 (48)	121 (59)
Severe	18 (10)	22 (6)	18 (5)	25 (12)	7 (3)	12 (6)
Serious	28 (15)	27 (7)	14 (4)	26 (13)	10 (5)	9 (4)
Leading to discontinuation	14 (8)	9 (2)	7 (2)	17 (8)	2 (1)	5 (2)
Common adverse events[a], n (%)						
Nausea	10 (5)	17 (5)	13 (3)	11 (5)	5 (2)	3 (1)
Worsening of CD	25 (13)	10 (3)	6 (2)	33 (16)	8 (4)	4 (2)
Nasopharyngitis	5 (3)	22 (6)	22 (6)	11 (5)	8 (4)	8 (4)
Abdominal pain	10 (5)	8 (2)	10 (3)	11 (5)	5 (2)	3 (1)
Arthralgia	7 (4)	15 (4)	11 (3)	9 (4)	8 (4)	9 (4)
Anaemia	6 (3)	11 (3)	10 (3)	11 (5)	5 (2)	6 (3)
Headache	8 (4)	24 (6)	20 (5)	11 (5)	11 (5)	10 (5)
Diarrhoea	4 (2)	2 (1)	5 (1)	2 (1)	3 (1)	2 (1)

Footnotes: [a]Occurring in ≥5% of patients in any group.
Abbreviations: CD: Crohn's disease; IV: intravenous; PBO: placebo; RIS: risankizumab.
Source: D'Haens et al. (2022).[24]

Table 30: Safety data for the FORTIFY study

Adverse event	Withdrawal group (PBO SC) (n=184)	RIS 180 mg (n=179)	RIS 360 mg (n=179)
Any adverse event, n (%)	135 (73)	128 (72)	129 (72)
Severe	23 (13)	12 (7)	21 (12)
Serious	23 (13)	22 (12)	24 (13)
Leading to discontinuation	6 (3)	3 (2)	6 (3)
Common adverse events[a], n (%)			
Nausea	13 (7)	9 (5)	4 (2)
Worsening of CD	32 (17)	19 (11)	21 (12)
Nasopharyngitis	25 (14)	17 (9)	17 (9)
Abdominal pain	13 (7)	8 (4)	9 (5)
Arthralgia	20 (11)	15 (8)	17 (9)
Anaemia	8 (4)	9 (5)	8 (4)
Headache	11 (6)	9 (5)	11 (6)
Diarrhoea	10 (5)	6 (3)	4 (2)

Footnotes: Safety analysis population included participants who were randomly assigned to a group who received at least one dose of study medication in 52-week maintenance period. [a]Occurring in ≥5% of patients in any dose group.
Abbreviations: CD: Crohn's disease; PBO: placebo; RIS: risankizumab; SC: subcutaneous.
Source: Ferrante *et al*. (2022).[10]

b) Please provide a table with the serious adverse events and discontinuation data for VIVID-1 and the risankizumab trials used to inform the company's original NMAs.

SAEs and discontinuation data for the VIVID-1 and risankizumab trials which informed the Company's original NMAs are presented in Table 31 below.

Table 31: Summary of NMA Input Data: SAEs, Induction, Mixed Population

Study	Assessment time point[a]	Treatments	N	SAEs, n	SAEs %
ADVANCE	12	RKZ 600mg	373	27	7.2%
		PCB	186	28	15.1%
Feagan 2017	12	PCB	39	12	30.8%
		RKZ 600mg	41	3	7.3%
MOTIVATE	12	RKZ 600mg	206	10	4.9%
		PCB	207	26	12.6%
VIVID-1	12	PCB	[redacted]	[redacted]	[redacted]
		MIRI 900mg	[redacted]	[redacted]	[redacted]
		UST 6mg/kg	[redacted]	[redacted]	[redacted]

Footnotes: [a]In weeks. [b]Reweighted available CDAI decrease ≥70 data, as described in the RKZ NICE submission for inclusion in base case
Abbreviations: NMA: network meta-analysis; PCB: placebo; RKZ: risankizumab; SAE: serious adverse event;

A20. Priority question: Based on the company's response to questions A13 - A14, please provide clarification of whether an OR<1 favours mirikizumab or risankizumab for each ITC reported in Tables 8 - 18.

For clarification question A13, an OR<1 favours risankizumab as this would imply that mirikizumab is less likely to achieve the given outcome (e.g. clinical response). However, for serious adverse events and all cause discontinuation (clarification question A14), the opposite is true; an OR<1 favours mirikizumab as this would, again, imply that mirikizumab is less likely to incur SAEs or lead to discontinuation.

A21. Priority question: The company has provided R files containing the workflow for the NMAs. However, the EAG is unable to validate the analyses by rerunning them due to errors that occur when trying to run the code. Please can the company provide working code and the underlying dataset for the EAG to validate the analyses.

The appropriate files have been provided in the folder 'Reference Pack 2' and can be found under 'Question A21. NMA Code'.

Section B: Clarification on cost-effectiveness data

Population

B1. The setting for patient population in the model (tab "Main", cell F23) doesn't seem to work in the model (the results do not change when the population is switched to "naive" (the conventional care failure population [CCF]).

a) Please provide the cost results for the CCF population.

b) Please advise how to produce the cost results for the CCF population.

The setting for the patient population in the model (tab "Main", cell F23) impacts the mean patient body weight only. In turn, mean patient body weight in the model is used to calculate the acquisition costs for ustekinumab and infliximab, as these are weight-based drugs. As noted in Section B.4.2.2 in the Company submission, it was assumed in the base case that any leftover drug that was not used by a specific patient would be discarded (i.e., vial wastage was assumed). Therefore, when vial wastage is selected, switching between the treatment-naïve and treatment-experienced populations in the model has no impact on the acquisition costs for ustekinumab and infliximab due to the small differences in the mean body weight between the CCF and BF subgroups; the base case results remain the same and thus have not been replicated here.

When vial sharing is selected (i.e., where any leftover drug is used for another patient such that costs are accrued only for the actual amount of medication administered), the changes in the

acquisition costs for ustekinumab and infliximab result in changes in the incremental costs with mirikizumab.

Mirikizumab drug acquisition cost

B2. Priority question: In the model, there is a drug acquisition cost for a 300 mg SC injection (£2,056.56), yet in the company submission, the 300 mg maintenance dose [redacted]?

[redacted]

Comparators

B3. Priority question: Please clarify why the end of the induction period for vedolizumab IV or SC is 10 weeks in the model rather than 14 weeks as per the Summary of Product Characteristics (SmPC)?

The summary of product characteristics (SmPC) for vedolizumab states that *"the recommended dose regimen of IV vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter",* and further notes that *"patients with Crohn's disease, who have not shown a response may benefit from a dose of IV vedolizumab at week 10"*. Following this, maintenance doses (IV or SC) should be continued in responding patients from Week 14.

As it was unknown what proportion of patients would achieve response, a conservative assumption was adopted: only 3 doses were modelled during the induction treatment phase.

Adverse events

B4. Priority question: Based on the data provided in response to questions A11 and A19, please provide a scenario that includes the costs of adverse events for mirikizumab, ustekinumab and risankizumab.

a) **As an additional scenario, if grade 3 and above adverse event data are available from VIVID-1, please provide a scenario that includes the costs of grade 3 and above adverse events for mirikizumab and ustekinumab.**

As noted in the Company submission, the exclusion of adverse events from the economic analysis is in line with in past cost comparison NICE appraisals in moderately to severely active CD (TA888 and TA905).[8, 9] In TA905, an assumption of equivalent safety was made between upadacitinib and the comparators (ustekinumab and vedolizumab) based on the results of the

NMA, thus supporting the approach of excluding AEs from the cost-comparison analysis.[8] While rationale for the exclusion of AEs were not reported in TA888, no queries were raised by the Committee in this regard, and it is in line with the assumption of equal efficacy.[9] For consistency with previous appraisals, and given the precedence, Lilly do not believe it is appropriate to perform scenario analyses including the costs of treating AEs.

Administration costs

B5. Priority question: For the IV administration cost, both TA888 and TA905 use the HRG code FD02H - Inflammatory Bowel Disease without Interventions, with CC Score 0. For consistency with the previous cost-comparisons in Crohn's Disease, please provide a scenario using HRG code FD02H from the 2023-25 NHS Payment Scheme (reference 114 from the company submission).

The administration cost for IV therapies has been updated in the revised model (Cells E91 and E92 on 'Treatment Costs' sheet) and aligned to the cost reported in the 2023–2025 NHS Payment Scheme. This cost has now been included in the base-case cost-comparison analysis, and therefore a scenario analysis has not been performed.

The cost-comparison results from the updated Company base case are presented in Appendix 1.

B6. Priority question: There is a Patient Access Scheme in place for mirikizumab but this has not been used in the cost-effectiveness results. Please provide the cost-effectiveness results using the existing Patient Access Scheme discount.

Lilly is currently awaiting acceptance of the proposed patient access scheme (PAS) discount by the Patient Access Scheme Liaison Unit (PASLU). Lilly will provide cost comparison results with the revised PAS incorporated once it is approved.

B7. Priority question: Based on the company's response to question B3, please provide a scenario that explores using 14 weeks as the end of the induction period for vedolizumab IV or SC. This scenario is consistent with the base case approach taken for TA888 and TA905.

B8. Priority question: The company has provided updated base case results, but did not provide updated scenario analysis. As indicated in the response to B6, the company will provide updated results with its patient access scheme (PAS) discount applied. When providing the updated results, please ensure

that all scenario analysis results are provided as well (essentially provide an update of Sections B.4.3-4.4 of the company submission).

B9. Based on the response to B1, please provide a scenario for the CCF population with vial sharing selected for committee consideration. For ease, the scenario can be included in the table of company scenarios that will be provided in response to question B8.

Company response to B7, B8 and B9.

Updated scenario analyses and the subsequent updated results at mirikizumab list price are presented in Table 32 and Table 33, respectively. Scenarios 5 and 6 have been added in line with clarification questions B7 and B9. As stated previously, the company will update these results with PAS price results when available.

Table 32: Overview of updated scenario analyses

#	Scenario	Base case	Scenario value(s)
1	Model horizon	3 years	2 years
2			5 years
3	Drug wastage	No vial sharing	Vial sharing assumed
4	Administration costs	Treatment administration and acquisition costs considered	Only treatment acquisition costs considered
5	Vedolizumab IV/SC induction duration	Vedolizumab IV/SC 10-week induction	Vedolizumab IV/SC 14-week induction
6	Drug wastage for CCF population	No vial sharing, treatment experienced population	Vial sharing, treatment naïve population

Abbreviations: CCF: conventional care failed; IV: intravenous; SC: subcutaneous.

Table 33: Updated results of scenario analyses

Scenario	Incremental costs (list price)		
	RIS	UST	VED
Base case	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]

Abbreviations: RIS: risankizumab; UST: ustekinumab; VED: vedolizumab.

Section C: Textual clarification and additional points

C1. In the NHS payment scheme, HRG code WF01B (301) - non-consultant led single professional first appointment is £163, not £162 as per the model. Please update the model accordingly.

As requested, Lilly has updated the cost of IV administration costs in line with question B5, and therefore no longer considers this adjustment necessary.

Appendix 1: Updated Base Case Results

Updated base case results for a 3-year time horizon with mirikizumab (at list price) are presented in Table 34.

The updated model includes the following changes:

- Question B5; the administration cost for IV therapies has been updated in Cells E91 and E92 on 'Treatment Costs' sheet = £313

- Additional error identified by EAG; updated formulas in rows 135:139 in the 'Treatment Costs' sheet to correct error whereby, the submission model only accounted for the first SC injection administration cost for the 7.5% of ustekinumab patients who remain on the standard dose and did not apply an administration cost for the 92.5% of patients on the escalated dose. As such, administration costs for the first-year maintenance treatment were £3 for ustekinumab instead of £46.

Table 34: Base case results for a 3-year time horizon at mirikizumab list price

Treatment	Per patient costs			Incremental costs versus mirikizumab
	Induction costs	Maintenance costs	Total treatment costs	
Mirikizumab	£19,448	[redacted]	[redacted]	-
Risankizumab	£10,917	£60,138	£71,056	[redacted]
Ustekinumab	£6,754	£38,913	£45,667	[redacted]
Vedolizumab IV/SC	£7,089	£46,932	£54,021	[redacted]

Abbreviations: IV: intravenous infusion; SC: subcutaneous injection

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

NICE medicines optimisation briefing

March 2024

Advice

A full single technology appraisal of mirikizumab is unlikely to add value. A fast-track appraisal with a cost comparison comparing mirikizumab to other specialist treatments licensed for moderately to severely active Crohn's disease is likely to be appropriate. However, only one phase 2 published study of mirikizumab for Crohn's disease is currently published. The decision on the appropriateness of mirikizumab to undergo fast-track appraisal with a cost comparison should be reviewed when the results of phase 3 clinical trials are fully published.

Rationale

Mirikizumab is a humanised monoclonal antibody. It has a marketing authorisation for use in moderately to severely active ulcerative colitis, which is another type of inflammatory bowel disease, treated in a similar way to Crohn's disease (Summary of product characteristics [SPC]). Mirikizumab has already been recommended for treating moderately to severely active ulcerative colitis (TA925).

One placebo controlled, phase 2 study assessing the clinical effectiveness and safety of mirikizumab for Crohn's disease is published (Sands et al. 2022). One phase 3 study assessing induction treatment in Crohn's disease (VIVID-1 trial; NCT03926130) completed in October 2023 and preliminary findings have been published in a conference abstract (Ferrante 2024). A further phase 3 study on maintenance

treatment in Crohn's disease (NCT04232553) is expected to be completed in December 2026. Therefore, no peer reviewed, phase 3 evidence is available that compares mirikizumab with placebo.

Furthermore, no published evidence is available to assess how the clinical effectiveness and safety of mirikizumab compares with medicines already recommended in technology appraisal guidance for the same patient population, and at a similar point in the treatment pathway.

Three other monoclonal antibodies, vedolizumab (TA352), risankizumab (TA888) and ustekinumab (TA456) have been recommended by NICE for treating moderately to severely active Crohn's disease. Other specialist treatments for moderately to severely active Crohn's disease include tumour necrosis factor (TNF)-alpha inhibitors (infliximab and adalimumab) and a Janus kinase (JAK) inhibitor (upadacitinib). Differences in acquisition cost and service delivery between treatments need to be considered, as well as factors that affect people's choice of treatment, such as route and frequency of administration.

Technology overview

Mirikizumab is a humanised monoclonal antibody that binds selectively with interleukin (IL)-23. IL-23 is a cytokine involved in inflammatory and immune responses. Blocking IL-23 reduces inflammation in several immune-related disorders, including Crohn's disease (SPC).

Mirikizumab is indicated for treating moderately to severely active ulcerative colitis in people 16 years and older who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment (SPC).

Mirikizumab is not yet licensed for people with Crohn's disease, who have tried conventional and biologic therapies. In the VIVID-1 trial, the dose of mirikizumab was 900 mg intravenously every 4 weeks for the

induction phase and then 300 mg subcutaneously every 4 weeks in the maintenance phase (conference abstract, Ferrante 2024).

Context

For treating moderately to severely active Crohn's disease, NICE has assessed:

- the TNF-alpha inhibitors, infliximab and adalimumab (TA187)
- three monoclonal antibodies, vedolizumab (TA352), ustekinumab (TA456) and risankizumab (TA888)
- the JAK inhibitor upadacitinib (TA905).

Mirikizumab has been recommended by NICE for treating moderately to severely active ulcerative colitis when conventional or biological treatment cannot be tolerated, or the condition has not responded well enough or lost response to treatment, only if a TNF-alpha inhibitor has not worked (that is the condition has not responded well enough or has lost response to treatment) or a TNF-alpha inhibitor cannot be tolerated or is not suitable (TA925).

Table 1: Characteristics of mirikizumab compared with other treatments used for moderately to severely active Crohn's disease at a similar point in the treatment pathway.

	Mirikizumab	Adalimumab Infliximab	Risankizumab	Vedolizumab	Ustekinumab	Upadacitinib
Mechanism of action	Humanised monoclonal antibody (IL-23 inhibitor)	TNF-alpha inhibitors	Humanised monoclonal antibody (IL-23 inhibitor)	Humanised monoclonal antibody ($\alpha_4\beta_7$ integrin blocker)	Fully human monoclonal antibody (IL 12 and 23 inhibitor)	JAK inhibitor
Indication	Moderately to severely active Crohn's disease (details to be confirmed when the marketing authorisation is granted)	Moderately to severely active Crohn's with inadequate response, contraindication or intolerance to conventional treatment Adalimumab SPC Infliximab SPC	Moderately to severely active Crohn's disease with inadequate response, contraindication or intolerance to conventional or a biologic treatment Risankizumab SPC	Moderately to severely active Crohn's disease in adults with inadequate response, lost response or intolerance to conventional treatment or TNF-alpha inhibitor Vedolizumab SPChttps://www.medicines.org.uk/emc/product/11361/smpc	Moderately to severely active Crohn's disease in adults with inadequate response, lost response, contraindication or intolerance to conventional or biologic treatment Ustekinumab SPC	Moderately to severely active Crohn's disease in adults with inadequate response, lost response or intolerance to conventional or a biologic treatment Upadacitinib SPC
Technology appraisal recommendation	Not applicable	Infliximab and adalimumab, within their licensed indications, are	Moderately to severely active Crohn's disease in people 16 years	Moderately to severely active Crohn's disease only if: a TNF-alpha	Moderately to severely active Crohn's disease, that is, for adults	Moderately to severely active Crohn's disease in adults, only if:

		recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional treatment (TA187)	and over, only if: the disease has not responded well enough or lost response to a previous biological treatment, or a previous biological treatment was not tolerated, or TNF-alpha inhibitors are not suitable (TA888)	inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment) or a TNF-alpha inhibitor cannot be tolerated or is contraindicated (TA352)	who have had an inadequate response with lost response to or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies (TA456)	the disease has not responded well enough or lost response to a previous biological treatment, or a previous biological treatment was not tolerated, or TNF-alpha inhibitors are contraindicated (TA905)
Dosage and route of administration	In the VIVID-1 trial: 900 mg by intravenous infusion every 4 weeks for the induction phase and then 300 mg by subcutaneous injection every 4 weeks in the maintenance phase (dosage to be confirmed when the marketing authorisation is granted)	Adalimumab: 80 mg at week 0, 40 mg at week 2, then 40 mg every 2 weeks by subcutaneous injection (increased if needed to 40 mg weekly or 80 mg every 2 weeks) Infliximab (intravenous): 5 mg/kg at weeks 0, 2 and 6, then every 8 weeks	600 mg every 4 weeks for 3 doses, doses to be given on weeks 0, 4, and 8 by intravenous infusion, then (by subcutaneous injection) 360 mg every 8 weeks, first subcutaneous dose to be given on week 12	300 mg at weeks 0, 2 and 6, then every 8 weeks by intravenous infusion; or maintenance 108 mg every 2 weeks by subcutaneous injection	260 mg (≤55 kg), 390 mg (>55 to ≤85 kg) or 520 mg (>85 kg) as a single dose intravenously, then 90 mg subcutaneously every 8 to 12 weeks	45 mg once daily orally for 12 weeks, then 15mg or 30 mg once daily orally

		Infliximab (subcutaneous): 120 mg at weeks 0, 1, 2, 3 and 4, then every 2 weeks				
Resource impact	Intravenous and subcutaneous (route to be confirmed when marketing authorisation is granted).	Intravenous treatment: invasive, higher service delivery costs than oral or subcutaneous treatments (clinic costs, health professional time) Subcutaneous treatment: lower service delivery costs than intravenous (delivered by homecare, self-administered at home after training)	Intravenous treatment: invasive, higher service delivery costs than oral or subcutaneous treatments (clinic costs, health professional time) Subcutaneous treatment: lower service delivery costs than intravenous (delivered by homecare, self-administered at home after training)	Intravenous treatment: invasive, higher service delivery costs than oral or subcutaneous treatments (clinic costs, health professional time) Subcutaneous treatment: lower service delivery costs than intravenous (delivered by homecare, self-administered at home after training)	Intravenous treatment: invasive, higher service delivery costs than oral or subcutaneous treatments (clinic costs, health professional time) Subcutaneous treatment: lower service delivery costs than intravenous (delivered by homecare, self-administered at home after training)	Oral treatment: convenient, non-invasive, lower service delivery costs than injections

Current practice

Medicines for treating moderately to severely active Crohn's disease are commissioned by integrated care boards for adults and by NHS England for children's services. Local treatment pathways for initial management follow NICE guidance.

The NICE guideline on the management of Crohn's disease (NG129) recommends people are treated according to disease presentation and severity as well as individual patient factors. Conventional treatment for moderately to severely active Crohn's disease includes:

- corticosteroids, aminosalicylates or enteral nutrition for induction
- azathioprine, methotrexate or mercaptopurine as add-on therapy for induction or as monotherapy for maintaining remission.

If conventional treatment is not effective or is contraindicated or not tolerated, the treatment pathway becomes complex and current practice varies. Specialist treatment with biologics (TNF-alpha inhibitors or monoclonal antibodies) or upadacitinib, can be considered. Individual patient factors affect choice, such as route and frequency of administration, severity of disease, extraintestinal manifestations, presence of fistulising disease, contraindications, comorbidities (such as cancer risk, co-existence of autoimmune disease) and age.

TNF-alpha inhibitors (infliximab or adalimumab; TA187) are often the first-choice biologics for moderately to severely active disease. Adalimumab and infliximab are licensed as subcutaneous injections which can be delivered by homecare services and self-administered at home. Infliximab is also licensed as an infusion which, when administered in specialist settings, is likely to increase service delivery costs (clinic costs and healthcare professionals' time).

The monoclonal antibodies, vedolizumab (TA352), ustekinumab (TA456) and risankizumab (TA888) are used in practice if TNF-alpha inhibitors are not effective or when they are contraindicated or not tolerated. Vedolizumab has traditionally been given as an intravenous infusion in secondary care but is now available as a subcutaneous injection allowing for greater convenience and is likely to reduce service delivery costs. Ustekinumab and risankizumab used as maintenance treatment are also given as a subcutaneous injection, allowing people to administer at home.

System intelligence suggests that the JAK inhibitor upadacitinib (TA905) is sometimes used as a first agent of choice if TNF-alpha inhibitors are not effective, before monoclonal antibodies are used. As an oral medicine, upadacitinib allows for greater convenience and less invasive treatment for people at home.

Mirikizumab is likely to be used after the TNF-alpha inhibitors, as an alternative to other monoclonal antibodies and upadacitinib. The choice of treatment is likely to depend on:

- individual patient factors (including comorbidities, contraindications, potential adverse effects, route of administration and preference)
- acquisition cost and overall cost of treatment (including drug delivery and monitoring), and
- local treatment pathways (including availability of infusion facilities and therapeutic drug monitoring).

Factors for decision making

Effectiveness

One phase 2 study assessing the clinical effectiveness of mirikizumab in people with Crohn's disease has been published.

The 52-week randomised, double-blind, placebo controlled phase 2 trial (Sands et al. 2022) evaluated the efficacy and safety of mirikizumab monotherapy in people aged 18 to 75 years with moderate to severe active Crohn's disease (n=191). Participants must have received prior treatment for Crohn's disease, with a history of intolerance or inadequate response to conventional therapy, or a history of corticosteroid dependence; and/or have received treatment with 1 biologic agent with or without a documented history of intolerance or inadequate response. Participants were divided into 4 groups: placebo (n=64), mirikizumab 200 mg (n=31), 600 mg (n=32), and 1,000 mg (n=64). Mirikizumab was given intravenously in all cases.

The primary outcome in the study was an endoscopic response at week 12, defined as a 50% reduction from baseline in the Simple Endoscopic Score for Crohn's Disease. Statistically significantly more people in the mirikizumab groups met the primary outcome than in the placebo group:

- mirikizumab 200 mg: 25.8% (8/31) response rate (95% confidence intervals [CI] 10.4% to 41.2%, p=0.079)
- mirikizumab 600 mg: 37.5% (12/32) response rate (95% CI 20.7% to 54.3%, p=0.003)
- mirikizumab 1,000 mg: 43.8% (28/64) response rate (95% CI 31.6% to 55.9%, p<0.001)
- placebo: 10.9% (7/64) response rate (95% CI 3.3% to 18.6%).

After 12 weeks, participants who showed endoscopic improvement from baseline with mirikizumab were re-randomised to continue treatment with intravenous (n=41) or subcutaneous (n=46) mirikizumab for a 40-week maintenance period.

At week 52, endoscopic response rates were 58.5% (24/41; 95% CI 43.5% to 73.6%) in the intravenous group and 58.7% (27/46; 95% CI 44.5% to 72.9%) in the subcutaneous group. Endoscopic remission was

achieved by 19.5% of people in the intravenous group (8/41; 95% CI 7.4% to 31.6%) and 32.6% of people in the subcutaneous group (15/46; 95% CI 19.1% to 46.2%).

One phase 3 study has assessed induction treatment in moderately to severely active Crohn's disease (VIVID-1 trial; NCT03926130). Full results have not yet been published, but preliminary results have been published in a conference abstract (Ferrante 2024). The abstract reported that 38.0% of participants in the mirikizumab group and 9.0% in the placebo group achieved the combined primary outcome of clinical response at week 12 plus endoscopic response at week 52 (difference 28.7%, 95% CI 20.6% to 36.8%, p<0.0001). No results have been reported that compare mirikizumab with an active comparator.

A further phase 3 study on maintenance treatment in Crohn's disease (NCT04232553) is expected to be completed in December 2026.

Safety

In the phase 2 study by Sands et al. 2022, treatment-emergent adverse events (TEAEs) were reported as follows: 70.3% in the placebo group, 58.1% in the 200 mg mirikizumab group, and 65.6% in both the 600 mg and 1,000 mg mirikizumab groups, during the induction period. Common TEAEs across all mirikizumab groups included headache, worsening of Crohn's disease, arthralgia, nasopharyngitis, increased weight, anaemia, and nausea. There were no significant differences in the frequency of TEAEs between the mirikizumab groups and the placebo group.

During the induction phase, 12 people experienced serious adverse events (SAEs); these included 7 people in the placebo group (with events such as worsening of Crohn's disease and hypokalaemia) and 5 people across all mirikizumab groups (with events such as chest pain, colon perforation and abdominal pain).

In the maintenance period, no SAEs were reported in the mirikizumab intravenous group, and 2 people experienced SAEs in the mirikizumab subcutaneous group.

Mirikizumab is contraindicated in people with clinically important active infections (for example, active tuberculosis). It should be used with caution in those with chronic infection, a history of recurrent infection, or known risk factors for infection. As with all therapeutic proteins, there is the potential for immunogenicity with mirikizumab (SPC).

Patient centred factors

As with many other treatments for moderately to severely active Crohn's disease (used after conventional treatment), mirikizumab is likely to be given by intravenous infusion or subcutaneous injection. This needs the person to attend clinic appointments to have an infusion or have training to use subcutaneous injections at home. Upadacitinib is an oral medicine, which some people may prefer, particularly if they have dexterity or needle phobia challenges.

Health inequalities

No issues related to health inequalities have been identified in previous technology appraisals (TA888).

Limitations of the evidence

No published phase 3 studies are currently available on the clinical effectiveness and safety of mirikizumab for Crohn's disease. Preliminary findings from 1 phase 3 study (VIVID-1 trial; NCT03926130) have been published in a conference abstract. However, results have not yet been reported in full and have not been peer reviewed.

The phase 2 trial by Sands et al. (2022) is well designed and reports appropriate outcomes of response using Simple Endoscopic Score for Crohn's Disease. However, it has a small sample size (n=191), is placebo controlled and is limited to a 52-week follow up.

Mirikizumab is not yet licensed for Crohn’s disease in the UK, Europe or US.

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

Cost-comparison Technology Appraisal

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report.
Clare Dadswell	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections.
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence.
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event
BF	Biologic failed
CCA	Cost-comparison appraisal
CCF	Conventional care failed
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CQ	Clarification question
EAG	External Assessment Group
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5 Dimensions 5 Level Version
HRQoL	Health-related quality of life
IBD-Q	Inflammatory Bowel Disease Questionnaire
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
LSM	Least squares mean
MAIC	Matched-adjusted indirect comparison
MCID	Minimal clinically important difference
MCMC	Monte Carlo Markov Chain
MeSH	Medical subject headings
N/A	Not applicable
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NRS	Numerical rating score
OBD	On-body device
OR	Odds ratio
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PBO	Placebo
PRO	Patient reported outcome
RCT	Randomised controlled trial
RD	Risk difference

SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SES-CD	Simple-Endoscopic Score for Crohn's Disease
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TNF-α	Tumour necrosis factor alpha
TEAE	Treatment emergent adverse event
VAS	Visual analogue score

1 Summary of EAG's view of the company's CCE case

A cost-comparison analysis was presented by the company to compare mirikizumab to risankizumab for people who have previously treated moderate to severely active Crohn's disease. To be considered for a cost-comparison technology appraisal, the National Institute for Health and Care Excellence (NICE) requires the intervention under review to be clinically similar to one treatment that NICE has previously recommended in technology appraisal guidance for the same indication. Risankizumab is recommended by NICE for people who are 16 years and over when their disease has either not responded well enough to, or lost response to, a previous biologic treatment, or when either a previous biologic was not tolerated, or TNF-*α* inhibitors are not suitable (TA888).

The company presented evidence for mirikizumab from the VIVID-1 trial, comparing effectiveness and safety data against placebo and ustekinumab. Using a pre-specified non-inferiority margin, mirikizumab was demonstrated to be non-inferior to ustekinumab for clinical remission outcomes. The two treatments also had a similar safety profile.

In the absence of direct comparisons between mirikizumab and risankizumab, the company used network meta-analyses (NMAs) for an indirect treatment comparison (ITC). The company also provided additional indirect comparisons (Bucher ITCs and unanchored matched-adjusted indirect comparisons [MAICs]) following a request from the EAG. The company assumed clinical similarity with risankizumab based on 95% credible intervals (CrIs) or 95% confidence intervals (CIs) crossing the line of no effect. However, the EAG considers that the wide 95% CrIs/CIs are likely to reflect uncertainties in the analysis, rather than demonstrating clinical similarity. The following factors should be noted when interpreting the results of the ITCs:

- Differences in trial design (treat through vs re-randomised designs) used by studies included in the NMA;
- The inclusion of other treatments not relevant to the decision problem in the NMA, which is likely to have introduced additional heterogeneity into the analysis;
- The inclusion of only those who responded to induction treatment in the unanchored MAIC analysis for outcomes in the maintenance period;
- The analysis of only the combined population, rather than separate subgroups (conventional care failed and biologic failed) in the unanchored MAIC for the maintenance period;
- A greater proportion of biologic failed than conventional care failed patients in the combined analysis of the maintenance period;

- The potential use of different definitions of clinical response by the two trials included in the MAIC; and
- The additional uncertainties associated with unanchored MAICs, which provide the majority of the analyses for the maintenance period, such as difficulties in adjusting for treatment effect modifiers and the residual bias caused by unobserved, and so unadjusted for, confounding factors.

Given the concerns outlined above, the EAG does not consider that the indirect comparisons presented by the company are sufficient to be confident of clinical similarity between mirikizumab and risankizumab. However, the results from the VIVID-1 trial provide robust evidence of non-inferiority between mirikizumab and ustekinumab in the relevant population. With the exception of its potential use of a first-line biologic, in most cases in UK clinical practice, ustekinumab would be used in the same position in the treatment pathway as risankizumab. It was included as a comparator in the decision problem and the results of the VIVID-1 trial appear more appropriate for a cost-comparison appraisal as the trial demonstrates non-inferiority between mirikizumab and ustekinumab.

The company's cost analysis only considered drug acquisition and administration costs for mirikizumab and risankizumab (company's preferred comparator) as it was assumed there would be no other cost differences between the two drugs. Moreover, the company has provided supportive cost analysis for two additional comparators, ustekinumab and vedolizumab. The company's approach is aligned with the cost-comparison analyses in other NICE guidance for Crohn's disease including TA888 (risankizumab) and TA905 (upadacitinib). However, for the reasons outlined above, the EAG considers that ustekinumab is the most appropriate comparator for the cost analysis and is associated with the lowest decision risk. The EAG highlights that the company's base case results and all scenarios considered indicate that mirikizumab is likely to be cost saving when compared to any of the comparators, whether primary or supportive, included in the cost model but reiterates the substantial uncertainty associated with the comparison with risankizumab.

Additionally, the EAG notes that confidential patient access scheme (PAS) discounts/ medicines procurement supply chain (MPSC) prices are available for all comparators. As such, the EAG has produced a confidential appendix to the EAG report and it is these results that will form the basis for decision making.

2 Background

Crohn's disease is classed as an inflammatory bowel disease, and is a chronic condition which can affect any part of the gastrointestinal tract.[2] Crohn's disease causes ulcers and inflammation of the gut and is characterised by flare-ups when symptoms are more severe, and periods of remission when symptoms are well controlled. Traditional treatment of Crohn's disease involves initial treatment using glucocorticosteroids and/or immunomodulators (conventional therapy), followed by progression to biologic therapy if their symptoms do not adequately respond to conventional therapy. Section B1.3 of the company submission (CS) summarises the disease, including its epidemiology, diagnosis and staging, burden of disease and current clinical pathway in the UK. Based on the information provided, and discussion with clinical experts, the EAG considers that this information accurately reflects clinical practice.

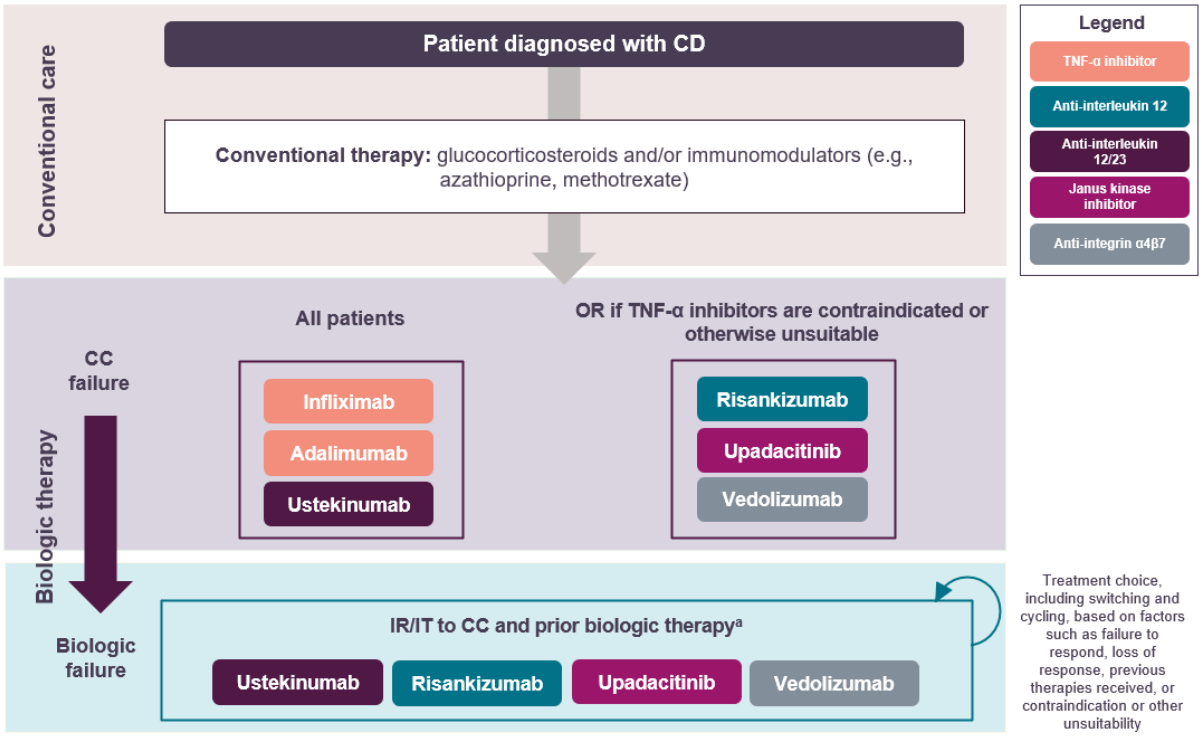
The focus of this cost-comparison appraisal is the use of mirikizumab for people who have moderately to severely active Crohn's disease. The company has compared mirikizumab to risankizumab, which is already recommended for use as biologic therapy in this population either when their disease has not responded well enough, or lost response to, another biologic treatment, where other biologic treatment was not tolerated, or when TNF-α inhibitors are not suitable [TA888].[1]

Mirikizumab is a recombinant humanised IgG4 monoclonal antibody that binds to the p19 subunit of the IL-23 cytokine, preventing the cytokine's interaction with its receptor. The IL-23 cytokine has a role in inflammation, and so the action of mirikizumab can reduce the inflammatory processes associated with Crohn's disease. Risankizumab is a humanised IgG1 monoclonal antibody with the same mechanism of action as mirikizumab. Both are administered using an IV infusion during the induction period, followed by subcutaneous injections during the maintenance period.

The current treatment pathway for Crohn's disease was presented in the CS and is reproduced in Figure 2 below. The company intends for mirikizumab to be positioned as an option for biologic therapy, alongside risankizumab, upadacitinib, vedolizumab and ustekinumab. The EAG's clinical experts noted that the treatment pathway is changing, with conventional therapies being used less frequently, and the use of early surgery or top-down therapy becoming more common for people who have more severe Crohn's disease. Top-down therapy involves the use of biologic treatments soon after diagnosis to try and achieve earlier remission or reduction of symptoms, often resulting in the use of TNF-α inhibitors or ustekinumab as first-line treatments. As such, the clinical experts

considered that, even with changes in practice, the position of mirikizumab in Figure 1 still reflects where it would commonly be used relative to other biologic treatments.

Figure 1. The current treatment pathway for Crohn's disease in England (reproduced from Figure 2 in company submission).



Abbreviations: CD: Crohn's disease; CT: conventional therapy; IR: inadequate response; IT: intolerant; TNF-α: tumour necrosis factor-alpha.

3 Critique of the decision problem in the company's submission

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE),[3] together with a rationale for any deviations from the decision problem. The company submission (CS) covers only a subpopulation of those included in the anticipated marketing authorisation for mirikizumab. Mirikizumab received a licence from the MHRA in April 2025 as a treatment *"for adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment."* The cost comparison only focuses on people in this group when either the disease has not responded well enough or lost response to a previous biological treatment, a previous biological treatment was not tolerated, or if tumour necrosis factor alpha (TNF-α) inhibitors are not suitable. This population matches that recommended for risankizumab in TA888.[1] The EAG therefore considers this an appropriate subgroup of the population on which to base the cost-comparison for mirikizumab. A summary of the final scope issued by NICE, the decision problem addressed in the CS and the EAG's critique of this is provided in Table 1.

Table 1. Summary of decision problem as outlined in the company submission

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with moderate to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.	Adult patients with moderately to severely active CD, only if: • The disease has not responded well enough or lost response to a previous biological treatment or • A previous biological treatment was not tolerated, or • TNF-α inhibitors are not suitable	It is anticipated that mirikizumab will be positioned after conventional care and after first-line biologic treatment options, except in the case of unsuitability to receive such biologic therapies.	The population addressed in the submission is narrower than in the original NICE scope. However, it matches that recommended for risankizumab in TA888[1] and so the EAG considers this appropriate.
Intervention	Mirikizumab	Mirikizumab (Induction: 900 mg by IV infusion Q4W. Maintenance: 300 mg by SC injection every 4 weeks after completion of induction dosing. Full maintenance dose from 1 200 mg pre-filled pen and 1 100 mg pre-filled pen)	N/A	N/A
Comparator(s)	• At least one of the following treatments, according to NICE guidance: • TNF-α inhibitors (infliximab and adalimumab) • Ustekinumab • Vedolizumab • Risankizumab • Upadacitinib	• Primary comparator: • Risankizumab • • Supportive comparators: • Ustekinumab • Vedolizumab	• It is anticipated that mirikizumab will be positioned after conventional therapy. Conventional therapy therefore does not represent a relevant comparator. • • Risankizumab is considered the primary comparator because: • Risankizumab recently received a positive recommendation from	The company have justified the position of mirikizumab in the treatment pathway based on its similar method of action to risankizumab. The EAG considers that this provides acceptable justification for mirikizumab being considered for the same subpopulation as was considered in TA888 for risankizumab.[1] While the EAG considered it reasonable for risankizumab to be the primary comparator based on the similarities in mechanism of action and method of administration,

			NICE in the same patient population • ITCs performed by the company for patients with moderately to severely active CD demonstrated similar efficacy in comparisons between mirikizumab and risankizumab (see Section B.3.9 of company submission) • Mirikizumab has the same mechanism of action as risankizumab, and they share a similar method of administration (intravenous during the induction period and subcutaneous during the maintenance period).	uncertainties in the evidence base mean that there is more robust evidence for ustekinumab to be the primary comparator, Direct evidence from the VIVID-1 trial provides more evidence of "clinical similarity".
Outcomes	• Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Hospitalisation rates • Adverse effects of treatment • HRQoL	• Measures of disease activity (clinical remission and relapse, endoscopic response) • Mucosal healing (endoscopic remission, histologic remission) • Adverse Events • HRQoL (EQ-5D-5L, IBD-Q) • Bowel urgency	Rates of CD-related surgery and hospitalisation were low for Risankizumab in the VIVID-1 trial and similar to those reported for patients who received ustekinumab or placebo. It was therefore assumed that treatment with mirikizumab was associated with a similar safety profile to risankizumab, ustekinumab and vedolizumab, in line with previous cost-comparison analyses in CD (TA905 and TA888).	The company provided the EAG with data on hospitalisation rates in response to clarification questions and this is now reported in section 4.3.8 of the EAG report.
Economic analysis	This technology has been selected to be appraised as a cost comparison. The time	A cost comparison analysis has been conducted to estimate the incremental costs of mirikizumab	Mirikizumab can be appropriately assessed through the NICE cost-comparison process due to the	The EAG considers the clinical similarity case is uncertain for the comparison with risankizumab. However, there is robust

	horizon should be sufficient to reflect any differences in costs between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention and comparator technologies will be taken into account.	versus risankizumab (with supportive comparisons to ustekinumab and vedolizumab also presented). • The base case model time horizon was set as 3 years. This is in line with clinical expert opinion provided to the NICE Committee in TA888 that median duration of treatment persistence with biologic therapies is approximately 2–3 years.4 Alternate time horizons of 2 years and 5 years were also tested as scenario analyses. • Costs were considered from an NHS and PSS perspective. • A PAS for mirikizumab was included as part of the analysis.	similarities in terms of both effectiveness and costs with risankizumab. Additionally, it is anticipated that mirikizumab will be positioned similarly to other available therapies, including risankizumab, within the treatment pathway. As such, a cost-comparison has been submitted. The cost-comparison analysis compares the drug acquisition and administration costs for mirikizumab versus risankizumab, with supportive analyses presented for mirikizumab versus ustekinumab and versus vedolizumab.	evidence to suggest that mirikizumab is clinically similar to ustekinumab based on direct evidence from VIVID-1 and this a cost-comparison analysis is appropriate.
Subgroups to be considered	None	• People who have previously failed on treatment with one or more biologics ("biologic failure") • People who have not received a prior biologic ("conventional care failure")	The VIVID-1 trial, which provides the key clinical evidence base for mirikizumab, included biologic failure and conventional care failure patients. Patients in the conventional care failure subgroup in the VIVID-1 trial had not received a prior biologic and so were biologic-naïve. Separate analyses were conducted in these subpopulations and are presented.	The biologic failure subgroup is important as this reflects the majority of the subpopulation in the cost comparison. The subpopulation for this cost comparison also includes people for who TNF-α inhibitors are not suitable. Although this group are not considered as a subpopulation in the evidence base, patients who had not received a prior biologic could be considered a surrogate for the group in which TNF-α inhibitors are not suitable. The EAG therefore considers it

				reasonable to assess the conventional care failure group as a marker for this subgroup.
Special considerations, including issues related to equity or equality	N/A	N/A	N/A	N/A

Abbreviations: EAG, external assessment group; NICE, National Institute for Health and Care Excellence; CD, Crohn's disease; ITC, indirect treatment comparisons; HRQoL, health-related quality of life; PSS, personal social services; PAS, patient access scheme

3.1 Population

Alignment to NICE final scope and population in England

The NICE final scope focuses on all adults with moderate to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment. The company chose to focus on a subpopulation of this group, representing people who had not responded well enough, or lost response to, a previous biological treatment, those who had not tolerated a previous biological treatment, or those for who TNF-α inhibitors are not suitable. This is in line with the population included in TA888 for risankizumab.[1] The EAG's clinical experts noted that this population reflects a high proportion of patients who are seen in clinical practice.

It was noted that TA888 for risankizumab[1] included people aged 16-17 years, but due to the anticipated marketing authorisation for mirikizumab, only those aged 18 years and over were considered for the current cost comparison. The EAG's clinical experts did not expect there to be any major differences in clinical effectiveness between those aged 16-17 years, and those aged 18 years and above, and so this difference is not anticipated to impact the comparisons between the two treatments.

Key inclusion criteria for the key trial in this appraisal (VIVID-1) were discussed with the EAG's clinical experts. These were:

- Adults aged between 18 and 80 years, with an established diagnosis of CD for at least three months;
- Patients had an inadequate response to, loss of response to, or intolerance to corticosteroids, immunomodulators, or an approved biologic therapy for CD.

The EAG's clinical experts broadly agreed with this for the key trial in this appraisal (VIVID-1). People over the age of 80 were excluded from VIVID-1, which the experts stated would not happen in clinical practice. However, given that very few patients would be over 80 years in clinical practice, this is not a major concern. The clinical experts also discussed the exclusion criteria and noted that patients with stomas were excluded. However, this is common in clinical trials and is not expected to have a major impact on the results, with the presence of a stoma not expected to be a treatment effect modifier. The experts noted that there was no information about patients with perianal disease, as this group could respond differently to treatment. In response to clarification questions, the company reported that perianal disease involvement was not recorded for VIVID-1. However,

they stated that the percentage with cutaneous fistulae, which they suggested as a marker of perianal CD, was similar across the three trial arms.

In summary, the EAG considers the data presented within the CS to be representative of patients with moderate to severe CD who would be eligible to receive mirikizumab in England. The population aligns with the NICE final scope and is therefore relevant to the decision problem that is the focus of this CCA.

3.2 Intervention

The intervention matches that in the NICE final scope. Mirikizumab received a licence from the MHRA in April 2025 as a treatment *"for adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment."*

As reported in the summary of product characteristics (SmPC), mirikizumab is a recombinant humanised IgG4 monoclonal antibody that binds to the IL-23 cytokine. Given that IL-23 is linked to chronic inflammatory processes in the intestine, the inhibition of IL-23 by mirikizumab acts to reduce the inflammatory processes underlying CD.

Different methods of delivery are used for mirikizumab in the induction and maintenance periods:

- 8-week induction period: 900 mg by intravenous (IV) infusion Q4W (Weeks 0, 4 and 8). Mirikizumab 300 mg (15 ml vial; 20 mg mirikizumab per mL) is available as a concentrate for solution for infusion.
- 52-week maintenance period: 300 mg by subcutaneous (SC) injection every 4 weeks after completion of induction dosing. A full maintenance dose consists of one 200 mg pre-filled pen and one 100 mg pre-filled pen. After training in SC injection technique, a patient may self-inject.

IV infusions during the induction period are provided in a hospital setting, whereas injections during the maintenance period are usually administered by patients in their own home. Method of administration for maintenance injections involves the use of a pre-filled pen. The EAG's clinical experts considered the method and frequency in the company submission and the VIVID-1 trial to be of a similar frequency to other similar biologic treatments.

3.3 Comparators

3.3.1 Primary comparator

Risankizumab (brand name Skyrizi®, AbbVie Ltd, Berkshire, UK) is presented as the primary comparator in the CS. Risankizumab has the same mechanism of action as mirikizumab and already has a marketing authorisation in the UK for patients 16 years and older with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable.[4] It has a similar method of administration to mirikizumab, with the induction dose provided by IV infusion (600 mg every 4 weeks for 8 weeks) and maintenance dose provided by subcutaneous injection (360 mg every 8 weeks). During the maintenance phase, risankizumab can be delivered using an on-body device, rather than using the pre-filled pens. NICE TA888 already recommends risankizumab for a similar population to that proposed for mirikizumab, with the exception of the risankizumab recommendation including 16–18 year olds.[1]

3.3.2 Supportive comparators

With no direct comparisons between mirikizumab and risankizumab, the primary data for mirikizumab came from the VIVID-1 trial, which was a three-arm design comparing mirikizumab to placebo and ustekinumab.[5] As a human monoclonal antibody that binds to the p40 subunit of the IL-12 and IL-23 cytokines, ustekinumab has a similar mechanism of action to mirikizumab, with a UK marketing authorisation and NICE TA456 recommending it for use for adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist or have medical contraindications to such therapies.[6]

Vedolizumab was also presented as a comparator. It has a UK marketing authorisation, with NICE TA352 recommending it for use with people with moderate to severely active Crohn's disease if a TNF-α inhibitor has either failed or cannot be tolerated or is contraindicated.[7] The CS highlighted how TA888 for risankizumab identified both ustekinumab and vedolizumab as the most appropriate comparators for risankizumab.[1]

TNF-α inhibitors and upadacitinib were also included as comparators in the NICE final scope,[3] but were not presented as comparators in the CS. The company justified the exclusion of TNF-α inhibitors because the proposal is for mirikizumab to be considered as a treatment option after TNF-α inhibitors, unless they are considered unsuitable. The EAG's clinical experts agreed that, while

there are some changes in clinical practice, TNF-α inhibitors are commonly used before other biologic treatments in practice, and so their exclusion as a comparator seems reasonable. The company did not provide a rationale for excluding upadacitinib as a comparator, and the EAG's clinical experts indicated that it is commonly used in clinical practice in a similar position to mirikizumab. The EAG has not identified any specific reason why upadacitinib should not be considered a potential comparator. However, the cost-comparison process only requires a company to compare its new treatment with one that is established in clinical practice and has positive guidance issued by NICE.

3.4 Outcomes

The outcomes in the CS broadly match those in the NICE final scope.[3] A comparison between the outcomes in the NICE final scope and the CS, and the reporting of those outcomes in the VIVID-1 trial and the NMA is reported in Table 2.

Table 2. Comparison of the outcomes in the NICE final scope and the company submission.

NICE scope outcomes	Company submission outcomes	Reported in the VIVID-1 trial	Reported in the NMA (induction period)	Reported in the NMA (maintenance period)
• Disease activity (remission, response, relapse)	• Measures of disease activity (clinical remission and response, endoscopic response)	• Clinical response • Clinical remission • Endoscopic response	• Enhanced clinical response • Clinical remission • Endoscopic response	• Clinical remission
• Mucosal healing	• Mucosal healing (endoscopic remission, histologic remission)	• Endoscopic remission	• Endoscopic remission	NR
• Surgery	NR	NR	NR	NR
• Hospitalisation rates	NR	NR	NR	NR
• Adverse effects of treatment	• Adverse events	• Treatment-emergent adverse events • Serious adverse events • Adverse events of special interest • Discontinuation due to adverse events	• Serious adverse events* • All-cause discontinuation*	NR
• HRQoL	• HRQoL	• EQ-5D-5L	NR	NR
NR	• Bowel urgency	• Bowel urgency	NR	NR

* Only reported for the combined population. No information by CCF and BF subgroup.

Abbreviations: NMA, network meta-analysis; EQ-5D, EuroQol 5 Dimensions 5 Level Version; NR, not reported

Surgery and hospitalisation rates were included in the NICE final scope but not reported in the CS. The company stated that, while these were secondary endpoints in the VIVID-1 trial, very few patients reported these outcomes, and the numbers were similar across trial arms. In response to clarification questions, the company provided this information, and this is reported in the EAG's critique of the clinical effectiveness results (section 4.3.8).

The company included clinical response in the outcomes, in line with the NICE final scope. Based on feedback from clinical experts, the assessment of response was based on endoscopic response and remission in addition to the enhanced clinical response and clinical remission outcomes, which have been used as measures in previous TAs.[1, 6, 7] The EAG's clinical experts agreed that the CDAI measures used for clinical response and remission outcomes, while commonly used in clinical trials, are difficult to implement in clinical practice. Instead, endoscopic measures are considered more relevant to clinical practice. The inclusion of endoscopic response and remission outcomes therefore appears to be an appropriate decision.

The company included bowel urgency outcomes for the comparison between mirikizumab and placebo. The company noted that urgency affects approximately 70% of patients with CD and can have a significant negative impact on quality of life. It therefore appears a reasonable measure against which to assess the efficacy of mirikizumab.

While the CS coverage of the decision problem and the VIVID-1 trial included most of the outcomes from the NICE final scope, the NMA results were more limited. This was most apparent for the maintenance period, where only the results for clinical remission were reported. The EAG's clinical experts indicated that assessing effectiveness following the maintenance period is key to decision-making. In clinical practice, some patients will take longer than the 12-week induction period to show a response, and many people will experience greater benefit by week 52. Given these concerns, the company provided additional results for the maintenance phase in response to the EAG's clarification questions.

Based on advice from clinical experts, the EAG considers that the outcomes presented in the VIVID-1 trial are clinically relevant to the decision problem. While the outcomes from the NMA are also relevant, the limited reporting on the maintenance period makes it difficult to compare the longer-term effectiveness of mirikizumab and risankizumab. Safety outcomes for the NMA are less of a concern, as the clinical experts did not expect many new adverse events during the maintenance period, with the exception of some hypersensitivity reactions.

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs) of both induction, and maintenance, treatment regimens for patients with moderately to severely active Crohn's disease (CD). The EAG considers the SLR methods used by the company to be robust, and the methods were reported in detail in Appendix D of the company submission (CS). Table 3 contains the EAG's assessment of the SLR methods used by the company.

Table 3. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**Appropriate.** The following databases were searched on 17 March 2020 and followed by 8 update searches with the most recent search on 8 January 2024 (update 8): - EMBASE; - MEDLINE Epub Ahead of Print and In-Process & Other Non-Indexed Citation; and - Cochrane Central Register of Controlled Trials (CENTRAL). The following trial registries were searched: - Clinicaltrials.gov; - European Union Clinical Trials Register; and - WHO International Clinical Trials Registry Platform Search Portal. In addition, the company searched: i) the abstracts of five relevant conferences from 2018 to present, and ii) the reference lists of the 5 most recent SLRs aligned with the research question. Full details of these searches were provided in CS Appendix D1.1
Search strategies	Appendix D.1.2	**Appropriate.** The search terms included an appropriate range of free text key words and MeSH and EMTREE terms. The search was broadly restricted by indication (Crohn's disease) study design (RCTs) and interventions (mirikizumab and comparator drugs). The EAG notes that the intervention search terms were broader than those specified in the NICE final scope.[3] In addition, the EAG notes that the searches were date restricted to records published from 1990 onwards and that VIVID-1 (the key trial of mirikizumab), was first registered on ClinicalTrials.gov in 2019.[8]
Inclusion criteria	Appendix D.1.3	**Reasonable although included interventions are broader than required by the NICE final scope.[3]** Hospitalisation rates was not specified as an outcome for inclusion in the SLR although it was listed in the NICE final scope. Also, similar to the search

		terms, the EAG notes that the inclusion criteria comprised of a broader list of interventions than required by the final scope issued by NICE.[3] In addition, the inclusion criteria restricted studies to those published in English.
Screening	Appendix D.1.3	**Appropriate.** Two independent reviewers were used at both title and abstract review and at full text review with involvement of a third reviewer where necessary.
Data extraction	Appendix D.1.3	**Appropriate.** Data extraction was performed by a single researcher and independently verified by another researcher.
Quality assessment of included study or studies	B.3.5 and Appendix D.3	**Appropriate.** The company used the quality assessment checklist for RCTs recommended by NICE from the Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Health Care (2009) seven-criteria checklist[9] for assessment of the studies included in the SLR. The company rated each item as yes, no or unclear, but no further detail was provided in support of the ratings.

Abbreviations: CS, company submission; EAG, External Assessment Group; MeSH, medical subject headings; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SLR, systematic literature review; WHO, World Health Organisation.

The company summarised the findings from the SLR and update searches, reporting that across all searches, after de-duplication a total of 10,529 citations were identified from the search of electronic databases up to January 2024. The title and abstract review of these articles resulted in a total of 341 full-text articles for full-text assessment.

Following full-text review, 166 publications were deemed eligible for inclusion with 100 of these from the electronic database searches and the remaining 66 from searches of conference proceedings and citation review However, 9 of the included publications reported results for non-randomised open label extensions which were deemed not relevant for extraction. After removal of these publications, a total of 157 publications reporting on 95 unique studies were included for data extraction. Further detail of the study flow across the SLR are presented in CS Appendix D1.4.1.

The EAG notes that VIVID-1 was not included in the list of the 95 studies included in the SLR provided in CS Appendix D, Table 32 as there were no published data regarding the VIVID-1 trial at the time of the SLR searches. VIVID-1 provides the key data for mirikizumab in the company submission and is a double-blind, placebo-controlled Phase III trial (VIVID-1) for mirikizumab in moderately to severely active CD. VIVID-1 is reported in the CS, with the results presented from the full clinical study report (CSR).[5]

Of the 96 included studies, a total of 26 studies were considered for inclusion in the company NMAs and the reasons for exclusion of the other 70 studies were detailed in Appendix D, Table 39. Further

detail and critique of VIVID-1 and the studies included in the company's indirect treatment comparisons are provided in the sections below.

4.2 Critique of trials of the technology of interest

4.2.1 VIVID-1

The company SLR identified one study that evaluated the efficacy of mirikizumab for people with moderate to severe CD. Summary information about the VIVID-1 trial is included in Table 4. A summary of the results of the VIVID-1 trial were presented in the CS, sections B.3.1 to B.3.8.

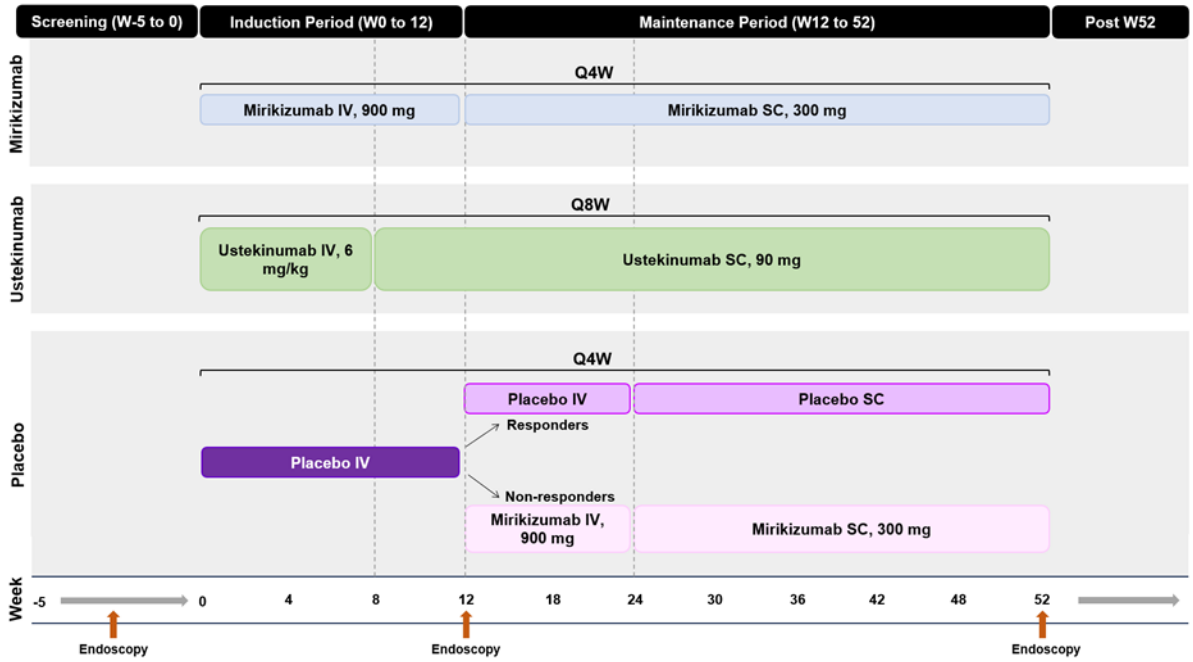
Table 4. Summary of the VIVID-1 trial

Intervention	Comparator	Population	Location	Study duration
Mirikizumab • 12-week induction period: 900 mg IV infusion at weeks 0, 4 and 8; • 12 to 52 week maintenance period: 300 mg SC injection every 4 weeks	Ustekinumab • 12-week induction period: 6 mg/kg IV infusion at week 0, 90 mg SC injection starting at week 8; • 12 - 52 week maintenance period: 90 mg SC injection once every 8 weeks Placebo • 12-week induction period: IV infusion at weeks 0, 4 and 8; • 12 - 52 week maintenance period: 300 mg SC injection every 4 weeks	Adults with moderate to severe active CD	International (328 centres)	52 weeks

Abbreviations: IV, intravenous; SC, subcutaneous; CD, Crohn's disease

VIVID-1 was a Phase III multicentre, randomised, double-blind trial using a treat-through design. The efficacy and safety of mirikizumab was compared to placebo and ustekinumab over the induction (12 weeks) and maintenance (12 to 52 weeks) periods of treatment for people with moderate to severe active CD. In the placebo arm, those who showed a response during the induction period continued with placebo. Those who did not respond during the induction period were switched to mirikizumab. More detailed information about the trial design is included in Figure 2 and section 3.3.1 of the CS. Information on dosing strategies are included in Table 4.

Figure 2. VIVID-1 trial design (reproduced from Figure 4 of the CS)



Outcomes were reported for the main trial population (PAS), as well as two subgroups representing people who had failed a previous biologic treatment (BF subgroup) and people who had failed conventional care (CCF subgroup). These subgroups align to the decision problem, with the BF subgroup representing the majority of this population in clinical practice, and the CCF subgroup suitable to act as a surrogate for those in which TNF-α inhibitors are not suitable (as discussed in Table 1).

Co-primary endpoints selected to compare mirikizumab to placebo were:

- Proportion of patients achieving clinical response (CDAI PRO) at 12 weeks and endoscopic response at 52 weeks (SES-CD total score); and
- Proportion of patients achieving clinical response (CDAI PRO) at 12 weeks and clinical remission at 52 weeks (CDAI).

Major secondary endpoints most relevant to the scope for comparisons between mirikizumab and placebo were clinical response (PRO) and endoscopic remission (SES-CD) at 12 weeks. Clinical remission (CDAI) and endoscopic response (SES-CD) were major secondary endpoints for both 12 and 52 weeks.

There were no primary endpoints for the comparison between mirikizumab and ustekinumab. Major secondary endpoints used for this comparison were:

- Proportion of patients achieving clinical remission (CDAI) at week 52; and
- Proportion of patients achieving endoscopic response (SES-CD) at week 52.

Other secondary endpoints relevant to the scope for comparisons between mirikizumab and ustekinumab were:

- Clinical response (CDAI) at weeks 12 and 52;
- Clinical remission (CDAI) at week 12;
- Endoscopic response (SES-CD) at week 12; and
- Endoscopic remission (SES-CD) at week 52.

Non-inferiority margins were used to assess the CDAI outcomes for ustekinumab. The company used the fixed 95%/95% margin method (also called the double CI method or the fixed-margin method) to establish a non-inferiority margin of 10%. While there is not currently a validated minimally important difference for CDAI, the EAG's clinical experts thought that this was a reasonable margin to assess non-inferiority. The company justified the use of the 10% margin based on Pouillon *et al.* 2020[10] and data modelled from three previous ustekinumab studies (UNITI1, UNITI2 and IM-UNITI).[11] From these previous studies, the company estimated a treatment versus placebo risk difference of 26.9% (95% CI: 19.5 to 34.6) for ustekinumab. The company used a more conservative estimate of this effect for ustekinumab (20%) to propose that the 10% non-inferiority margin was sufficient as it would ensure that mirikizumab retained at least 50% of the expected risk difference for ustekinumab on clinical remission (CDAI) at week 52. That is, if the lower 95% confidence interval for the estimated risk difference for CDAI for mirikizumab compared to ustekinumab didn't cross "–10%" then the company could claim that mirikizumab is non-inferior to ustekinumab.

Table 5 presents the EAG's quality assessment of the VIVID-1 trial. The EAG considers VIVID-1 to be a high-quality trial at low risk of bias for the co-primary endpoints and the major secondary endpoints. This assessment is similar to the company's assessment of VIVID-1 trial, presented in the CS section B.3.5.

Table 5. EAG's summary of the design, conduct and analysis of the VIVID-1 trial.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Statistical analysis plan – Section 1.2	**Appropriate** Participants were randomised using 6:3:2 randomisation. Randomisation was achieved using a computer-generated random sequence from an interactive web-response system. The web-response system assigned patients to groups based on biologic-failed status, baseline corticosteroid use, baseline SES-CD total score, region (North America/Europe/Other) and baseline SF≥7 and/or baseline AP≥2.5.
Eligibility criteria	CS Table 8	**Appropriate** The EAG's clinical experts agreed that the inclusion and exclusion criteria for VIVID-1 were appropriate. Patients aged over 80 years were excluded from the trial even though they would be treated in practice. However, this would be a very small percentage of patients.
Blinding and allocation concealment	Statistical analysis plan – Section 1.2	**Appropriate** The study was double-blind with allocation to trial arms determined using an interactive web-response system.
Baseline characteristics	CS Tables 9-10	**Some concerns** The EAG's clinical experts thought that the demographics of participants broadly reflected clinical practice. There were some differences in disease biomarkers between groups which the experts thought could affect a person's response to treatment. There were some differences between baseline characteristics of the BF and CCF subgroups, such as duration of CD and percentage with ileal disease. However, these were similar across arms within each subgroup, and so not considered a major concern. Baseline characteristics were not reported as part of the CS but were provided at the clarification stage. These are reported in section 10.1 of the appendix. Information on smoking status for each subgroup was provided at the clarification stage (section 10.1 of the appendix). Smoking status was highlighted by the experts as a potential treatment modifier. The company provided this information at the clarification stage (section 10.1 of the appendix), but differences between arms were relatively small.
Dropouts	VIVID-1 HTA Evidence Package, section 4.1	**Some concerns** Higher rate of dropouts for the placebo arm than the mirikizumab or ustekinumab arms in both the induction and maintenance period: Placebo: Induction 7.0%, Maintenance 15.6%; Mirikizumab: Induction 2.8%, Maintenance 10.7%; Ustekinumab: Induction 3.5%, Maintenance 10.5%.
Statistical analysis		
Sample size and power	CS Table 13	**Appropriate**

		The study was designed to have >90% power to demonstrate the superiority of mirikizumab to: • placebo for both co-primary endpoints assuming co-primary endpoint response of 33% for mirikizumab and 10% for placebo; • ustekinumab for endoscopic response at 52 weeks assuming a difference of at least 16% between the treatments. The study was not powered or multiplicity controlled for most of the endpoints comparing mirikizumab with ustekinumab. However, outcomes measured by CDAI were assessed using the non-inferiority margin of 10%.
Handling of missing data	CS Table 13 and VIVID-1 SAP section 5.1.5	**Appropriate** Missing data for binary outcomes or for people discontinuing due to AEs or lack of efficacy was imputed using non-responder imputation. Continuous endpoints used the missing at random assumption. For people with sporadic data, or people who discontinued due to other reasons, multiple imputation was used.
Outcome assessment	CS Table 11	**Appropriate** Clinical response outcomes were assessed using CDAI and PRO measures. Although CDAI measures are not commonly used in practice, the EAG's clinical experts were satisfied that this is common in clinical trials. Endoscopic response and remissions measures reflected those used in clinical practice. Fatigue was assessed using a validated tool. Three data sets were used for efficacy outcomes: • PAS: Primary analysis set population, including all participants with CES-CD ≥7 (or ≥4 for isolated ileal disease) who took at least 1 dose of a study intervention even if it was not their assigned intervention; • PAS not-biologic-failed (CCF): All patients from the PAS population who had not previously failed a biologic treatment. Also referred to as the conventional care-failed subgroup; • PAS biologic-failed (BF): All patients from the PAS population who had previously failed at least one biologic treatment.

Abbreviations: CS, company submission; EAG, External Assessment Group; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; AP, abdominal pain; BF, biologic failed subgroup; CCF conventional care failed subgroup; CDAI, Crohn's disease activity index; AEs, adverse events; PRO, patient reported outcomes

4.3 Clinical effectiveness results

Results of the VIVID-1 trial are presented in sections B.3.6 to B.3.7 and B.3.10 of the CS. The results most relevant to the scope of the cost comparison are presented below, grouped by the outcomes outlined by the company in the decision problem.

4.3.1 *Mirikizumab vs placebo: measures of disease activity*

Clinical response, endoscopic response and clinical remission

A significantly higher percentage of people in the mirikizumab group achieved the co-primary endpoints than in the placebo group. These effects were apparent across the PAS population and the BF and CCF subgroups (Table 6 and Table 7), reflecting improvements in disease activity with mirikizumab in those who had failed a previous biologic and those who had failed conventional care.

Table 6. Clinical response at week 12 (PRO) and endoscopic response (SES-CD) at week 52 from the VIVID-1 trial (RD>0 favours mirikizumab). Reproduced from Table 15 of the company submission

Population	% responders		Risk difference (95% CIs)
	Placebo	Mirikizumab	
PAS	9.0	38.0	28.7 (20.6 to 36.8), p<0.001
BF	6.2	36.7	30.5 (23.1 to 37.9), p<0.001
CCF	11.8	39.3	27.5 (19.1 to 35.9), p<0.001

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals

Table 7. Clinical response at week 12 (PRO) and clinical remission (CDAI) at week 52 from the VIVID-1 trial (RD>0 favours mirikizumab). Reproduced from Table 16 of the company submission

Population	% responders		Risk difference (95% CIs)
	Placebo	Mirikizumab	
PAS	19.6	45.4	25.8 (15.9 to 35.6), p<0.001
BF	12.4	43.4	31.0 (22.3 to 39.8), p<0.001
CCF	26.5	47.3	20.8 (10.6 to 31.1), p<0.001

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals

Secondary endpoints relating to disease activity support the results of the co-primary endpoints for the superiority of mirikizumab over placebo (Table 8). The EAG notes that:

At 12 weeks:

- A significantly higher percentage achieved clinical response with mirikizumab in the PAS group and [redacted];
- A higher percentage achieved clinical response with mirikizumab in [redacted];
- A significantly higher percentage achieved clinical remission with mirikizumab in the PAS group;

- A higher percentage achieved clinical remission with mirikizumab in [redacted].

At 52 weeks:

- A significantly higher percentage achieved clinical remission with mirikizumab in the PAS group and BF and CCF subgroups.

The benefits of mirikizumab over placebo were most pronounced at 52 weeks, supporting the views of the EAG's clinical experts that not everyone will have responded to treatment by the 12-week timepoint. Given that some people will not have fully responded to treatment at 12 weeks, the EAG considers the 52-week timepoint to be most important when assessing the efficacy of mirikizumab.

The EAG notes the high placebo response rate, particularly for clinical response (PRO) outcomes. A high placebo response has previously been reported for clinical trials of inflammatory bowel disease, and may reflect the natural course of the disease, such as periods of spontaneous remission.[12] It may also be partially due to responses to concomitant medication. The EAG's clinical experts noted that some people can have relatively severe disease when assessed by endoscopy, but experience few symptoms, while others may have mild disease with more severe symptoms. High placebo response rates were also evident in other trials used for the indirect treatment comparisons (see section 4.4.1). Despite this, the benefits of mirikizumab over placebo were still apparent, particularly in the PAS group and the BF subgroup.

Table 8. Clinical response at 12 weeks and clinical remission at 12 and 52 weeks from the VIVID-1 trial (RD>0 favours mirikizumab). Reproduced from Table 17 to 19 of the company submission

Population	% achieving clinical remission		Risk difference (95% CIs)
	Placebo	Mirikizumab	
Clinical response: Week 12 (PRO)			
PAS	51.8	70.6	18.9 (7.5 to 30.3), p<0.001
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Clinical remission: Week 12 (CDAI)			
PAS	25.1	37.7	12.4 (2.2 to 22.7), p=0.001
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Clinical remission: Week 52 (CDAI)			
PAS	19.6	54.1	34.6 (24.7 to 44.4), p<0.001

BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals; PRO, patient reported outcomes; CDAI, Crohn's disease activity index

4.3.2 Mirikizumab vs placebo: mucosal healing

Endoscopic remission

A higher percentage of patients achieved endoscopic remission for mirikizumab than placebo at 12 weeks. Differences between the trial arms were [redacted] (Table 9). Differences were more apparent at week 52, where less than [redacted] of those in the placebo group achieved endoscopic remission, compared to [redacted] with mirikizumab, reflecting a [redacted] difference in the PAS group, the BF subgroup and the CCF subgroup, respectively.

Table 9. Endoscopic remission (SES-CD ≤4) from the VIVID-1 trial at weeks 12 and 52 (RD>0 favours mirikizumab). Reproduced from Table 20 of the company submission

Population	% achieving endoscopic remission		Risk difference (95% CIs)
	Placebo	Mirikizumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals

4.3.3 Mirikizumab vs placebo: HRQoL

Change in EQ-5D-5L from baseline

Information for change in HRQoL for all groups was provided by the company as part of clarification responses. The LSM differences for mirikizumab compared to placebo are presented in Table 10. Mirikizumab resulted in greater improvements in HRQoL than placebo at week 12 and week 52, with the greatest benefits of mirikizumab seen for the BF subgroup. As for the other outcomes, the

difference between groups were most apparent at week 52 with [redacted] improvements in HrQoL for mirikizumab than placebo for the PAS population and both subgroups.

Table 10. Change in HRQoL (EQ-5D-5L VAS) from baseline from the VIVID-1 trial at weeks 12 and 52 (LSM>0 favours mirikizumab). Reproduced from Table 24 of the company submission and responses to clarification questions

Population	LSM Change from baseline		LSM difference (95% CIs)
	Placebo	Mirikizumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; LSM, least square mean; CIs confidence intervals

4.3.4 Mirikizumab vs placebo: Bowel urgency

NRS ≤2 in patients with baseline urgency ≥3 at weeks 12 and 52

At week 12, [redacted] were observed between mirikizumab and placebo in the PAS group and BF subgroup (Table 11). By 52 weeks, there was an increase in the percentage with NRS ≤2 in the mirikizumab group but a decrease in the placebo group. Bowel urgency was therefore [redacted] with mirikizumab than placebo at 52 weeks for the PAS group and both subgroups.

Table 11. Bowel urgency (NRS ≤2) from the VIVID-1 trial at weeks 12 and 52 (RD>0 favours mirikizumab). Reproduced from Table 23 of the company submission

Population	% achieving NRS ≤2		Risk difference (95% CIs)
	Placebo	Mirikizumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]

CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; NRS, numeric rating scale; CIs confidence intervals

4.3.5 *Mirikizumab vs ustekinumab: Measures of disease activity*

Clinical remission, clinical response and endoscopic response

Clinical remission was a secondary endpoint at 12 weeks, and a major secondary endpoint at 52 weeks (Table 12), both assessed using non-inferiority analysis. At 12 weeks, the percentage achieving clinical response remission was similar between mirikizumab and ustekinumab and the 95% CI was within the 10% non-inferiority margin for the PAS population and CCF subgroup. Results for the BF subgroup were similar, but marginally crossed the non-inferiority margin.

At 52 weeks, a significantly higher percentage achieved remission with mirikizumab than ustekinumab in the PAS population. Differences between treatments were not significant for the BF or CCF populations, and the 95% CI was within the 10% margin for the PAS group and both subgroups. Thus, mirikizumab met the criteria for non-inferiority compared to ustekinumab at both 12 and 52 weeks for the PAS group and CCF subgroup, and was non-inferior at 52 weeks for the BF subgroup.

Non-inferiority analysis using the 10% margin was also used for clinical response. Effect estimates marginally favoured mirikizumab for the PAS group and both subgroups, with 95% CIs within the non-inferiority margins at both timepoints

Table 13). Non-inferiority was therefore demonstrated for mirikizumab during both the induction and maintenance periods.

Table 12. Clinical remission from the VIVID-1 trial at weeks 12 and 52 (mirikizumab vs ustekinumab) (RD>0 favours mirikizumab). Reproduced from Table 25 of the company submission

Population	% achieving clinical remission		Risk difference (95% CIs)
	Mirikizumab	Ustekinumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]

BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals

Table 13. Clinical response (CDAI) from the VIVID-1 trial at weeks 12 and 52 (mirikizumab vs ustekinumab) (RD>0 favours mirikizumab). Reproduced from Table 27 of the company submission

Population	% achieving clinical response		Risk difference (95% CIs)
	Mirikizumab	Ustekinumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals

The percentage achieving endoscopic response was similar between mirikizumab and ustekinumab for the PAS group and both subgroups at both 12 and 52 weeks (Table 14). The differences between treatments were slightly greater in the BF subgroup, favouring mirikizumab. While non-inferiority margins were not used for endoscopic response, differences between the two treatments were statistically non-significant.

Table 14. Endoscopic response from the VIVID-1 trial at weeks 12 and 52 (mirikizumab vs ustekinumab) (RD>0 favours mirikizumab). Reproduced from Table 26 of the company submission

Population	% achieving endoscopic response		Risk difference (95% CIs)
	Mirikizumab	Ustekinumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals

4.3.6 Mirikizumab vs ustekinumab: Mucosal healing

Endoscopic remission

The percentage achieving endoscopic remission was similar between mirikizumab and ustekinumab for the PAS population and both subgroups (Table 15). As for endoscopic response, non-inferiority margins were not used to compare the effectiveness of each treatment, but differences between the two treatments were statistically non-significant.

Table 15. Endoscopic remission from the VIVID-1 trial at weeks 12 and 52 (mirikizumab vs ustekinumab) (RD>0 favours mirikizumab). Reproduced from Table 28 of the company submission

Population	% achieving endoscopic remission		Risk difference (95% CIs)
	Mirikizumab	Ustekinumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; CIs confidence intervals

4.3.7 Mirikizumab vs ustekinumab: HRQoL

Change in EQ-5D-5L from baseline

Information for change in HRQoL for all groups was provided by the company in response to the EAG's clarification questions (Table 16). Effect estimates marginally favoured mirikizumab, with the benefits of mirikizumab most apparent at week 52, with [redacted] in HRQoL for the PAS and BF populations. However, with the 95% CIs close to the line of no effect, it is not clear whether this represents a clinically important difference.

Table 16. Change in HRQoL (EQ-5D-5L VAS) from baseline from the VIVID-1 trial at weeks 12 and 52 (RD>0 favours mirikizumab). Reproduced from Table 29 of the company submission

Population	LSM Change from baseline		LSM difference (95% CIs)
	Ustekinumab	Mirikizumab	
Week 12			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]
Week 52			
PAS	[redacted]	[redacted]	[redacted]
BF	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, primary analysis set; BF, biologic failed subgroup; CCF, conventional care failed subgroup; LSM, least square mean; CIs confidence intervals

4.3.8 Adverse effects

The VIVID-1 trial presented information on treatment-emergent adverse events (TEAE), serious adverse events (SAE), adverse events of special interest and discontinuation due to adverse events (Table 17). The percentage with at least one TEAE or severe TEAE was higher for mirikizumab than ustekinumab in the induction phase and similar between the two groups during the maintenance phase. However, given that these were treatment-emergent and not treatment-related adverse events, not all events would have been a direct result of treatment.

Both treatments resulted in a smaller percentage of people experiencing a SAE than placebo. While a slightly higher percentage experienced a SAE with mirikizumab than ustekinumab during the induction period, SAEs were similar for the two treatments during the maintenance period. The all-cause discontinuation rates were similar for the two treatments in the induction period ([redacted] and [redacted] for mirikizumab and ustekinumab respectively), suggesting no major concerns in relation to treatment discontinuation for mirikizumab. All-cause discontinuation was not reported for the maintenance period but, given that the EAG's clinical experts did not expect major differences in the safety of biologic treatments between the induction and maintenance periods, it seems reasonable that discontinuation rates should remain similar between the two treatments.

Table 17. Adverse events in the induction and maintenance phases of the VIVID-1 trial. Reproduced from Table 35 of the company submission

Adverse event	Intervention		
	Placebo	Mirikizumab	Ustekinumab
Induction phase			
≥1 TEAE (%)	[redacted]	[redacted]	[redacted]
≥1 Severe TEAE (%)	[redacted]	[redacted]	[redacted]
≥1 SAE (%)	[redacted]	[redacted]	[redacted]
Treatment discontinuation due to AEs (%)	[redacted]	[redacted]	[redacted]
Maintenance phase			
≥1 TEAE (%)	73.0%	78.6%	[redacted]
≥1 Severe TEAE (%)	[redacted]	[redacted]	[redacted]
≥1 SAE (%)	[redacted]	[redacted]	[redacted]
Treatment discontinuation due to AEs (%)	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment emergent adverse event; SAE, serious adverse event; AEs adverse events

Information was not recorded for adverse events of Grade 3 and above in the VIVID-1 trial. However, in response to clarification questions, the company provided information on TEAEs in the maintenance phase that were assessed by the investigator as severe. The severe TEAEs that occurred in over 1% of patients are presented in Table 18. With the exception of blood and lymphatic system disorders, both treatments resulted in fewer of the most common adverse events than placebo, and the differences between mirikizumab and ustekinumab appear to be relatively small. Based on this information, and comparisons of the TEAEs experienced by less than 1% of patients (Appendix 10.2), mirikizumab and ustekinumab appear to have a similar safety profile for common adverse events in the maintenance phase.

Table 18. Serious treatment emergent adverse events occurring in >1% of patients in the maintenance phase of the VIVID-1 trial

Adverse event	Intervention		
	Placebo	Mirikizumab	Ustekinumab
Infections and infestations - n (%)	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders - n (%)	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders - n (%)	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders - n (%)	[redacted]	[redacted]	[redacted]

The EAG's clinical experts did not raise any concerns about specific adverse events that could arise from biologic treatment of moderate to severe CD. However, they highlighted how hypersensitivity reactions could occur in the maintenance phase even if they were not apparent during the induction

phase. Hypersensitivity reactions (immediate, non-immediate and infusion site reactions) were not considered severe treatment emergent adverse events in the CS but were reported as an adverse event of special interest (CS section B.3.10.4). The percentage of hypersensitivity reactions (immediate, non-immediate and infusion site) in each group were:

- Induction period: Placebo [redacted]; Mirikizumab [redacted]; Ustekinumab [redacted];
- Maintenance period: Placebo [redacted]; Mirikizumab [redacted]; Ustekinumab [redacted].

Hypersensitivity reactions were similar between mirikizumab and ustekinumab during the induction period, but notably higher for mirikizumab in the maintenance period. The biggest difference between the active treatments was due to infusion site reactions ([redacted] for mirikizumab; [redacted] for ustekinumab). However, the company reported that the differences in hypersensitivity reactions on the day of treatment were not clinically significant between mirikizumab and ustekinumab. The EAG's clinical experts did not highlight hypersensitivity as a major area for concern, stating that most hypersensitivity reactions would be treated in an outpatient setting, and that only the most severe cases would require inpatient treatment and potential changes in treatment.

In response to clarification questions, the company provided data on hospitalisations and rates of CD-related surgery. Both treatments resulted in lower rates of hospitalisation and surgery than placebo, and the differences between treatments were non-significant in both the BF and CCF subgroups (Table 19).

Table 19. CD-related surgeries and hospitalisations in the VIVID-1 trial (RD>0 favours mirikizumab)

	Intervention			Mirikizumab vs ustekinumab RD (95% CIs)
	Placebo	Mirikizumab	Ustekinumab	
Rates of CD-related hospitalisation, n (%)				
BF	[redacted]	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]	[redacted]
Rates of CD-related surgery, n (%)				
BF	[redacted]	[redacted]	[redacted]	[redacted]
CCF	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD, Crohn's disease; RD, risk difference

4.4 Critique of the indirect treatment comparison

The systematic literature review (SLR) in section 4.1 was used to identify studies for the indirect treatment comparison (ITC). No studies were identified that directly compared the efficacy and safety of mirikizumab to risankizumab. The company therefore performed network meta-analyses (NMAs) to provide indirect comparisons between the two treatments. NMAs were performed for the biologic failed (BF) and conventional care failed (CCF) subgroups for the following outcomes and timepoints:

Induction period (12 weeks) – efficacy and safety outcomes

- Enhanced clinical response;
- Clinical remission;
- Endoscopic response;
- Endoscopic remission;
- Serious adverse events;
- All-cause discontinuations.

Maintenance period (52 weeks) – efficacy outcomes

- Clinical remission.

The company acknowledged that the different trial designs were a limitation of the analysis, resulting in more limited reporting of outcomes in the maintenance period. Three studies used a treat-through design,[5, 13, 14] where participants are randomised to a treatment or placebo at baseline, then continue with that treatment for the duration of the trial. Eight studies used a re-randomised responder design, where people are assigned to an active treatment for the induction period.[11, 15-21] Once the induction period is complete, those who responded to treatment progress to the maintenance period of the trial where they are re-randomised, either continuing with the active treatment or being re-assigned to placebo. By including only the people who have responded to treatment during the induction period, those who are assigned to the placebo arm during the maintenance period will have different treatment histories to those who were assigned to the placebo arm at randomisation in a treat-through study design.

The company noted that the different trial designs would violate the similarity and homogeneity assumptions of an NMA. The use of a re-randomised design may also improve the response of the

placebo group more than in those trials that used a treat-through design. To account for the differences in trial design, and the potential effects on placebo response, the company used statistical adjustment involving the recalculation of the placebo arms for the maintenance phase of the treat-through trials. The company provided more detail about these adjustments in Appendix D1.7.7, supporting their decision based on similar adjustments which have been made in previous NICE TAs for ulcerative colitis.[7, 22-24]

The VIVID-1 trial used a treat-through design and so the company applied the adjustments described above to allow for comparisons with the re-randomised trials. Following adjustment, the company reported that they could not provide a justifiable recalculated arm to use in the NMAs for the maintenance period. With no other trials in the network that included mirikizumab, VIVID-1 could therefore only be connected to the NMAs for the maintenance phase via the ustekinumab arm. However, two of the other trials which included ustekinumab (SEAVUE and SEQUENCE) were excluded from the NMAs because of issues with adjustment for their treat-through design. For SEAVUE, the company reported that the adjustments resulted in implausibly high levels of responders. For SEQUENCE, adjustments were not possible because it did not report the clinical response data necessary for the recalculation of the placebo arm. With the exclusion of SEAVUE and SEQUENCE, VIVID-1 could only be connected to maintenance period NMAs via the one remaining study that included ustekinumab (IM UNITI). The only relevant outcome reported by IM UNITI was clinical remission, limiting the NMA analysis of the maintenance phase to this single outcome.

Safety outcomes were only reported for the induction period because of the issues with different trial designs, as described above. The company concluded that the varied treatment histories in the placebo arm meant that no reliable conclusions could be drawn from the maintenance period safety data. The EAG's clinical experts did not consider the lack of safety data in the maintenance phase a major issue, as few additional adverse events are expected in the maintenance period beyond those which are experienced during the induction period.

In the base case, nineteen studies were included in NMAs for the induction period, and 10 were included for the maintenance period. The eight interventions included in the induction period NMAs were:

- Adalimumab 160 mg at week 1, 80 mg at week 2 or 80 mg at week 1, 40 mg at week 2;
- Infliximab 5 mg / kg at weeks 0, 2 and 6;

- Mirikizumab 900 mg every 4 weeks for 12 weeks;
- Risankizumab 600 mg at weeks 0, 4 and 8;
- Upadacitinib 45 mg once per day for 12 weeks. Optional additional 30 mg once per day for 12 weeks;
- Ustekinumab 6 mg/kg, 260 mg, 390 mg or 520 mg based on weight;
- Vedolizumab 300 mg at weeks 0, 2 and 6;
- Placebo.

Studies including certolizumab and natalizumab were excluded from the base case induction NMA given that these treatments are FDA-only approved.

Eight interventions were included in the maintenance period NMAs:

- Adalimumab 40 mg every 2 weeks;
- Infliximab 40 mg every week or 80 mg every 2 weeks;
- Mirikizumab 300 mg every 4 weeks;
- Risankizumab 360 mg every 8 weeks;
- Ustekinumab 90 mg every 8 or 12 weeks;
- Upadacitinib 15 mg once per day or 30 mg once per day;
- Vedolizumab 300 mg every 4 or 8 weeks, or 108 mg every 2 weeks;
- Placebo.

Methods and results from the NMAs are presented by the company in CS section B.3.9, the appendices section D and the NMA report appendices.

4.4.1 Critique of trials identified and included in the indirect treatment comparison

The company's SLR searched for RCT evidence for biologic treatments and biosimilars used for the treatment of people with moderate to severe CD. The review identified 157 publications which reported on 95 studies (CS appendices Figure 1, section D.1.4.1). Of these, 60 publications did not match the NMA protocol, either due to the inclusion of different treatments or doses to the protocol, or not reporting relevant outcomes. Studies were only included in the NMA if they used EMA and FDA approved doses.

The EAG agreed with the company assessment of the risk of bias for the VIVID-1 trial (Table 14 of the CS). As described above, the company chose to exclude one of the studies (SEAVUE) from the NMA

due to the inflated number of responders compared to other studies once the data had been readjusted to account for the treat-through trial design. While this decision may avoid the risk of overestimating the efficacy of ustekinumab and adalimumab in comparison to other treatments in the networks, it raises concerns about the methods used for adjustment that were also applied to the VIVID-1 trial. Without further information about the cause of the over-inflated estimates seen for the SEAVUE trial, it is possible that the adjustments for VIVID-1 could have resulted in similar effects, albeit less pronounced than those for SEAVUE. This uncertainty should therefore be considered when interpreting the results of the indirect comparisons from the NMAs.

An overview of the studies included in the NMAs, including trial design, treatments and doses, are presented in Table 20 and Table 21.

Table 20. Overview of studies included in the induction NMAs

Study	Subgroups reported	Number of patients	Length of induction period	Induction treatment and dose	Comparator
ADVANCE [17]	BF and CCF	141	12 weeks	Risankizumab 600 mg at week 0, 4, 8	Placebo
CLASSIC I[25]	CCF	225	4 weeks	Adalimumab 1: 160 mg at week 0 and 80 mg at week 2 (if faster response required) 2: 80 mg at week 0 and 40 mg at week 2	Placebo
Feagan 2017[26]	Mixed (AEs)	80	12 weeks	Risankizumab 600 mg at week 0, 4, 8	Placebo
GAIN[27]	BF	325	4 weeks	Adalimumab 160 mg at week 0 and 80 mg at week 2 (if faster response required)	Placebo
GALAXI 1[28]	BF and CCF	51	12 weeks	Ustekinumab Approx. 6 mg/kg, 260 mg or 390 mg or 520 mg based on weight, single dose	Placebo
GEMINI 2[18]	BF and CCF	189	6 weeks	Vedolizumab 300 mg week 0, 2 and 6	Placebo
GEMINI 3[29]	BF and CCF	101	6 weeks	Vedolizumab 300 mg week 0, 2 and 6	Placebo
MOTIVATE[17]	BF	378	12 weeks	Risankizumab 600 mg at week 0, 4, 8	Placebo
Sandborn 2012[30]	BF	263	6 weeks	Ustekinumab Approx. 6 mg/kg, 260 mg or 390 mg or 520 mg based on weight, single dose	Placebo
SEAVUE[13]	CCF	386	8 weeks	Ustekinumab	Adalimumab

				90 mg (SC) every 12 weeks (or 8 weeks if needed)	1: 160 mg at week 0 and 80 mg at week 2 (if faster response required)
Targan 1997[31]	CCF	51	4 weeks	Infliximab 5 mg/kg week 0, 2 and 6	Placebo
U-EXCEED[19]	BF	495	12 weeks	Upadacitinib 45 mg per day for 12 weeks	Placebo
U-EXCEL[19]	BF and CCF	287	12 weeks	Upadacitinib 45 mg per day for 12 weeks	Placebo
UNITI 1[11]	BF	496	6 weeks	Ustekinumab Approx. 6 mg/kg, 260 mg or 390 mg or 520 mg based on weight, single dose	Placebo
UNITI 2[11]	CCF	418	6 weeks	Ustekinumab Approx. 6 mg/kg, 260 mg or 390 mg or 520 mg based on weight, single dose	Placebo
VIVID-1[5]	BF and CCF	548	12 weeks	1: Mirikizumab 900 mg every 4 weeks for 3 doses 2: Ustekinumab Approx. 6 mg/kg, 260 mg or 390 mg or 520 mg based on weight, single dose	Placebo
Watanabe 2011[32]	BF and CCF	38	4 weeks	Adalimumab 1: 160 mg at week 0 and 80 mg at week 2 (if faster response required) 2: 80 mg at week 0 and 40 mg at week 2	Placebo
Watanabe 2020[21]	BF and CCF	36	10 weeks	Vedolizumab 300 mg week 0, 2 and 6	Placebo
Abbreviations: BF, biologic failed; CCF conventional care failed					

Table 21. Overview of studies included in the maintenance NMAs

Study	Subgroups reported	Number of patients	Length of maintenance period	Maintenance treatment and dose	Comparator
ACCENT I	CCF	223	52 weeks	Infliximab 5 mg per kg every 8 weeks	Placebo
CHARM[16]	BF and CCF	237	52 weeks	Adalimumab 1: 40 mg every 2 weeks 2: 40 mg every week	Placebo
FORTIFY[33]	BF and CCF	338	52 weeks	Risankizumab 1: 180 mg every 8 weeks 2: 360 mg every 8 weeks	Placebo
GEMINI 2[18]	BF and CCF	237	46 weeks	Vedolizumab 1: 300 mg every 8 weeks 2: 300 mg every 4 weeks	Placebo
IM UNITI[11]	BF and CCF	174	44 weeks	Ustekinumab* 90mg every 12 weeks 90mg every 8 weeks if needed	Placebo
U-ENDURE[19]	BF and CCF	377	52 weeks	Upadacitinib 15 mg per day 30 mg per day	Placebo
VISIBLE 2[20]	BF and CCF	210	46 weeks	Vedolizumab 108 mg every 2 weeks	Placebo
VIVID 1*	BF and CCF	254	40 weeks	Mirikizumab 300 mg every 4 weeks	Ustekinumab 90 mg every 8 weeks
Watanabe 2020[21]	BF and CCF	15	46 weeks	Vedolizumab 300 mg every 8 weeks	Placebo

Abbreviations: BF, biologic failed; CCF conventional care failed

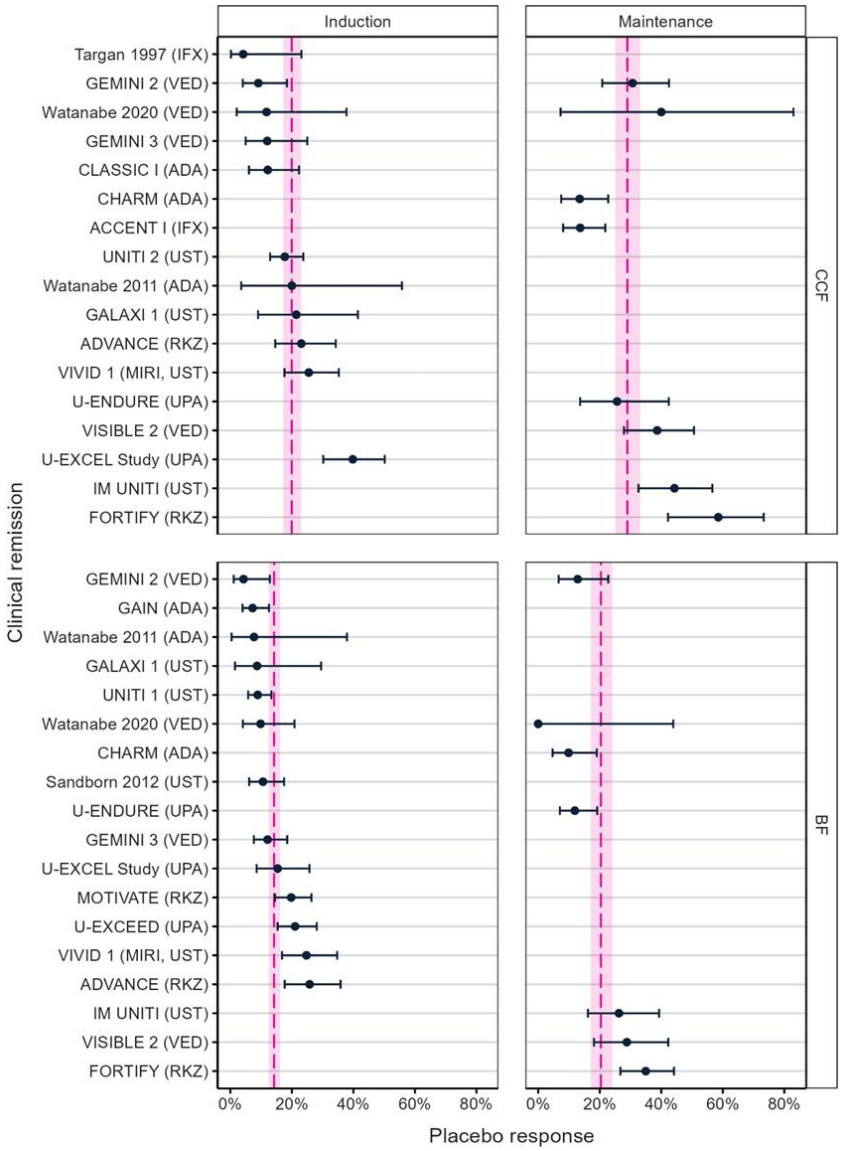
* VIVID 1 values adjusted based on week 12 CDAI responders for re-randomisation trial comparability. Placebo arm not included in maintenance NMAs following adjustments.

The key baseline characteristics are reported in Tables 1 to 4 in section 1.2 of the NMA report appendices. The company highlighted differences between the trials for sex, baseline CDAI score, time since diagnosis and use of concomitant medication.

The EAG's clinical experts discussed how time since diagnosis can be a prognostic factor for CD, with earlier age of onset a potential indicator of a more severe disease course. However, they did not think that either age of onset or sex was likely to be a treatment effect modifier. They also highlighted that the use of steroids was higher in some studies than in UK practice, and that the use of concomitant medications can mask the need for biologic treatment. However, it was not expected that the differences in concomitant medications would have a major effect on response to biologic treatment.

While the higher use of steroids may not have a major impact on response to biologic treatment, it may impact on placebo response rate. One notable difference between the trials was placebo response rate for the clinical remission outcomes. For both the CCF and BF populations, more recent trials showed a greater placebo response than older trials, particularly during the maintenance period (Figure 3). This was reflected in the key trials for the comparisons of mirikizumab and risankizumab (VIVID-1, FORTIFY, ADVANCE and MOTIVATE[5, 17, 33]) which are some of the most recent trials and showed some of the highest levels of placebo response. The company considered this effect, noting that the differences could be partly due to advancements in care for CD, resulting in different prior and concomitant treatments between the older and newer studies. However, this effect introduces limitations to the analysis, whereby treatments assessed in the older trials, which report lower placebo response rates, may appear more effective than those considered in the more recent trials in the NMA. This potentially leads to overestimation of the effects of other treatments in the NMA, as they are not compared to the current standard of care. However, the company noted that adjustments for placebo response rates have been used in previous NICE TA submissions for CD[6, 7] and so all NMAs were performed with and without adjustment for baseline risk. The choice of model was made based on a range of parameters, discussed in section 4.4.2 below.

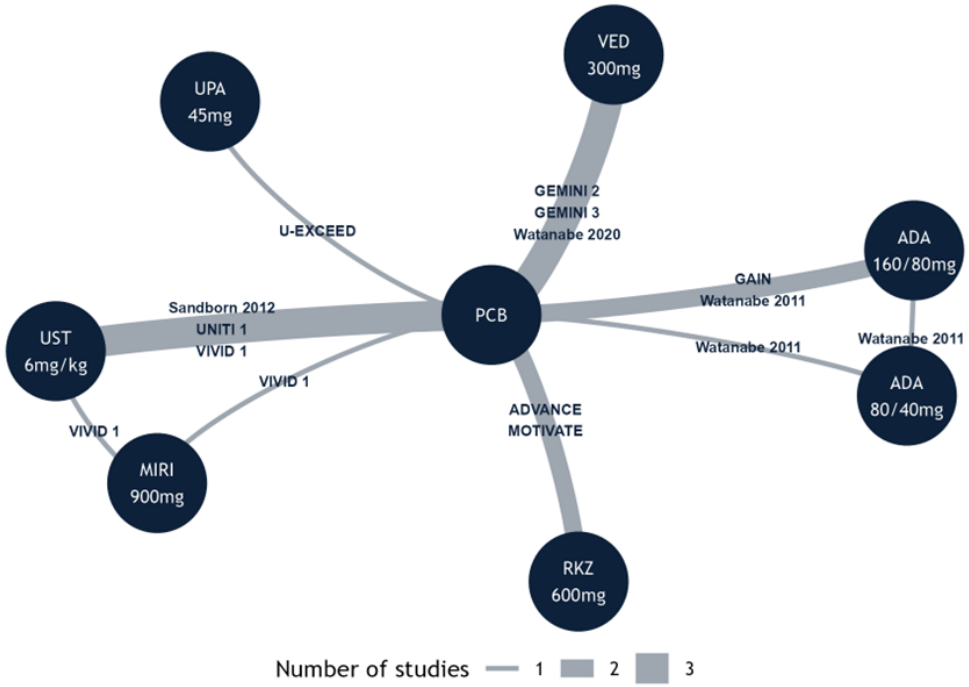
Figure 3. Placebo response rates for studies in the induction and maintenance periods, by CCF and BF subgroups. (Recreated from company appendix, Figure 4).



4.4.2 *Critique of the methods used for the indirect treatment comparison*

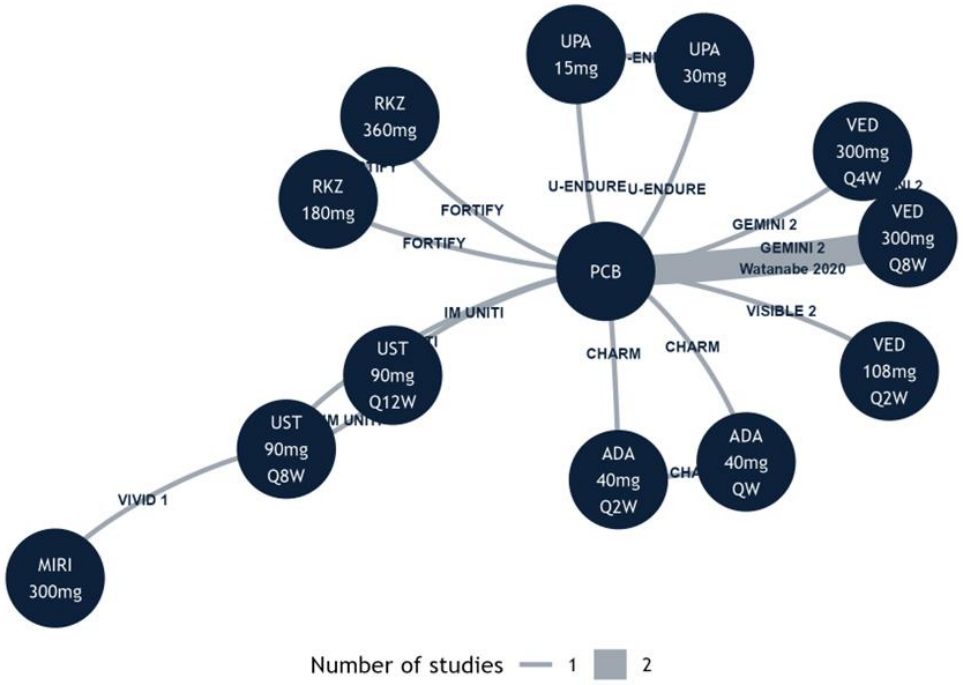
Bayesian NMAs with Monte Carlo Markov Chain (MCMC) sampling were performed using the Stan package in R (version 4.2.1). Four simulation chains were used for the MCMC simulation, with 5,000 burn-in iterations followed by 5,000 further iterations for the analysis. Example network plots from one of the co-primary endpoints in the induction phase and the major secondary endpoint for the maintenance phase are presented in Figure 4 and Figure 5.

Figure 4. Network plot for enhanced clinical response in the induction period for the BF population (reproduced from Figure 25 of the company appendices)



Abbreviations: ADA: adalimumab; BF: biologic-failed; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UST: ustekinumab; VED: vedolizumab

Figure 5. Network plot for clinical remission in the maintenance period for the BF population (reproduced from Figure 33 of the company appendices)



Abbreviations: ADA: adalimumab; BF: biologic-failed; MIRI: mirikizumab; PCB: placebo; RKZ: risankizumab; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab

The EAG notes the range of interventions in each network that are not relevant to the decision problem, which aims to compare the effects of mirikizumab and risankizumab. The additional studies do not form loops in the network with mirikizumab or risankizumab and, as such, do not contribute to the effect estimates for mirikizumab or risankizumab. The additional studies also compound the uncertainties associated with different trial designs, as discussed in section 4.4.1. Although the company has used methods of adjustment to address the variation in trial design, this does not entirely remove this uncertainty. As such, rather than contributing to the mirikizumab and risankizumab effect estimates, the additional studies are likely to introduce additional heterogeneity into the analysis, which can result in wider 95% Credible Intervals (95% CrI) surrounding the effect estimates. Wider 95% CrIs reflect the additional uncertainty introduced into the NMA, making it difficult to appropriately interpret the estimated relative effect estimates for mirikizumab and risankizumab.

With the uncertainties introduced by the additional treatments in the network, the EAG requested simplified indirect treatment comparisons (ITCs) including only the studies that evaluated mirikizumab or risankizumab. The comparisons requested by the EAG were:

- Bucher ITCs for the effectiveness outcomes in the induction period (VIVID-1 and ADVANCE for the CCF population; VIVID-1, ADVANCE and MOTIVATE for the BF population);
- Bucher ITCs for the safety outcomes for the combined population (VIVID-1, ADVANCE, MOTIVATE and Faegan 2017);
- Unanchored Matched-Adjusted Indirect Comparisons (MAICs) for the effectiveness outcomes in the maintenance period (VIVID-1 and FORTIFY); and
- Unanchored MAICs for the safety outcomes for the maintenance period (VIVID-1 and FORTIFY).

A summary of the NMA models originally submitted by the company and the additional analyses requested by the EAG is reported in Table 22.

Table 22. Company choice of NMA model for each outcome and additional analyses requested by the EAG

Outcome	Models originally submitted by the company	Additional analysis provided following EAG request
Induction period		
Enhanced clinical response	CCF: FE with baseline risk adjustment BF: FE without baseline risk adjustment	Bucher ITCs
Clinical remission	CCF: FE with baseline risk adjustment BF: FE without baseline risk adjustment	Bucher ITCs
Endoscopic response	CCF: FE without baseline risk adjustment BF: FE without baseline risk adjustment	Bucher ITCs
Endoscopic remission	CCF: FE without baseline risk adjustment BF: FE without baseline risk adjustment	Bucher ITCs
Maintenance period		
Clinical remission	CCF: FE without baseline risk adjustment BF: FE without baseline risk adjustment	Unadjusted MAIC*
Enhanced clinical response	NR	Unadjusted MAIC*
Endoscopic response	NR	Unadjusted MAIC*
Endoscopic remission	NR	Unadjusted MAIC*
Safety outcomes (induction period)		
Serious AEs	Combined analysis: RE without baseline risk adjustment	Bucher ITC
All-cause discontinuation	Combined analysis: RE without baseline risk adjustment	Bucher ITC
Safety outcomes (maintenance period)		
Discontinuation due to AEs	NR	Unadjusted MAIC*

* Results provided by the company for the combined population only (not stratified by CCF and BF subgroups)

Abbreviations: CCF, conventional care failed; BF, biologic failed; ITCs, indirect treatment comparisons; FE, fixed effects; RE, random effects; AEs, adverse events; NR, not reported

The company performed the requested unanchored MAICs using the R package MAIC in R 4.3.2. The analysis was performed according to the recommendations in NICE Decision Support Unit Technical Support Document 18.[34] Individual patient data from the VIVID-1 study was adjusted to align the baseline characteristics more closely with those reported for the FORTIFY study. Using a combination of literature searches and discussion with a clinical expert, the company identified potential treatment effect modifiers and prognostic factors that could influence treatment response. These factors were incorporated into the base case MAIC and a sensitivity analysis was performed. However, the company noted that while colonic disease was considered a potential treatment effect modifier, no information was provided on this in either study. One of the limitations of an unadjusted MAIC is the difficulty associated with adjusting for all potential treatment effect

modifiers and prognostic factors, which can lead to an unknown degree of bias in the estimates.[34] In addition to the factors such as colonic disease that cannot be adjusted for, unanchored MAICs are at risk of unknown confounders. These factors are usually accounted for by randomisation, but the lack of a common comparator in an unanchored MAIC means it is not possible to determine whether there are unidentified differences between the populations which could affect the outcomes. The uncertainty over the effects of not being able to adjust for all factors must therefore be considered when interpreting the results.

The differences in trial design between the VIVID-1 and FORTIFY studies also lead to some limitations when considering the results. In FORTIFY, only those who had responded to treatment in the induction period progressed to the maintenance period of the study. Consequently, only those who had responded to induction treatment in the VIVID-1 trial could be included in the unanchored MAICs. The EAG's clinical experts discussed how many people may not respond during the 12-week induction period, and a response will only be seen later in the maintenance period. As such, the results of the unadjusted MAICs may not reflect many of the people who are treated for moderate to severe CD. The differences in trial design also led to the outcomes for the maintenance period being reported as a combined analysis, rather than separate CCF and BF subgroups. Any interpretation of these results must therefore consider whether the results of the combined population can be extrapolated to those who show a delayed response to treatment, and those who have different treatment histories.

4.4.3 Results of the indirect treatment comparison

The results of the company NMAs are presented in section B.3.9.4 of the CS and section D.1.10 of the Appendices document. Comparisons were presented between all treatments in the network. The evaluation in this section will focus on the comparisons between mirikizumab and risankizumab for the BF and CCF populations.

All NMA outcomes were dichotomous, and the company modelling assumed binomial likelihood. A logit model for binomial data was used, as described in the NICE DSU TSD 2.[35] Both fixed effects (FE) and random effects (RE), and adjusted and unadjusted models were considered. Model choice was based on DIC, Dbar, posterior distribution (pD) to assess the goodness of fit and overfitting. Models with lower DIC were preferred, with a difference of 3 points considered meaningful. Where results were similar between models, the posterior credible interval for β for meta-regression was assessed to determine if a significant relationship existed between baseline risk and outcome. The company

used evidence of a significant relationship to justify the use of an adjusted model. While the EAG accepts this as a reasonable method of assessing the relationship with baseline risk, the CS reports that a number of population characteristics have already been shown to impact on placebo response rates in trials for CD (Section D.1.6.2 of the appendices document). As such, a decision to use adjusted models for all outcomes would have been preferred. Similar conclusions were reached during the assessment of risankizumab for CD in TA888, where the committee stated that the use of adjusted NMA outcomes was preferable for decision making.[1]

The majority of the company's analyses focused on the induction rather than the maintenance period, based on the limitations in relation to treatment design, outlined in section 4.4. Results were reported separately for the CCF and BF populations for the effectiveness outcomes, and as a combined subgroup for safety outcomes. For each outcome, the company used the 95% credible intervals (CrIs) as a method of assessing clinical similarity between mirikizumab and risankizumab. It was proposed that treatment equivalence can be determined if the 95% CrIs cross the line of no effect (crossing 1 in the case of ORs). With this indicating no statistically significant difference between two treatments, it was interpreted it as a potential indication of similar treatment effects. However, the EAG considers this an inappropriate interpretation of the 95% CrIs – in essence, deriving a strong conclusion of equivalence that conventionally requires large randomised controlled trials, from a highly uncertain finding. As discussed in section 4.4, there are several potential sources of uncertainty in the NMAs presented in the CS including differences in trial design (treat-through vs re-randomised studies), the limited number of studies contributing to the comparisons between mirikizumab and risankizumab, and the concern about the additional heterogeneity introduced with the inclusion of treatments beyond mirikizumab and risankizumab.

The sections below include the results from the CS that are most relevant to the decision problem, the additional analyses requested by the EAG, and the EAG's interpretation of these results.

4.4.3.1 Treatment effectiveness – induction period

Results of the NMAs in the CS are reported in Table 23. Based on the ORs reported in the CS and the responder information reported for the VIVID-1 trial, the EAG also calculated the percentage of people who are expected to respond to each treatment.

In the CCF population, NMA effect estimates favoured risankizumab for all outcomes (Table 23). In the BF population, risankizumab was favoured for all outcomes except endoscopic remission. Based

on the assessment of the 95% CrIs as discussed above, the company reported evidence of clinical similarity between mirikizumab and risankizumab for enhanced clinical response, clinical remission, endoscopic response and endoscopic remission in the induction period. However, as outlined in section 4.4, the EAG considers that it is likely that the width of the 95% CrIs reflect the uncertainty associated with the analysis in addition to the true effects of each treatment.

In an attempt to reduce some of the uncertainty associated with the analysis, the EAG requested Bucher ITCs for only those studies which assessed mirikizumab or risankizumab (VIVID-1, ADVANCE and MOTIVATE). Effect estimates from these ITCs (Table 23) were non-significant and similar to most of those reported for the NMAs, while the 95% CIs demonstrated a similar degree of uncertainty. This uncertainty was particularly reflected by the results for endoscopic response in the BF population, where the effect estimate from the NMA favoured risankizumab, while the Bucher ITC favoured mirikizumab.

To contextualise the difference between the treatments, the EAG estimated the percentage of responders for each outcome by rearranging the OR formula so that risankizumab responders could be calculated from the OR from the NMA and the percentage responders presented for mirikizumab from VIVID-1 (Table 23). These results further highlight the uncertainty associated with the estimates from the NMA analysis in relation to the magnitude of the effect for each treatment. In particular the EAG notes:

- For some outcomes, the difference between mirikizumab and risankizumab in the NMA was non-significant and 95% CrIs crossed the line of no effect, meeting the company's assumptions for potential clinical similarity. However, the absolute differences between the treatments appear considerable. For instance, endoscopic response in the CCF population is reported to reflect clinical similarity, but the absolute estimates demonstrate that approximately 40% are estimated to achieve endoscopic response with mirikizumab, compared to 57% with risankizumab. The EAG does not consider that a difference of this magnitude can provide a basis on which to be confident of clinical similarity;
- Other outcomes show a similar percentage of responders for each treatment. However, the 95% CrIs indicate a wide range in which the true response rate may fall, making it difficult to be certain of the relative effects of the two treatments. For instance, the estimates for enhanced clinical response in the CCF population reflect a 60% and 62%

response rate for mirikizumab and risankizumab respectively. However, the 95% CrIs indicate that the true response rate for risankizumab could range between 44% and 100%. Similar results are seen across the outcomes for both the CCF and BF populations, making it difficult to draw strong conclusions on clinical similarity.

Table 23. Indirect treatment comparisons of efficacy outcomes during the induction period (OR>1 favours mirikizumab). Reproduced from Table 34 of the company submission

Outcome	NMA results OR (95% CrI)	Bucher ITC OR (95% CrI)	EAG estimated % responders (calculated from NMA)
CCF population			
Enhanced clinical response (decrease in CDAI ≥100)	0.90 (0.57 to 1.40)	0.66 (0.31 to 1.36)	Mirikizumab: 60% Risankizumab: 62% (44% to 100%)
Clinical remission (CDAI <150)	0.68 (0.38 to 1.29)	0.60 (0.27 to 1.33)	Mirikizumab: 40% Risankizumab: 49% (38% to 100%)
Endoscopic response (decrease in SES-CD >50% from baseline, or ≥ 2 point reduction from baseline for people with isolated ileal disease and baseline SES-CD of 4)	0.46 (0.18 to 1.17)	0.44 (0.17 to 1.12)	Mirikizumab: 38% Risankizumab: 57% (49% to 100%)
Endoscopic remission (SES-CD ≤4 and at least 2 point reduction from baseline, with no subscore >1 in any individual variable)	0.73 (0.27, 2.00)	0.73 (0.27 to 1.96)	Mirikizumab: 22% Risankizumab: 28% (14% to 100%)
BF population			
Enhanced clinical response (decrease in CDAI ≥100)	0.79 (0.48 to 1.33)	0.89 (0.50 to 1.59)	Mirikizumab: 61% Risankizumab: 67% (50% to 100%)
Clinical remission (CDAI <150)	0.71 (0.40 to 1.23)	0.66 (0.35 to 1.23)	Mirikizumab: 36% Risankizumab: 44% (36% to 100%)
Endoscopic response (decrease in SES-CD >50% from baseline, or ≥ 2 point reduction from baseline for people with isolated ileal disease and baseline SES-CD of 4)	0.84 (0.49 to 1.51)	1.18 (0.49 to 2.86)	Mirikizumab: 27% Risankizumab: 30% (20% to 61%)
Endoscopic remission (SES-CD ≤4 and at least 2 point reduction from baseline, with no subscore >1 in any individual variable)	1.63 (0.39, 11.4)	1.48 (0.31 to 7.1)	Mirikizumab: 13% Risankizumab: 9% (1% to 22%)

Abbreviations: CCF, conventional care failed; BF, biologic failed; CDAI, Crohn's Disease Activity Index; SES-CD, Simple-Endoscopic Score for Crohn's disease

4.4.3.2 *Treatment effectiveness – maintenance period*

In the maintenance period, the only NMA that could be performed was for clinical remission (Table 24). Consideration should be given to the degree of confidence that can be drawn from the analysis of a single outcome in the maintenance phase. This is particularly important given that the only available outcome was clinical remission, while the company and the EAG's clinical experts highlighted that endoscopic outcomes are considered the most relevant to clinical practice.

Effect estimates from the NMAs favour mirikizumab in both the CCF and BF populations. Differences between the treatments were non-significant and meet the company's assumption that the 95% CrIs crossing the line of no effect could indicate clinical similarity. However, the EAG's calculated percentage responders again reflect the uncertainties in these estimates (Table 24). For instance, while there appears to be a considerably higher percentage of responders with mirikizumab in the CCF population (72% compared with 53% for risankizumab), the 95% CrIs indicate that between 6% and 84% of people may respond with risankizumab. Like the induction period, this high degree of uncertainty means that it is not possible to draw strong conclusions on the comparative effectiveness of the two treatments.

With the EAG's concerns about the limited number of NMA outcomes for the maintenance period, and the uncertainty associated with the estimates, the company provided the results from unanchored MAICs for clinical remission, clinical response, endoscopic remission and endoscopic response (Table 25). The unanchored MAICs appear to have been performed with appropriate methodology, but with a lack of individual patient data for the FORTIFY study, estimates could only be provided for the overall population, rather than stratified by the CCF and BF subgroups.

Table 24. NMA comparisons of efficacy outcomes during the maintenance period (OR>1 favours mirikizumab). Reproduced from Table 34 of the company submission

Outcome	NMA results OR (95% CrI)	EAG estimated % responders
CCF population		
Clinical remission (CDAI <150)	2.29 (0.63 to 8.29)	Mirikizumab: 72% Risankizumab: 53% (6% to 84%)
BF population		
Clinical remission (CDAI <150)	1.68 (0.56 to 5.07)	Mirikizumab: 64% Risankizumab: 51% (10% to 92%)

Abbreviations: CCF, clinical care failed; BF, biologic failed; CDAI, Crohn's Disease Activity Index

Table 25. Unanchored MAIC comparisons of efficacy outcomes during the maintenance period (OR>1 favours mirikizumab)

Outcome	Unanchored MAIC results OR (95% CI)
Clinical remission (CDAI <150)	1.777 (1.16 to 2.72)
Clinical response (decrease in CDAI ≥100)	2.803 (1.76 to 4.47)
Endoscopic remission (SES-CD ≤4 and at least 2 point reduction from baseline, with no subscore >1 in any individual variable)	0.779 (0.51 to 1.2)
Endoscopic response (decrease in SES-CD >50% from baseline, or ≥ 2 point reduction from baseline for people with isolated ileal disease and baseline SES-CD of 4)	1.365 (0.90 to 2.07)

Abbreviations: CCF, clinical care failed; BF, biologic failed; CDAI, Crohn's Disease Activity Index; SES-CD, Simple-Endoscopic Score for Crohn's disease

Results of the unanchored MAICs for clinical remission and clinical response favoured mirikizumab, with a significant difference reported for each clinical response (clinical remission [p=0.008], clinical response [p<0.001]). Differences between the treatments were non-significant for the endoscopic response and endoscopic remission outcomes. Based on the company's assumption that the 95% CIs crossing the line of no effect can potentially indicate clinical similarity, the unanchored MAICs suggest clinical equivalence between mirikizumab and risankizumab for most outcomes, while mirikizumab appears to be more effective than risankizumab for clinical remission and response. However, there are a number of factors that should be considered when interpreting these results. The main concerns raised by the EAG in relation to the results of the MAIC are:

- The estimates from the unanchored MAICs are based solely on people who were classified as responders during the induction period. As discussed in section 4.4.2, many people do not show a response to treatment until the maintenance period. These people may therefore show a greater response to treatment in the maintenance period, but are not represented by the results of this analysis;
- The different lengths of the maintenance period of the two trials included in the unanchored MAIC. In FORTIFY, patients who had previously responded to treatment were enrolled in a 52-week maintenance period. The responders from the VIVID-1 trial were identified at the end of the 12-week induction period, with treatment during the maintenance period assessed from weeks 12 to 52;
- The two trials report different definitions of clinical response (a decrease in CDAI score ≥100 points from baseline and/or CDAI <150 for VIVID-1; a decrease in CDAI score ≥ 100

points from baseline for FORTIFY). It is unclear from the methods provided for the MAIC whether only those that met the same definition from each trial were included in the analysis;

- There is an inherent uncertainty associated with unanchored MAICs, based on the assumption that all prognostic factors and treatment effect modifiers have been accounted for in the analysis. While the company attempted to identify and adjust for these factors, this is generally considered difficult, if not impossible, to achieve.[34] As discussed in section 4.4.2, the studies did not provide evidence for at least one treatment effect modifier (colonic disease), and so this could not be accounted for in the analysis. In addition, there are unknown confounders that would usually be accounted for by randomisation but cannot be adjusted for when using unanchored MAICs. As such, the estimates are associated with an unknown degree of bias; and
- There is a greater proportion of people from the BF than the CCF subgroup in the combined analysis (72.3% and 27.7%, respectively in the FORTIFY trial, against which the VIVID-1 trial was matched). Given the uncertainties associated with the NMA evidence base, it is unclear whether people in each of the subgroups are likely to respond in the same way as each other to treatment. It is therefore difficult to establish whether the results of the unanchored MAICs accurately reflect the response of each subgroup, or whether the unbalanced number of people from each group could have affected the estimates.

Given the above concerns, the EAG does not consider that the unanchored MAICs provide sufficient evidence of clinical similarity between mirikizumab and risankizumab in the maintenance period. Instead, the results further highlight the uncertainties associated with the evidence base. Given the uncertainty that has been noted consistently across the NMAs, Bucher ITCs and unanchored MAICs, the EAG proposes that the indirect comparisons do not provide robust evidence of clinical similarity for the effectiveness of mirikizumab and risankizumab. In contrast, the VIVID-1 trial offers higher quality, robust evidence of non-inferiority between mirikizumab and another biologic (ustekinumab) in the treatment pathway for people with moderate to severe CD. The comparison between mirikizumab and ustekinumab from VIVID-1 therefore appears to be the most appropriate evidence base for this cost comparison.

4.4.3.3 Treatment safety

NMA results were presented for serious adverse events (SAEs) and all-cause discontinuation and were provided for the combined population, rather than stratified by the BF and CCF subgroups (Table 26). Results were presented for the induction period only, as the company noted that their adjustment for trial design meant that adverse events in the maintenance period would come from people with different treatment histories (Section 4.4). While the EAG acknowledges the limitations introduced into the analysis with the different trial designs, limited analyses of adverse events make it difficult to accurately compare the safety profiles of the two treatments.

As part of the EAG's request for simplified analyses, ITCs were requested for the induction period, and unanchored MAICs were requested for the maintenance period for a wider range of outcomes (treatment emergent adverse events (TEAEs), serious adverse events (SAEs), all-cause discontinuations and discontinuations due to AEs). Results were provided by the company for:

- Induction period: All-cause discontinuations and SAEs. Data for TEAEs and discontinuations due to AEs was not available for the VIVID-1 trial.
- Maintenance period: Discontinuation due to AEs. There was insufficient data to enable comparisons between the VIVID-1 IPD and aggregated FORTIFY data for all-cause discontinuations, SAEs and TEAEs (Table 26).

Table 26. Adverse events and discontinuations during the induction and maintenance periods (OR<1 favours mirikizumab)

Outcome	NMA results OR (95% CrI)	Unanchored MAIC results OR (95% CI)
Induction period		
SAEs	2.36 (0.92 to 6.67)	1.68 (0.82 to 3.44)
All-cause discontinuations	1.63 (0.52 to 5.74)	1.51 (0.64 to 3.56)
Maintenance period		
Discontinuations due to AEs	NR	0.815 (0.281 to 2.367)

Abbreviations: NR, not reported; ITC, independent treatment comparison

Effect sizes were smaller with the Bucher ITCs than the NMAs and narrower 95% CrIs may reflect reduced uncertainty compared to the wider NMA comparisons. Both methods of analysis indicated no significant differences between the treatments for the induction or maintenance periods. While effect estimates favoured risankizumab in the induction period, mirikizumab was favoured in the maintenance period. Using the company's assumption of potential clinical similarity, these results

could be interpreted as evidence of similar safety profiles for the two treatments. However, the concerns that the EAG has about the uncertainty of the effectiveness data (sections 4.4.3.1 and 4.4.3.2) also apply to the outcomes relating to AEs and discontinuations. Despite the additional analyses provided by the company, there is a limited amount of information on which to draw conclusions about the relative safety of each treatment.

The EAG was interested in common AEs that occurred with each treatment. As part of clarification responses, the company provided additional information on AEs occurring in ≥5% of patients in the maintenance phase (Table 27). The common AEs showed a similar prevalence between the two treatments. The EAG note that hypersensitivity reactions were reported as a common AE in the maintenance phase of the VIVID-1 trial, with a greater number of reactions reported for mirikizumab than ustekinumab. Similar data were not provided as part of the indirect treatment comparisons and so it is unclear how hypersensitivity compares between mirikizumab and risankizumab.

Table 27. Adverse events occurring in ≥5% of patients in the VIVID-1 and FORTIFY trials

Outcome	VIVID-1 (Mirikizumab) n (%)	FORTIFY (Risankizumab 360 mg) n (%)
Anaemia	42 (6.7)	8 (4)
Arthralgia	41 (6.5)	17 (9)
Headache	41 (6.5)	11 (6)
Upper respiratory tract infection	38 (6.0)	NR
Nasopharyngitis	36 (5.7)	17 (9)
Diarrhoea	35 (5.6)	4 (2)
Abdominal pain	[redacted]	9 (5)
Crohn's disease	[redacted]	NR
Pyrexia	[redacted]	NR

Abbreviations: NR, not reported

4.5 Conclusions of the clinical effectiveness section

The company has submitted evidence in support of the clinical similarity of mirikizumab to risankizumab. Both treatments have the same mechanism of action and similar methods of administration. The EAG considers risankizumab a potentially appropriate comparator for the clinical efficacy and safety of mirikizumab.

The clinical evidence for mirikizumab comes from the VIVID-1 trial, which compared the efficacy and safety of mirikizumab to placebo and ustekinumab.[5] The EAG considered VIVID-1 to be a high-quality

trial which included the relevant population, intervention, comparators and outcomes to match the NICE final scope and answer the decision problem. The EAG's clinical experts considered that the population matched those most frequently seen in clinical practice and that the interventions and comparators were relevant to practice in England.

The company presented evidence for outcomes relating to measures of disease activity, mucosal healing, health-related quality of life (HRQoL) and adverse effects. The EAG considers that VIVID-1 provides evidence of:

- The superiority of mirikizumab to placebo during the induction period (12 weeks) and maintenance period (52 weeks);
- Non-inferiority of mirikizumab to ustekinumab for clinical remission outcomes during the induction and maintenance periods; and
- Similar safety profiles and discontinuation rates between mirikizumab and ustekinumab. However, there is the potential for more hypersensitivity reactions with mirikizumab than ustekinumab during the maintenance period.

No trials made direct comparisons between mirikizumab and risankizumab. The company performed NMAs between trials that used a range of biologic treatments for people with moderate to severe CD. The NMA demonstrated uncertainty in the comparative effectiveness of mirikizumab and risankizumab, with many of the effect estimates favouring risankizumab. Uncertainty in the analyses resulted in wide 95% CrIs, and while many of the 95% CrIs crossed the line of no effect, the EAG does not consider that this provides clear evidence of clinical similarity between mirikizumab and risankizumab.

The EAG was concerned that the NMAs included trials of treatments which did not contribute to the effect estimates for comparisons between mirikizumab and risankizumab and therefore were not relevant to the decision problem. Instead, the additional trials were likely to introduce further heterogeneity to the analysis, making it more difficult to determine the comparative effects of each treatment. This decision was further supported by the EAG's estimation of percentage responders, which demonstrated that, even when the 95% CrIs from the NMAs crossed the line of no effect, the differences in number of responders between the two treatments could be considerable. The company provided simplified ITC comparisons at the clarification stage (Bucher ITCs and unanchored matched-adjusted indirect comparisons [MAICs]), which included only the trials for mirikizumab and

risankizumab. The Bucher ITC comparisons further reflected the uncertainties in the analysis, with wide 95% CIs making it difficult to be confident of the comparative effectiveness between the treatments. Effect estimates from the unanchored MAICs favoured mirikizumab for clinical remission, clinical response and endoscopic response. However, the EAG considers that unanchored MAICs are associated with a high degree of uncertainty, which should be considered when interpreting the results. This uncertainty arises from a number of factors including:

- the inclusion of only people who responded to treatment during the induction period;
- different time periods used to assess treatment effects in the maintenance period;
- the greater proportion of people from the biologic failed (BF) than conventional care failed (CCF) subgroup in the unanchored MAIC analysis, and uncertainties surrounding whether people in each of these subgroups would respond in the same way to treatment;
- the potential use of different definitions of clinical response from the two trials; and
- the inherent difficulties in identifying and adjusting for all prognostic factors and treatment effect modifiers with the unanchored MAIC.

Results from the unanchored MAICs are therefore considered less robust comparisons than methods that retain the benefits of randomisation within the analyses, such as direct comparisons in RCTs or NMAs of RCTs. As such, the EAG is not confident that the results of the unanchored MAICs reflect clinical similarity between mirikizumab and risankizumab.

The EAG considers the use of thresholds such as the minimum clinically important difference (MCID), sometimes expressed as a non-inferiority margin, to be a useful method of evaluating clinical similarity between treatments. However, this was not considered by the company as part of the indirect comparisons, with differences between the treatments being non-significant (i.e. 95% CrIs or 95% CIs crossing the line of no effect) instead being considered a potential indicator of clinical similarity. The EAG considers that, while wide 95% CrI/CIs reflect uncertainty in an ITC as might be expected when only a small number of trials are available for analysis, they do not demonstrate clinical similarity. This uncertainty is particularly important to consider for the outcomes from the maintenance period, which have the additional uncertainties that arise with the use of unadjusted MAICs. As such, the EAG does not think that clinical similarity can be effectively demonstrated from the results of the indirect comparisons presented by the company.

Non-inferiority margins were used in the VIVID-1 trial, with values of 10% used for the comparisons between mirikizumab and ustekinumab for outcomes measured by CDAI (clinical remission and clinical response). Results from VIVID-1 showed non-inferiority of mirikizumab to ustekinumab for:

- Clinical remission in the induction (12 weeks) period for the full population (PAS) group and CCF subgroup;
- Clinical remission in the maintenance (52 weeks) period for the PAS group and BF and CCF subgroups; and
- Clinical response in the induction and maintenance periods for the PAS group and BF and CCF subgroups.

For clinical response and remission outcomes, mirikizumab therefore appears to be non-inferior to ustekinumab for all people specified in the decision problem, particularly during the maintenance phase. For other outcomes, the majority of effect estimates marginally favoured mirikizumab but 95% CIs crossed the line of no effect, demonstrating uncertainty. The EAG considers that in the absence of more robust evidence, mean estimates indicating a non-statistically significant benefit for mirikizumab can be used as a surrogate for non-inferiority. As such, the EAG considers that the direct comparison between mirikizumab and ustekinumab from the VIVID-1 trial provides stronger evidence of clinical similarity than the indirect analysis with risankizumab. Although the VIVID-1 trial makes comparisons with a different biologic than proposed in the decision problem, ustekinumab is in the same position as risankizumab in the treatment pathway and therefore appears to be an appropriate alternative for the cost comparison. Ustekinumab was also considered an appropriate comparator for risankizumab in its cost comparison analysis.[1]

Based on the comparisons between mirikizumab and ustekinumab in the VIVID-1 trial, the EAG concludes that:

- The direct evidence from the comparisons between mirikizumab and ustekinumab in the VIVID-1 trial are the most appropriate for the evaluation of the cost comparison;
- Evidence for clinical remission and clinical response from the VIVID-1 trial demonstrates non-inferiority of mirikizumab to ustekinumab in both the induction and maintenance periods;
- Non-inferiority is evidenced for all populations covered in the decision problem, as demonstrated across the VIVID-1 PAS population and BF and CCF subgroups;

- Mirikizumab appears to have a similar safety profile and treatment discontinuation rate to ustekinumab, with the exception of additional hypersensitivity reactions during the maintenance period.

5 Summary of the EAG's critique of cost comparison evidence submitted

For the purposes of the cost-comparison analysis, the company has considered drug acquisition and administration costs for mirikizumab and risankizumab (company's preferred comparator). Moreover, the company has provided supportive cost analysis for two additional comparators, ustekinumab and vedolizumab.

In addition to the company's primary assumption of clinical similarity for mirikizumab, risankizumab, ustekinumab and vedolizumab, the other key assumptions that underpin the company's cost analysis for all included drugs are as follows:

- Adherence to treatment is likely to be similar based on the assumption of similar clinical effectiveness.
- The drug safety profiles are comparable based on the company's network meta-analysis (NMA) and Bucher indirect treatment comparison (ITC) of serious adverse events (SAEs) in the induction phases of trials included in the network and direct trial evidence from VIVID-1 for mirikizumab versus ustekinumab (see Section 4.4.3.3).
- Treatment discontinuation is likely to be similar based on the company's NMA and Bucher ITC of all-cause discontinuation in the induction phases of trials included in the network and direct trial evidence from VIVID-1 for mirikizumab versus ustekinumab (see Section 4.4.3.3).
- The next line of treatment is the same for all patients after they discontinue treatment with any of the drugs included in the analysis.
- Monitoring, tests and disease management costs are likely to be similar for all drugs considered in the analysis based on the assumption of similar clinical effectiveness.

Based on the assumptions outlined above, the company considered that there will be no other cost differences between mirikizumab, risankizumab, ustekinumab and vedolizumab except in the drug acquisition and administration costs of the drugs. The company's approach is aligned with the cost-comparison analyses in other NICE guidance for Crohn's disease including TA888 (risankizumab) and TA905 (upadacitinib).[1, 36]

As discussed in Section 4.5, the External Assessment Group (EAG) considers that the comparison of mirikizumab and ustekinumab in the VIVID-1 trial (direct evidence) provides the most robust source of clinical similarity (non-inferiority) compared with the company's preferred choice of risankizumab,

based on indirect evidence. The following sub-sections present the detail of the company's approach to the cost-comparison analysis and the EAG's critique. Additionally, the EAG presents results for all comparators included in the company's analysis for committee's consideration, but reiterates that the EAG's preferred comparator for the analysis is ustekinumab.

5.1 Population

As mentioned in Sections 4.2.1 and 0, the company has provided clinical analysis for the conventional care-failed (CCF) and biologic-failed (BF) subgroups. In their original submission, the company stated that base case results were only supplied for the BF population, as the approach to the cost analysis is identical for both subgroups except for the baseline characteristics that are used to inform the dose calculations for ustekinumab in the induction phase of treatment (dose is weight-dependent, see Section 5.3). Therefore, the company considered that there would be no substantial differences in costs between the two populations. The baseline characteristics of each population relevant to the cost analysis are presented in Table 28. However, in their clarification response the company explained that because vial wastage is assumed, the dose for ustekinumab is the same for both the CCF and the BF populations, thus there is no difference in costs between the two populations.

As discussed later in Section 5.3, the EAG considers the inclusion of vial wastage is an appropriate assumption. Therefore, the EAG considers that the company's base case results are representative of both the CCF and the BF populations and is appropriate.

Table 28. Baseline characteristics included in the cost analysis (reproduced from Table 40 of the company submission)

Weight distribution	CCF population	BF population
Mean weight, kg (SE)	[redacted]	[redacted]
Weight ≤55 kg, %	[redacted]	[redacted]
Weight >55 kg and ≤85 kg, %	[redacted]	[redacted]
Weight >85 kg, %	[redacted]	[redacted]

Abbreviations: BF, biologic failed; CCF, conventional care failed; SE, standard error.

5.2 Perspective, time horizon and discounting

The perspective of the analysis is based on the UK national health service (NHS). For the base case, the company assumed a time horizon of three years, based on clinical expert advice provided to the committee for TA888 which stated that, "*2 to 3 years is the reported median duration of treatment*

persistence with biologics".[1] The company explored time horizons of two and five years in scenario analysis (See Section 6.1.1). The company did not apply discounting of costs in the base case, citing cost-comparison guidance from NICE, which states that, "*discounting of costs is not normally required in a cost-comparison analysis, but can be applied if relevant*".[37]

5.2.1 EAG critique

The EAG's clinical experts agreed that a time horizon of three years was sufficient to capture the important differences in costs between the drugs, including capturing discontinuations for most patients. Additionally, the committee for TA888 agreed that a shorter time horizon for a cost-comparison analysis was appropriate and for TA905 the committee made no comment on the company base case time horizon of one-year (scenarios exploring second and subsequent years of treatment were included in the CS).[1]

With regards to discounting of costs, as the base case time horizon of the cost analysis is greater than one year, the EAG considers that discounting should have been applied in the company's base case. As such, the EAG ran a scenario that applies a 3.5% discount rate to costs, as per the NICE methods guide and results are presented in Section 6.2. Inclusion of a 3.5% discount rate to costs had minimal impact on incremental costs.

5.3 Drug acquisition costs

Table 29 and Table 30 presents the drug acquisition costs and dosing regimens applied in the company's cost analysis. Comparator list prices were sourced from the British National Formulary.[38] Confidential patient access scheme (PAS) discounts/ medicines procurement supply chain (MPSC) prices are available for all comparators. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG scenario analyses. Please refer to Appendix 10.3 for details on the source of the confidential price for each treatment.

At the factual accuracy stage of this topic, the company provided an updated list price for the maintenance dose of mirikizumab along with base case results including a PAS discount of [redacted] for mirikizumab. All results presented in this document include the mirikizumab PAS discount.

Based on the Summary of Product Characteristics (SmPCs), dose escalation is not permitted for patients on mirikizumab and risankizumab.[4] The SmPCs for ustekinumab and vedolizumab permits dose escalation based on response.[39, 40]

Consistent with simplifying assumptions accepted in TA888[1] and TA905,[36] the company assumed that in the maintenance phase of treatment:

- 92.5% of patients on ustekinumab and 30% of patients on intravenous (IV) infusions of vedolizumab receive an escalated (high) dose.
- No patients on vedolizumab subcutaneous (SC) injections receive an escalated dose (100% on standard maintenance dose).
- There is a 50:50 split between vedolizumab patients on IV infusions and SC injections.

Table 29. Drug acquisition costs

Treatment	Dose	Pack size	List price and PAS price per pack
Mirikizumab	300 mg/ 15 ml concentrate for solution for infusion vials	1 vial	£2,056.56 ([redacted] with PAS discount applied)
	100mg/1ml solution for injection pre-filled pens	Combination pack of one 200 mg pre-filled pen and one 100 mg pre-filled pen*	[redacted] ([redacted] with PAS discount applied)
	200mg/1ml solution for injection pre-filled pens		
Risankizumab	600mg/10ml concentrate for solution for infusion vials	1 vial	£3,326.09
	360mg/2.4ml solution for injection cartridges (OBD)	1 cartridge	£3,326.09
Ustekinumab	130mg/26ml concentrate for solution for infusion vials	1 vial	£2,147.00
	90mg/1ml solution for injection pre-filled pens	1 pre-filled disposable injection	£2,147.00
Vedolizumab	300mg powder for concentrate for solution for infusion vials	1 vial	£2,050.00
	108mg/0.68ml solution for injection pre-filled pens	1 pre-filled disposable injection	£512.50

Abbreviations: IV, intravenous; OBD, on-body device; PAS, patient access scheme; SC, subcutaneous

*In their response to clarification question B2, the company stated that the two SC injections for the maintenance dose of mirikizumab (one 200 mg pre-filled pen and one 100 mg pre-filled pen) are to be sold as a single combination pack. As such, the total cost for the two pens is [redacted]

Table 30. Treatment regimens included in the company's cost analysis

Treatment	Induction	Maintenance	
		Standard dose	High dose
Mirikizumab	900 mg by IV infusion Q4W (Weeks 0, 4 and 8)	300 mg by SC injection every 4 weeks. A full maintenance dose consists of one 200 mg pre-filled pen and one 100 mg pre-filled pen.	N/A
Risankizumab[4]	600 mg administered by IV infusion at Week 0, Week 4, and Week 8.	360 mg administered by SC injection at Week 12, and every 8 weeks thereafter. An on-body-device (OBD) that can be used to deliver the 360 mg risankizumab solution for injection.	N/A
Ustekinumab[39]	6 mg/kg weight based IV dosing at week 0: <55kg: 260 mg; >55 & <85 kg: 390 mg; >85kg: 520 mg.	90 mg SC injection every 12 weeks from week 8.	90 mg SC injection every 12 weeks from week 8.
Vedolizumab[40] (IV)	300 mg IV infusion administered on weeks 0, 2 and 6.	300 mg IV infusion administered every 8 weeks, assumed to be from week 10.	300 mg IV infusion administered every 4 weeks.
Vedolizumab[40] (SC)		108 mg SC every 2 weeks, assumed to be from week 10.	

Abbreviations: IV, intravenous; N/A, not applicable; SC, subcutaneous

Note: In TA888 and TA905, the end of the induction period was assumed to be 14 weeks based on the SmPC.[40] The company provided a scenario using 14 weeks, which increased incremental drug acquisition costs for mirikizumab compared with vedolizumab. However, the EAG notes that vedolizumab is not considered relevant for the cost-comparison analysis as it is not the company or EAG's preferred comparator.

Table 31 presents the drug acquisition costs for the first year and subsequent years of treatment, as well as the total drug acquisition costs based on the company's base case time horizon of three years. Treatment discontinuation was not considered for the analysis, based on the assumption of clinical similarity and consistent with the approach taken in TA888 and TA905.[1, 36] The company assumed vial wastage for the base case, which the EAG considers is appropriate. However, the company provided a scenario that explored vial sharing, presented in Section 6.1.1.

Table 31. Drug acquisition costs by year and 3-year total costs

Treatment	First year (induction + maintenance)	Subsequent years (maintenance only)	Total (3 years)
Mirikizumab	[redacted]	[redacted]	[redacted]
Risankizumab	£26,683	£21,694	£70,071
Ustekinumab	£18,001	£13,653	£45,308
Vedolizumab	£18,579	£15,376	£49,332

5.3.1 EAG critique

Overall, the EAG considers that the company's approach to drug acquisition costs is appropriate and consistent with TA888 and TA905. One minor deviation of the company's approach compared to the approach taken in TA888 and TA905 is that the induction period for vedolizumab was assumed to end at 10 weeks in the current analysis rather than 14 weeks as per the previous TAs and in line with the SmPC for vedolizumab.[40] In their clarification response, the company explained that according to the vedolizumab SmPC it states that, "*patients with Crohn's disease, who have not shown a response may benefit from a dose of IV vedolizumab at week 10*"[40] and as it was unknown what proportion of patients would achieve response, a conservative assumption was adopted to only estimate 3 doses for the induction treatment phase. In their clarification response, the company did provide a scenario using 14 weeks. When 14 weeks is used for the end of the induction period, total drug acquisition and administration costs for vedolizumab decreased from £54,021 to £52,740, which in turn decreased the cost savings associated with mirikizumab from [redacted] to [redacted]. Therefore, the EAG disagrees with the company that their approach is conservative, but notes that as vedolizumab is not the company or EAG's preferred comparator, it is not considered relevant for the cost-comparison analysis.

As mentioned previously the EAG considers that ustekinumab is a more appropriate comparator for the analysis given there is robust, head-to-head, randomized control trial (RCT) data, VIVID-1, which demonstrates mirikizumab is non-inferior to ustekinumab based on a prespecified non-inferiority margin. In addition, the data on all-cause discontinuation for mirikizumab and ustekinumab from VIVID-1 provide a more robust estimate of similarity in treatment discontinuation compared with indirect data for the company's preferred comparator, risankizumab.

Based on all-cause discontinuation data from VIVID-1 (Section 4.3.8), the EAG is satisfied that there are no clinically meaningful differences in treatment discontinuation for patients on either mirikizumab or ustekinumab. Therefore, the EAG considers that the company's approach to assume treatment discontinuation is the same for the comparison with mirikizumab and ustekinumab is reasonable and is supported by advice from the EAG's clinically experts.

The EAG highlights that based on the company's NMA (Table 34 of the CS) and the Bucher ITC (Table 21 of the company's clarification response) for all-cause discontinuation, the odds ratio (OR) for mirikizumab compared with risankizumab suggest that treatment discontinuation is higher for patients on mirikizumab (see Table 32 for results). However, the company considered that because

the 95% credible intervals around the OR encompassed 1 (see company's response to clarification question A14), there was no evidence of a statistically significant difference between mirikizumab and risankizumab.

The EAG does not agree with the company regarding the conclusion of clinical similarity of mirikizumab with risankizumab. When there is substantial uncertainty in an NMA, credible intervals will be wide and, as such, will more than likely encompass 1. As discussed in Section 4.4.3, an assessment of the credible intervals that excludes a prespecified minimal clinically important difference (MCID) for an outcome would have been more appropriate.

Table 32. Company Odds ratios for all-cause discontinuation – mirikizumab versus risankizumab

Estimation method	Odds ratio (95% CrI)
Company NMA (Table 34 of the CS)	1.63 (0.52 to 5.74)
Bucher ITC (company response to CQ A14)	1.51 (0.64 to 3.56)

Abbreviations: CQ, clarification question; CrI, credible interval; CS, company submission; ITC, indirect-treatment comparison; NMA, network meta-analysis.

For the cost analysis, patients discontinuing treatment earlier on mirikizumab compared to risankizumab would result in lower drug acquisition costs, which could be considered a "perverse benefit" for mirikizumab. Furthermore, the EAG's clinical experts considered that there are unlikely to be any clinically meaningful differences in treatment discontinuation between any of the treatments included in the cost-analysis. As such, excluding treatment discontinuation from the cost-analysis entirely can be considered a reasonable, simplifying assumption.

5.4 Drug administration costs

The company included administration costs for all IV infusions and for the first administration of an SC injection (or on-body device [OBD] for risankizumab). The company assumed that during the first administration of an SC injection (or OBD), patients would receive training by a nurse to self-administer treatment at home, which is consistent with the assumptions made in TA888 and TA905 and endorsed by the EAG's clinical experts. Unit cost of drug administrations included in the cost analysis are outlined in Table 33 and the total drug administration costs by treatment are presented in Table 34.

The EAG considers that the company's assumptions for the drug administration cost of SC injections/ OBD and the unit cost used are consistent with TA888 and TA905 and supported by the EAG's clinical experts.

Table 33. Unit cost of drug administrations

Mode of administration	Unit cost	Source
IV infusion (all administrations)	£313.00	2023–2025 NHS Payment Scheme. FD02H - Inflammatory Bowel Disease without Interventions, with CC Score 0.[41]
SC injection/ OBD (first administration only)	£46.00	Cost per working hour of band 5 qualified nurse. PSSRU 2022.[42]

Abbreviations: IV, intravenous; OBD, on-body device; SC, subcutaneous.

Note: During the clarification stage, the company updated the source of the cost of IV infusions to align with TA888 and TA905 (response to question B5).

Table 34. Total cost of drug administration by treatment

Treatment	Total cost of drug administration
Mirikizumab	£985
Risankizumab	£985
Ustekinumab	£359
Vedolizumab	£4,689

Note: In TA888 and TA905, the end of the induction period was assumed to be 14 weeks based on the SmPC. The company provided a scenario using 14 weeks, which increased incremental drug administration costs for mirikizumab compared with vedolizumab. However, the EAG notes that as vedolizumab is not the company or EAG's preferred comparator, it is not considered relevant for the cost-comparison analysis. See Section 5.3.1 for more details.

5.5 Adverse events

In the company's original submission and response to clarification, the NMA and Bucher ITC of safety outcomes were focused on serious adverse events (SAEs) in the induction phase of treatment for the safety population (Table 34 and Figure 31 of the CS and Table 22 of the company's clarification response). Table 35 presents the ORs from the company's NMA and Bucher ITC for SAEs for the comparison of mirikizumab versus risankizumab.

As discussed in Section 4.4.3.3, results were only presented for the induction period as the company noted that the adjustment for trial design meant that adverse events in the maintenance period would come from people with different treatment histories. Additionally, the EAG's clinical experts advised that most AEs would occur in the induction period of treatment.

Table 35. Company Odds ratios for serious adverse events (overall population, induction period) – mirikizumab versus risankizumab

Estimation method	Odds ratio (95% CrI)
Company NMA (Table 34 of the CS)	2.36 (0.92, 6.67)
Bucher ITC (company response to CQ A14)	1.68 (0.82, 3.44)

Abbreviations: CQ, clarification question; CrI, credible interval; CS, company submission; ITC, indirect-treatment comparison; NMA, network meta-analysis.

Based on the results from the NMA and Bucher ITC of SAEs, the company considered that because the credible intervals around the OR encompassed 1 (see company's response to clarification question A14), there was no evidence of a statistically significant difference between mirikizumab and risankizumab. As such, the company did not include the cost of adverse events (AEs) in the model and considered their approach was consistent with TA888 and TA905 which excluded the costs of AEs.[1, 36] However, the EAG disagrees with the company's conclusion of similar safety profiles for mirikizumab and risankizumab and this is discussed in Section 4.4.3.

5.5.1 EAG critique

Based on the company's NMA and the Bucher ITC for SAEs (Table 35), the OR for mirikizumab compared with risankizumab suggests that SAEs are greater for patients on mirikizumab, although there is considerable uncertainty in the analysis. Thus, the EAG considers that for the cost-comparison of mirikizumab with risankizumab, it is appropriate to capture the difference in AE costs. However, inclusion of AE costs for an economic model tends to focus tends on Grade 3 and above AEs as these would typically have the greatest cost implications.

In their clarification response, the company stated that in VIVID-1, AEs were reported as mild, moderate and severe, rather than stratified by Grade as per the Common Terminology Criteria for Adverse Events (CTCAE). Thus, the EAG considers that severe AEs are likely to have the greatest cost implications. However, the EAG notes that for risankizumab, data on severe AEs were not publicly available, thus inclusion of AE costs for the analysis is problematic.

Given the company's indirect comparisons of SAEs, which favour risankizumab but are subject to substantial uncertainty, and the challenges of estimating clinically meaningful AE costs, the EAG believes a cost-comparison analysis for the company's preferred comparator is challenging. The challenges inherent in a cost-comparison of mirikizumab against risankizumab do not arise when

ustekinumab is used as the primary comparator. As discussed previously, the EAG considers that ustekinumab is a more appropriate comparator for the analysis given there is robust, head-to-head, RCT data for the drugs from VIVID-1. As such, a comparison of AEs for mirikizumab and ustekinumab from VIVID-1 is likely to provide the most reliable data to base an assumption of similar safety profiles compared with data estimated from the NMA or Bucher ITC for risankizumab.

As mentioned in Section 4.3.8, hypersensitivity reactions (immediate, non-immediate and infusion site) were noted as an AE of special interest in VIVID-1 and occurrence was similar for mirikizumab and ustekinumab for the induction phase but differed substantially for the maintenance phase (higher for mirikizumab). However, as discussed above, severe AEs incur the most clinically significant costs. In their clarification response (Table 7), the company provided data from VIVID-1 on severe treatment emergent adverse events (TEAEs) for the study treatment period, which covers both week 12 and week 52, but hypersensitivity was not an explicit category. However, severe general disorders and administration site conditions was a category (and which the EAG assumes would include severe hypersensitivity) and occurred in [redacted] of mirikizumab patients but [redacted] were reported for ustekinumab patients. The EAG considers that as the difference between the two treatments is under [redacted], this is unlikely to represent a clinically meaningful difference and the cost difference is likely to be minimal.

Therefore, based on the AE data from VIVID-1 (see Section 4.3.8), the EAG is satisfied that there are no clinically meaningful differences in the types of AEs, frequency and severity experienced by patients on either mirikizumab or ustekinumab. Thus, the exclusion of AE costs in the analysis for the comparison with mirikizumab and ustekinumab is reasonable.

6 Company and EAG cost comparison results

6.1 Company base case results

Table 36 presents the company base case results and demonstrates that mirikizumab results in cost savings across all comparisons. As mentioned in Section 5, the company's preferred comparator is risankizumab, but the EAG considers that more robust evidence of clinical similarity exists for the comparison with ustekinumab and thus is the EAG's preferred comparator.

Table 36. Company's base case results

Interventions	Total Costs (£)	Incremental costs (£)
Mirikizumab	[redacted]	-
Risankizumab*	71,056	[redacted]
Ustekinumab†	45,667	[redacted]
Vedolizumab	54,021	[redacted]

Abbreviations: EAG, External Assessment Group

* Company preferred comparator

† EAG preferred comparator

6.1.1 Company's sensitivity and scenario analyses

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters including several analyses requested by the EAG at the clarification stage. These scenarios are presented in Table 37. Mirikizumab remained cost saving across all scenarios tested.

Table 37. Company scenario analysis

Scenario	Incremental costs (£) – mirikizumab vs		
	Risankizumab*	Ustekinumab†	Vedolizumab
Base case	[redacted]	[redacted]	[redacted]
Time horizon – 2 years	[redacted]	[redacted]	[redacted]
Time horizon – 5 years	[redacted]	[redacted]	[redacted]
Vial sharing (no drug wastage) – BF population	[redacted]	[redacted]	[redacted]
Treatment administration costs excluded	[redacted]	[redacted]	[redacted]
Vedolizumab IV/SC 14-week induction – response to EAG CQ B7	[redacted]	[redacted]	[redacted]
Vial sharing, CCF population baseline characteristics – response to EAG CQ B8	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failed; CCF, conventional care failed; CQ, clarification question; EAG, External Assessment Group; IV, intravenous; SC, subcutaneous.

* Company preferred comparator
† EAG preferred comparator

6.2 Additional economic analysis undertaken by the EAG

The EAG mostly agreed with the company's approach to the cost analysis and is satisfied that any areas of uncertainty were explored in the company's scenario analysis and scenarios provided on request in their clarification response. The EAG ran one scenario exploring a discount rate of 3.5% for costs and results are presented in Table 38. The scenario demonstrates minimal impact on the cost results. As such, the EAG did not consider it necessary to provide an alternative EAG base case.

Table 38. EAG scenario analysis

Scenario	Incremental costs (£) – mirikizumab vs		
	Risankizumab*	Ustekinumab†	Vedolizumab
Base case	[redacted]	[redacted]	[redacted]
3.5% discount rate for costs	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group.
* Company preferred comparator
† EAG preferred comparator

6.3 Summary statement

The company's base case results and all scenarios considered indicate that mirikizumab results in lower costs compared to any of the comparators (primary or supportive) included in the cost model.

The External Assessment Group (EAG) does not agree that the primary comparator for the analysis should be risankizumab. There is substantial uncertainty in the indirect treatment comparisons (ITCs) of mirikizumab versus risankizumab (network meta-analysis [NMA], Bucher ITC and unanchored matched-adjusted indirect comparison [MAIC]) to determine that the clinical similarity criterion for a cost comparison analysis has been met.

Instead, the EAG prefers the comparison of mirikizumab with ustekinumab, where there is direct, head-to-head, randomised controlled trial (RCT) data from VIVID-1, which demonstrates that mirikizumab is non-inferior to ustekinumab based on a prespecified non-inferiority margin. Therefore, the EAG considers that the decision risk is lower when the primary comparator is ustekinumab and notes that this comparison results in marginal cost savings associated with mirikizumab. The EAG notes that confidential patient access scheme (PAS) discounts/ medicines procurement supply chain (MPSC) prices are available for all comparators. As such, the EAG has

produced a confidential appendix to the EAG report and it is these results that will form the basis for decision making.

7 Equalities and innovation

The company has not described any equalities or innovation considerations associated with mirikizumab in the company submission. Additionally, the External Assessment Group (EAG) is unaware of any equality or innovation considerations.

8 EAG commentary of the robustness of the evidence submitted by the company

The External Assessment Group (EAG) consider none of the issues below would preclude a cost-comparison approach from being appropriate but highlights them as limitations or factors to be aware of.

Clinical

The EAG does not consider that the company has provided robust evidence of clinical similarity between mirikizumab and risankizumab based on the results of the indirect treatment comparisons (ITCs) from the NMAs, Bucher ITCs and unanchored matched-adjusted indirect comparisons (MAICs). This conclusion is based on concerns about uncertainties in the evidence base which include a range of factors, such as differences in trial design between the included studies, the inclusion of additional treatments which add heterogeneity to the analysis, and limited outcomes on which to compare the treatments during the maintenance period.

The EAG notes that the unanchored MAICs for the maintenance period favoured mirikizumab for some outcomes. However, this analysis was associated with further uncertainties, including:

- The inclusion of only those who responded to treatment in the induction period in the analysis;
- Different time periods over which each study assessed the effects of treatment in the maintenance period;
- Use of a combined group, rather than separate biologic failed and conventional care failed subgroups, with a greater proportion of people included from the biologic failed group; and
- Inherent difficulties associated with adjusting for all prognostic factors and treatment effect modifiers, which are particularly challenging for unanchored MAICs (but also affect anchored MAICs to some extent).

Given these uncertainties, the EAG does not think that the evidence is sufficient to meet the company's assumption of the case for clinical similarity based on the 95% credible intervals or confidence intervals cross the line of no effect. Instead, it is likely to reflect the heterogeneity arising from the uncertainties outlined above. However, the EAG believes that the direct comparisons in the CS between mirikizumab and ustekinumab provided from the VIVID-1 trial,[5] alongside the company's

analysis of non-inferiority margins, provides evidence of clinical similarity between mirikizumab and ustekinumab both for efficacy and safety outcomes. Given that ustekinumab is in the same position in the treatment pathway as risankizumab, the EAG considers it an appropriate comparator for the cost comparison of mirikizumab, with robust evidence of clinical similarity provided by the VIVID-1 trial. The EAG also notes that ustekinumab was considered an appropriate comparator for risankizumab in its cost comparison analysis (TA888).

Economic

The EAG considers that the company's approach is mostly aligned with the cost-comparison analyses in other NICE guidance for Crohn's disease including TA888 (risankizumab) and TA905 (upadacitinib). However, for the reasons outlined above, the EAG considers that ustekinumab is the most appropriate comparator for the cost analysis and is associated with the lowest decision risk.

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10 Appendices

10.1 Additional baseline characteristics

The baseline characteristics in Table 30 and Table 31 were provided by the company at the clarification stage. Baseline characteristics for the full PAS population are in Tables 9 and 10 of the CS.

Table 39. Subgroup baseline characteristics. Reproduced from the company response to clarification questions.

Characteristics	BF			CCF		
	Placebo (n=[redacted])	Mirikizumab (n=[redacted])	Ustekinumab (n=[redacted])	Placebo (n=[redacted])	Mirikizumab (n=[redacted])	Ustekinumab (n=[redacted])
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region, n (%)						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Central/South America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe/Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF biologic failed; CCF conventional care failed

Table 40. Subgroup baseline patient disease characteristics and prior therapies. Reproduced from the company response to clarification questions.

Characteristics	BF			CCF		
	Placebo (n=[redacted])	Mirikizumab (n=[redacted])	Ustekinumab (n=[redacted])	Placebo (n=[redacted])	Mirikizumab (n=[redacted])	Ustekinumab (n=[redacted])
Duration of CD (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease location, n (%)						
Ileal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colonic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ileal-colonic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior surgical bowel resection						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDAI measures						
CDAI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDAI ≥300, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SES-CD measures						
SES-CD, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SES-CD ≥12, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-reported outcomes (PRO)						
AP, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AP average ≥2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF average ≥7, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease biomarkers						
CRP (mg/L), median (range: Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Faecal calprotectin (µg/g), median (range: Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF biologic failed; CCF conventional care failed

Table 41. Subgroup baseline smoking status. Reproduced from the company response to clarification questions.

Characteristics	BF			CCF		
	Placebo (n=[redacted])	Mirikizumab (n=[redacted])	Ustekinumab (n=[redacted])	Placebo (n=[redacted])	Mirikizumab (n=[redacted])	Ustekinumab (n=[redacted])
Never, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF biologic failed; CCF conventional care failed

10.2 Severe treatment emergent adverse events

Table 42. Severe treatment emergent adverse events by System Organ Class in the VIVID-1 trial. Reproduced from the company response to clarification questions.

System Organ Class	Treatment, n (%)		
	Placebo (n=[redacted])	Mirikizumab (n=[redacted])	Ustekinumab (n=[redacted])
Patients with ≥1 severe TEAE	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]	[redacted]

Cardiac disorders	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]
Congenital, familial and genetic disorders	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment emergent adverse event

10.3 Price sources for treatments included in the confidential appendix

Table 43. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Risankizumab	Simple PAS
Vedolizumab	Simple PAS
Ustekinumab	MPSC price

Abbreviations: PAS, Patient access scheme, CAA, MPSC, medicines procurement supply chain.

Single Technology Appraisal

Mirikizumab for treating moderately to severely active Crohn's disease [ID6244]

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 **5pm on Wednesday 4 September 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Corrections and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1, Page 13 states: "The analysis of only the combined population, rather than separate subgroups (conventional care failed and biologic failed) for the maintenance period;"	Lilly suggest the following wording amendment: "**In the unanchored MAIC, t**he analysis of only the combined population, rather than separate subgroups (conventional care failed and biologic failed) for the maintenance period;"	The present wording is misleading as the original submitted NMA provided comparative efficacy analyses in the maintenance period for the biologic-failed (BF) and conventional care-failed (CCF) subgroups separately.	Thank you for highlighting this issue. The EAG report has been updated accordingly.
Section 1, Page 14 states: "Given that ustekinumab is in the same position in the treatment pathway as risankizumab and was included as a comparator in the decision problem, the results of the VIVID-1 trial appear more appropriate for a cost-comparison appraisal and appear to demonstrate clinical similarity between mirikizumab and ustekinumab."	Lilly suggest amending this sentence to reflect the NICE recommendations for risankizumab and ustekinumab. For example: "**Ustekinumab is recommended by NICE for use in patients who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies. As such, unlike risankizumab, it may be used as a first-line biologic in cases of TNF-alpha contraindication. However, in most cases in UK clinical practice, it is anticipated that**	The present wording is incorrect in suggesting that ustekinumab and risankizumab are at exactly the same position in the treatment pathway, given the NICE recommendations for them differ with respect to their use in the first-line biologic setting.	Thank you for your comment. The wording in the report has been updated to say that, in most cases in UK clinical practice, ustekinumab would be used in the same position in the treatment pathway.

	ustekinumab would be used in the same position in the treatment pathway as risankizumab: in patients in whom the disease has not responded well enough or lost response to a previous biological treatment, or a previous biological treatment was not tolerated, or tumour necrosis factor (TNF)-alpha inhibitors are not suitable. As such, and given that ustekinumab was included as a comparator in the decision problem, the results of the VIVID-1 trial appear more appropriate for a cost-comparison appraisal and appear to demonstrate clinical similarity between mirikizumab and ustekinumab."		
Section 1, Page 14 states: "Nonetheless, the company's base case results and all scenarios considered indicate that mirikizumab does not result in similar or lower costs irrespective of whether the comparator for the cost-analysis is risankizumab or	This wording should be amended for clarity, as follows: "**Regarding the economic results presented to date,** the EAG notes that at the time of writing this report, the company has indicated that a patient access scheme (PAS) discount is pending approval by the Patient Access Scheme Liaison Unit (PASLU). As such, the company will provide an	To avoid confusion, Lilly propose that this wording should make clear that the cost comparison results presented in the submission and throughout the EAG report are based on the anticipated list price of mirikizumab and all comparators.	As the company has provided updated results with PAS included, the wording and results have been updated in the EAG report.

ustekinumab. Therefore, while the EAG's view is that the cost-comparison criterion for clinical similarity has been met for the comparison with ustekinumab, the EAG considers the criterion of cost savings or no cost difference has not been met. However, the EAG does not consider that a cost-utility approach would be more appropriate. The EAG notes that at the time of writing this report, the company has indicated that a patient access scheme (PAS) discount is pending approval by the Patient Access Scheme Liaison Unit (PASLU). As such, the company will provide an updated cost-analysis in due course." **Section 6.1, Page 80 states:**	updated cost-analysis in due course **in which a discounted price for mirikizumab is considered. As such, all results presently available represent comparisons of mirikizumab and all comparators at their anticipated list prices.** **In these analyses,** the company's base case results and all scenarios considered indicate that mirikizumab does not result in similar or lower costs irrespective of whether the comparator for the cost-analysis is risankizumab or ustekinumab. Therefore, while the EAG's view is that the cost-comparison criterion for clinical similarity has been met for the comparison with ustekinumab, the EAG considers the criterion of cost savings or no cost difference has not been met **in the current analyses**." "Regardless of the comparator drug, mirikizumab does not yield cost savings **in these current list price analyses**."	Where relevant, it should be noted that the patient access scheme (PAS) discount for mirikizumab is currently undergoing discussion with PASLU, and any discounts for comparators cannot be considered in the presented Company analyses due to the confidential nature of the discounts. As such, throughout the EAG report, all wording related to the cost inputs or results from the cost-comparison analysis should highlight the context noted above.	

"Regardless of the comparator drug, mirikizumab does not yield cost savings." **Section 6.3, Page 82 states:** "Therefore, the EAG considers that the decision risk is lower when the primary comparator is ustekinumab, but reiterates that even with this comparison mirikizumab does not yield any cost savings."	"Therefore, the EAG considers that the decision risk is lower when the primary comparator is ustekinumab, but reiterates that even with this comparison mirikizumab does not yield any cost savings **in these current list price analyses**."		
Section 2, Page 15 states: "Mirikizumab is a recombinant humanised IgG4 monoclonal antibody that binds to the p19 subunit of the IL-23 cytokine, preventing its interaction with the IL-12 cytokine."	This wording should be amended for clarity, as follows: "Mirikizumab is a recombinant humanised IgG4 monoclonal antibody that binds to the p19 subunit of the IL-23 cytokine, **preventing the cytokine's interaction with it's receptor**."	The current wording could be interpreted to mean that mirikizumab binding to the p19 subunit of the IL-23 cytokine prevents interaction of IL-23 with the IL-12 cytokine, which is inaccurate. Mirkizumab does not interact with the IL-12 cytokine pathway.	Thank you for highlighting this issue. The EAG report has been updated accordingly.

Section 3.3.2, Page 24 states: "Ustekinumab has a similar mechanism of action to mirikizumab…"	The wording here should be amended as follows: "**As a human monoclonal antibody that binds to the p40 subunit of the IL-12 and IL-23 cytokines, u**stekinumab has a similar…"	Lilly propose that this additional wording helps to rationalise the choice of ustekinumab as a supportive comparator in this submission.	Thank you for highlighting this issue. The EAG report has been updated accordingly.
Section 3.4, Table 2, Page 26 states: "• Measures of disease activity (clinical remission and relapse, endoscopic response)"	The bullet should be amended to: "• Measures of disease activity (clinical remission and **response**, endoscopic response)"	Lilly apologise that clinical relapse was erroneously noted as an outcome measure in Table 1, Section B.1.1 of the original CS. Clinical relapse was not an outcome presented in the submission, but clinical response was assessed in VIVID-1.	Thank you for highlighting this issue. The EAG report has been updated accordingly.
Section 4.1, Page 29 states: "The EAG notes that VIVID-1 was not included in the list of the 95 studies included in the SLR provided in CS Appendix D, Table 32 although it provides the key data for mirikizumab in the company submission. VIVID-1 is a double-blind,	The wording here should be amended as follows: "The EAG notes that VIVID-1 was not included in the list of the 95 studies included in the SLR provided in CS Appendix D, Table 32 **as there were no published data regarding the VIVID-1 trial at the time of the SLR searches. VIVID-1** provides the key data for mirikizumab in the company submission **and** is a double-blind,	The present wording does not clarify that the reason VIVID-1 was not identified in the SLR searches is because data from it were not published at the time the SLR searches were performed. This may erroneously suggest that VIVID-1 was intentionally excluded from the SLR by Lilly. This should be clarified.	Thank you for highlighting this issue. The EAG report has been updated accordingly.

placebo-controlled Phase III trial (VIVID-1) for mirikizumab in moderately to severely active CD and it is reported in the CS that the results are presented from the full clinical study report (CSR).[5]"	placebo-controlled Phase III trial (VIVID-1) for mirikizumab in moderately to severely active CD**. VIVID-1 is reported in the CS and the results are presented from the full clinical study report (CSR).**[5]"		
Section 4.2.1, Table 5, Page 33 states: "Some concerns Higher rate of dropouts for the placebo arm than the mirikizumab or ustekinumab arms in both the induction and maintenance period:…"	Further clarification on why the higher drop-out rate in the placebo arm is a source of concern for the EAG is requested.	Lilly agree that a greater proportion of patients discontinued from the placebo arm of the VIVID-1 trial than the mirikizumab or ustekinumab treatment arms. As noted in the treatment disposition diagram in Figure 39 of the CS Appendices (Appendix D.2), a greater proportion of patients discontinued on placebo due to experiencing adverse events or a lack of efficacy, in comparison to those treated with mirikizumab or ustekinumab. Lilly believe this to be in line with clinical expectations and should not be a cause for	Thank you for highlighting this. As this is not a factual accuracy error, no changes have been made to the EAG report.

		concern with the EAG, given that patients who received placebo were administered with pharmacologically inert substitute therapies which were not expected to treat or halt progression of the underlying pathology. Therefore, Lilly request the EAG provide further clarification as to why they consider these differences in trial discontinuation to be a cause of “some concerns”.	
Section 4.3.8, Table 19, Page 44 states: “Mirikizumab vs risankizumab RD (95% CIs)”	The title for this row should be amended to: “Mirikizumab vs **ustekinumab** RD (95% CIs)”	Data on risk differences between mirikizumab and risankizumab were not available from the VIVID-1 trial as risankizumab was not a study intervention in VIVID-1. The data presented in Table 9 align with the risk differences presented for mirikizumab versus ustekinumab, and this should be made clear in the	Thank you for highlighting this issue. The EAG report has been updated accordingly.

		heading for this column of the table.	
Section 4.4, Page 46, states: "Twenty-three studies were included in NMAs for the induction period, and 10 were included for the maintenance period. The 10 interventions included in the induction period NMAs were: • Adalimumab 160 mg at week 1, 80 mg at week 2 or 80 mg at week 1, 40 mg at week 2; • Certolizumab 400 mg at weeks 0, 2 and 4; • Infliximab 5 mg / kg at weeks 0, 2 and 6; • Mirikizumab 900 mg every 4 weeks for 12 weeks; • Natalizumab 300 mg every 4 weeks;	This wording should be amended as follows: **In the base case, 19** studies were included in NMAs for the induction period, and 10 were included for the maintenance period. The **eight** interventions included in the **base case** induction period NMAs were: • Adalimumab 160 mg at week 1, 80 mg at week 2 or 80 mg at week 1, 40 mg at week 2; • ~~**Certolizumab 400 mg at weeks 0, 2 and 4;**~~ • Infliximab 5 mg / kg at weeks 0, 2 and 6; • Mirikizumab 900 mg every 4 weeks for 12 weeks; • ~~**Natalizumab 300 mg every 4 weeks;**~~ • Risankizumab 600 mg at weeks 0, 4 and 8;	The number of included studies and list of included interventions currently presented for the induction NMA are not representative of the presented base case induction NMA. In the wider NMA, 23 studies were included in the induction NMA, which relates to 10 interventions (see Table 33 and Table 34 in Section D.1.5 of the CS appendices document). However, as noted in Table 35 in Section D.1.5 of the CS appendices, studies in which the intervention was natalizumab (ENACT 1 and ENCORE) or certolizumab pegol (PRECISE 1 and Sandborn 2021) were excluded from the base case analysis. As outlined in Section D.1.5 of the CD appendices, these exclusions were due to natalizumab and	Thank you for highlighting this issue. The EAG report has been updated accordingly.

• Risankizumab 600 mg at weeks 0, 4 and 8; • Upadacitinib 45 mg once per day for 12 weeks. Optional additional 30 mg once per day for 12 weeks; • Ustekinumab 6 mg/kg, 260 mg, 390 mg or 520 mg based on weight; • Vedolizumab 300 mg at weeks 0, 2 and 6; • Placebo”	• Upadacitinib 45 mg once per day for 12 weeks. Optional additional 30 mg once per day for 12 weeks; • Ustekinumab 6 mg/kg, 260 mg, 390 mg or 520 mg based on weight; • Vedolizumab 300 mg at weeks 0, 2 and 6; • Placebo **Studies including certolizumab and natalizumab were excluded from the base case induction NMA given that these treatments are FDA-only approved.**”	certolizumab representing FDA-only approved regimens. As such, this section should be updated as suggested to reflect the base case induction NMA.	
Section 4.4.1, Table 21, Page 51 states: “Length of maintenance period”	The title for this row should be amended to: “Length of **trial** period”	The values presented in this column of Table 21 of the EAG Report, are reflective of the total trial duration (i.e. timepoint of analysis) rather than the length of the maintenance period, as presented in Table 36 of the CS appendices. The title for this column should therefore be amended accordingly. However, if the intention of the EAG was to highlight the	Thank you for highlighting this issue. The EAG report has been updated to reflect the length of the maintenance period.

		duration of the maintenance period in the respective trials, the values in this column should be aligned with those presented in the “Maintenance period length (weeks)” column in Table 36 of the CS Appendices.	
Section 4.4.1, Table 21, Page 51	Data for the ACCENT trial are missing.	A row for data from the ACCENT trial for infliximab is not presented in Table 21, and should be included for completeness and alignment with the CS.	Thank you for highlighting this issue. The EAG report has been updated accordingly.
Section 4.4.2, Page 55 states: “…preferred by the company…” **and Section Table 22, Page 56 states:** “Company preferred model”	These wordings should be amended to: “…**originally submitted by the company**…”	The current wording implies that Lilly maintain a preference for the submitted NMA as compared with the additional analyses requested by the EAG (Bucher ITCs and unadjusted MAIC). A preference of this kind has not been communicated by Lilly. As such, this wording should be amended for clarity.	Thank you for highlighting this issue. The EAG report has been updated accordingly.

Section 4.4.3, Page 58 states: "For each outcome, the company used the 95% credible intervals (CrIs) as a method of assessing clinical similarity between mirikizumab and risankizumab. It was proposed that treatment equivalence can be determined if the 95% CrIs cross the line of no effect (crossing 1 in the case of ORs). With this indicating no statistically significant difference between two treatments, it was interpreted it as an indication of similar treatment effects. However, the EAG considers this an inappropriate interpretation of the 95% CrIs – in essence, deriving a strong conclusion of equivalence that conventionally requires large randomised controlled	This wording in these sections should be amended to reflect the rationale provided by Lilly in response to EAG Clarification Question A12 accurately. For example: **Page 58:** "For each outcome, the company used the 95% credible intervals (CrIs) as a method of assessing **whether statistically significant differences in** clinical **efficacy were observed** between mirikizumab and risankizumab. It was proposed that **the 95% CrIs crossing the line of no effect (crossing 1 in the case of ORs) is indicative of an absence of statistically significant differences between the compared treatments, suggesting potential clinical similarity.** However, the EAG considers **that** deriving a strong conclusion of equivalence conventionally requires large randomised controlled trials." **Page 61:** "Differences between the treatments were non-significant and **thus indicate potential clinical similarity**."	Lilly would like to clarify that the 95% credible intervals were used to assess whether statistically significant differences in the efficacy between any compared treatments were observed. As indicated by Lilly in response to EAG Clarification Question A.12, these intervals including 1 is indicative of an absence of statistically significant differences between the compared treatments, suggesting potential clinical similarity. It is inappropriate to refer to this as a threshold or criterion to evidence clinical similarity that has been defined by Lilly.	Thank you for highlighting this issue. The EAG report has been edited to remove reference to a threshold for clinical similarity.

trials, from a highly uncertain finding." **Similar wording is also present throughout the report, such as Section 4.4.3.2, Page 61:** "Differences between the treatments were non-significant and meet the company's criteria for clinical similarity." **And, Section 4.4.3.2, Page 62:** "Based on the company's threshold for clinical similarity, the unanchored MAICs suggest clinical equivalence between mirikizumab and risankizumab for most outcomes, while mirikizumab appears to be more effective than risankizumab for clinical response."	**Page 62: "**Based on **a lack of statistically significant differences between mirikizumab and risankizumab,** the unanchored MAICs **could support** clinical equivalence between mirikizumab and risankizumab for most outcomes, while mirikizumab appears to be more effective than risankizumab for clinical response."		

Section 4.4.3.1, Page 59 states, "Based on the ORs reported in the CS and the responder information reported for the VIVID-1 trial, the EAG also calculated the percentage of people who are expected to respond to each treatment."	Further clarification on the approach to deriving responders in Section 4.4.3.1. should be included.	Currently, it is unclear as to how the EAG have derived the numbers presented in this section. For the benefit of the reader, Lilly suggest the EAG include further methodological details on the approach to estimating responders for mirikizumab and risankizumab based on the NMA data, as presented in Section 4.4.3.1.	Thank you for highlighting this issue. More information has been provided about the information used to calculate risankizumab responders.
Section 4.4.3.2, Page 61 states: "NMAs were only performed for clinical remission in the maintenance period (Table 24)."	The wording here should be amended as follows: "**In the maintenance period, the only NMA which could be performed was for clinical remission** (Table 24) **due to the limitations associated with the comparator trial design in the maintenance period, as discussed in Sections 4.4.1 and 4.4.2**."	The present wording may be misinterpreted to mean that clinical remission could be considered in the maintenance period only, whereas clinical remission represented a response in the induction NMA as well. In addition, wording should be provided to make clear that clinical remission representing the only outcome in the maintenance NMA was due to limitations in data availability, rather than due to company preference.	Thank you for highlighting this issue. The EAG report has been updated accordingly.

Section 5.3.1, Page 75 states: "The EAG does not agree with the company regarding the conclusion of clinical similarity with risankizumab."	The wording here should be amended as follows: "The EAG does not agree with the company regarding the conclusion of clinical similarity **of mirikizumab** with risankizumab"	The present wording should be amended to make clear that the comparison being discussed is between mirikizumab and risankizumab.	Thank you for highlighting this issue. The EAG report has been updated accordingly.

Issue 2 Data and typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.2, Page 37 states: "A higher percentage of patients achieved endoscopic remission for mirikizumab than placebo at 12 weeks, but differences were non-significant…"	The wording here should be amended as follows: "A higher percentage of patients achieved endoscopic remission for mirikizumab than placebo at 12 weeks. **These differences were [redacted] in the PAS and CCF populations only**."	The presented p-values for endoscopic remission at Week 12 were [redacted] i.e., <0.05 for the comparison in the PAS and CCF population. The wording should therefore be corrected in line with the presented data.	Thank you for highlighting this issue. The EAG report has been updated accordingly.

Section 4.3.4, Page 38 states: "There were no significant differences between mirikizumab and placebo at week 12 in any group (Table 11)."	The wording here should be amended as follows: "**At week 12, [redacted] were observed between mirikizumab and placebo in the PAS and BF groups** (Table 11)."	The presented p-values for bowel urgency at Week 12 were [redacted] i.e., <0.05 for the comparison in the PAS and BF population. The wording should therefore be corrected in line with the presented data.	Thank you for highlighting this issue. The EAG report has been updated accordingly.
Section 4.3.7, Table 17, Page 42 states that the proportion of patients in the placebo treatment arm in the induction phase who experienced treatment discontinuation due to AEs is [redacted]	The quoted value for treatment discontinuation due to AEs for placebo in the Induction phase should be corrected from [redacted] to [redacted].	Transcription error.	Thank you for highlighting this issue. The EAG report has been updated accordingly.
Section 4.3.7, Page 43 states:	Broken cross-references	Minor typographical errors.	Thank you for highlighting this issue.

<table>
<tr>
<td>“Based on this information, and comparisons of the TEAEs experienced by less than 1% of patients (Appendix 0),…”

References to “Section 0” are also presented on Pages 58, 59 and 64.</td>
<td></td>
<td></td>
<td>The EAG report has been updated accordingly.</td>
</tr>
<tr>
<td>Section 4.3.7, Table 19, Page 44 states:
<table>
<tr><th rowspan="2"></th><th colspan="3">Intervention</th></tr>
<tr><th>Placebo</th><th>Mirikizumab</th><th>Ustekinumab</th></tr>
<tr><td colspan="4">Rates of CD-related hospitalisation, n (%)</td></tr>
<tr><td>BF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>CCF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td>
<td>The presented rates of CD-related hospitalisation are incorrect, and should be amended as such:
<table>
<tr><th rowspan="2"></th><th colspan="3">Intervention</th></tr>
<tr><th>Placebo</th><th>Mirikizumab</th><th>Ustekinumab</th></tr>
<tr><td colspan="4">Rates of CD-related hospitalisation, n (%)</td></tr>
<tr><td>BF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>CCF</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td>
<td>Error in reproduction of clinical trial data. Data should be aligned with Clarification Questions response document Page 12 (Table 6, Question A.7).</td>
<td>Thank you for highlighting this issue. The EAG report has been updated accordingly.</td>
</tr>
<tr>
<td>Section 4.4.3.2, Page 62 states:

“Results of the unanchored MAICs for clinical remission and clinical response favoured mirikizumab, with a significant difference reported for clinical response (p=0.008).”</td>
<td>The wording here should be amended as follows:

“Results of the unanchored MAICs for clinical remission and clinical response favoured mirikizumab, with a significant difference reported for clinical remission (p=0.008) and clinical response (p<0.001).”</td>
<td>The wording should be amended to state statistical significance of the clinical remission endpoint, while also correcting the p-value presented for clinical response.</td>
<td>Thank you for highlighting this issue. The EAG report has been updated accordingly.</td>
</tr>
</table>

Section 4.4.3.2, Page 62 states: "…while mirikizumab appears to be more effective than risankizumab for clinical response."	The wording here should be amended as follows: "…while mirikizumab appears to be more effective than risankizumab for **clinical remission and** clinical response."	The wording should be amended to state statistical significance of the clinical remission endpoint.	Thank you for highlighting this issue. The EAG report has been updated accordingly.
Section 4.4.3.3, Table 26, Page 64 erroneously presents ORs for discontinuations due to AEs in the maintenance period from Bucher ITCs.	A new column should be added to this table with the heading **"Unanchored MAIC results OR (95% CI)"**, and the presented values for Discontinuations due to AEs should be moved to a cell in this new column.	Comparative safety analyses (i.e., discontinuations due to AEs) in the maintenance period were not performed using Bucher ITCs, but rather through unanchored MAICs, as reported in Section 4.4.3.3 of the EAG Report. Therefore, the ORs presented under the Bucher ITC heading in Table 26 are in actuality from the unanchored MAIC,	Thank you for highlighting this issue. The EAG report has been updated accordingly.

		and this should be made clear in the report.	
Section 4.4.3.3, Table 26, Page 64 states: "1.67 (0.81 to 3.44)"	The values should be amended here as follows: "**1.68** (**0.82** to 3.44)"	Error in rounding of data.	Thank you for highlighting this issue. The EAG report has been updated accordingly.

Section 4.4.3.3, Table 27, Page 65 states:

Outcome	VIVID-1 (Mirikizumab) n (%)	FORTIFY (Risankizumab) n (%)
Anaemia	[redacted]	8 (4)
Arthralgia	[redacted]	17 (9)
Headache	[redacted]	11 (6)
Upper respiratory tract infection	[redacted]	17 (9)
Nasopharyngitis	[redacted]	4 (2)
Diarrhoea	[redacted]	9 (5)
Abdominal pain	[redacted]	21 (12)
Crohn's disease	[redacted]	NR
Pyrexia	[redacted]	4 (2)

The data, column heading and confidentiality highlighting should be amended as such:

Outcome	VIVID-1 (Mirikizumab) n (%)	FORTIFY (Risankizumab 360 mg) n (%)
Anaemia	42 (6.7)	8 (4)
Arthralgia	41 (6.5)	17 (9)
Headache	41 (6.5)	11 (6)
Upper respiratory tract infection	**38 (6.0)**	**NR**
Nasopharyngitis	**36 (5.7)**	**17 (9)**
Diarrhoea	**35 (5.6)**	**4 (2)**
Abdominal pain	[redacted]	**9 (5)**
Crohn's disease	[redacted]	NR
Pyrexia	[redacted]	**NR**

Error in reproduction of clinical trial data. Data should be aligned with Section B.3.10.1 of the CS (Table 36) for mirikizumab, and with Clarification Questions response document Page 39 (Table 30, Question A.19a) for risankizumab. The risankizumab dose should be specified in the column heading, to distinguish from the other treatment arm of the FORTIFY trial (risankizumab 180 mg).

Additionally, some safety data from the VIVID-1 trial are published in Ferrante *et. al* (2024), and therefore do not

Thank you for highlighting this issue. The EAG report has been updated accordingly.

		require confidentiality marking.	

Issue 3 Confidentiality marking errors

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3, Table 1, Page 18	The formulation for the maintenance dose of mirikizumab is unpublished, commercially sensitive information. These data are missing confidentiality highlighting.	"Maintenance: [redacted] after completion of induction dosing. Full maintenance dose from [redacted])"	Thank you for highlighting this error. The EAG report has been amended accordingly.
Section 3.2, Page 23	Wording on the mechanism of action of mirikizumab does not require confidentiality marking, as it is in the public domain.	"The CS reports that mirikizumab is a recombinant humanised IgG4 monoclonal antibody that binds to the IL-23 cytokine. Given that IL-23 is linked to chronic inflammatory processes in the intestine, the inhibition of IL-23 by mirikizumab acts to reduce the inflammatory processes underlying CD."	Thank you for highlighting this error. The EAG report has been amended accordingly.
Section 3.2, Page 23	The formulation for the induction dose of mirikizumab is publicly	"8-week induction period: 900 mg by intravenous (IV) infusion Q4W (Weeks 0, 4 and 8).	Thank you for highlighting this error. The EAG report

	available and does not require confidentiality marking.	Mirikizumab 300 mg (15 ml vial; 20 mg mirikizumab per mL) is available as a concentrate for solution for infusion."	has been amended accordingly.
Section 3.2, Page 23	The confidentiality marking for the subcutaneous dose has been incorrectly applied, and is missing underlining alongside the turquoise highlighting.	"[redacted]	Thank you for highlighting this error. The EAG report has been amended accordingly.
Section 4.3.1, Pages 35 – 36	The subgroup data, including statistical significance, for the clinical response and clinical remission endpoints are unpublished and should therefore be marked as confidential.	"A significantly higher percentage achieved clinical response with mirikizumab in the PAS group and [redacted]	Thank you for highlighting this error. The EAG report has been amended accordingly.
		"A higher percentage achieved clinical response with mirikizumab in [redacted]"	Thank you for highlighting this error. The EAG report has been amended accordingly.
		"A higher percentage achieved clinical remission with mirikizumab in [redacted]	Thank you for highlighting this error. The EAG report

		[redacted]"	has been amended accordingly.
Section 4.3.2, Page 37	Endoscopic remission data, including statistical significance, are unpublished and should therefore be marked as confidential.	"Differences were more apparent at week 52, where less than [redacted] of those in the placebo group achieved endoscopic remission, compared to [redacted] with mirikizumab, reflecting a [redacted] difference in the PAS group, the BF subgroup and the CCF subgroup, respectively."	Thank you for highlighting this error. The EAG report has been amended accordingly.
Section 4.3.3, Pages 37–38	EQ-5D-5L VAS data, including statistical significance, are unpublished and should therefore be marked as confidential.	"most apparent at week 52 with [redacted] improvements in HrQoL for mirikizumab than placebo for the PAS population and both subgroups".	Thank you for highlighting this error. The EAG report has been amended accordingly.
Section 4.3.7, Pages 41–42	These clinical data for the comparisons of mirikizumab versus ustekinumab are unpublished and therefore should be marked as confidential.	"Effect estimates marginally favoured mirikizumab, with the benefits of mirikizumab most apparent at week 52, with [redacted] in HRQoL for the PAS and BF populations."	Thank you for highlighting this error. The EAG report has been amended accordingly.