NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]

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 ulcerative colitis [ID3973]

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:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Addendum to the company submission**

3. **Clarification questions and company responses**

4. **Patient group, professional group, and NHS organisation submission** from:
   a. a. Crohn's & Colitis UK

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]

Document B

Company evidence submission

December 2022

File name	Version	Contains confidential information	Date
ID3973_Eli Lilly_Mirikizumab in Ulcerative Colitis_Document B_Fully Redacted	1.0	Yes	8th December 2022

Instructions for companies

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

This submission must not be longer than 100 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and [redacted] 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 [redacted] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [redacted] in the footer with appropriate text. (To change the footer, double click over the footer text. Double click back in the main body text when you have finished.)

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].[1] Mirikizumab is positioned for use as an alternative to ustekinumab (Stelara®) and vedolizumab (Entyvio®), which have received the following positive recommendations for reimbursement by NICE:

- Ustekinumab: as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if:
    - A tumour necrosis factor-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment), *or*
    - A tumour necrosis factor-alpha inhibitor cannot be tolerated or is not suitable
- Vedolizumab: as an option for treating moderately to severely active ulcerative colitis in adults

In alignment with the anticipated use of mirikizumab in UK clinical practice and with the patient populations in which ustekinumab is recommended by NICE, this submission focusses on a sub-population of the full anticipated marketing authorisation of mirikizumab. This population is defined as adult patients with moderately to severely active ulcerative colitis for whom:

- Conventional treatment cannot be tolerated or is not working well enough and other biologic treatment is not suitable ("biologic-naïve"), *or*
- Biological treatment cannot be tolerated or is not working well enough ("biologic-failed")

Throughout the submission, the term "biologic-failed" encompasses prior failure with anti-TNF antibodies, anti-integrin antibodies or tofacitinib. This is in line with the definition of "biologic-failed" patients within the pivotal LUCENT trials, as outlined in Section B.3.4.1.

Comparator

The manufacturer 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] An indirect treatment comparison was conducted to estimate the relative efficacy of mirikizumab against the full range of comparators specified in the final scope (see Section B.3.9.6) with the results of this analysis indicating that that mirikizumab has similar or better efficacy than ustekinumab and vedolizumab in the induction and maintenance phases.

Additionally, the criteria for the selection of an appropriate comparator 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.

As such, ustekinumab and vedolizumab are deemed to be the most appropriate comparators for this appraisal.

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 moderately to severely active ulcerative colitis who are intolerant of, or whose disease has had an inadequate response, or loss of response to previous biologic therapy (such as a TNF-alpha inhibitor or vedolizumab), or conventional therapy (oral corticosteroids and/or immunomodulators).	Adults with moderately to severely active ulcerative colitis for whom conventional treatment cannot be tolerated or is not working well enough and other biologic treatment is not suitable, or biological treatment cannot be tolerated or is not working well enough	The population addressed in this submission is a sub-population 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	N/A – in line with final NICE scope.
Comparator(s)	• TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • Tofacitinib • Ustekinumab • Vedolizumab • Filgotinib • Ozanimod • Upadacitinib (subject to ongoing NICE appraisal) • Conventional therapies, without biological treatments	• Ustekinumab • Vedolizumab	It is anticipated that mirikizumab will be positioned after conventional therapy, which is typically prescribed as a first-line treatment for moderately to severely active UC. Therefore, conventional therapy does not represent a relevant comparator. Mirikizumab is positioned as an alternative to ustekinumab and vedolizumab in UK clinical practice for the treatment of moderately to severely active UC in patients who are intolerant of, or have failed treatment with, prior biologic therapy. This patient population is in line with the patient populations in which ustekinumab and vedolizumab are recommended by NICE, and with the

			anticipated use of mirikizumab in UK clinical practice. Ustekinumab and vedolizumab are considered the relevant comparators within the scope of the appraisal for the following reasons: • Evidence from the indirect treatment comparison demonstrates that mirikizumab has a similar efficacy, and could possibly have greater efficacy, than ustekinumab and vedolizumab in the intended treatment population • Ustekinumab shares a similar mechanism of action to mirikizumab, and both ustekinumab and vedolizumab share a similar method of administration to mirikizumab. • In the recent NICE appraisal of ustekinumab (TA633),[3] vedolizumab was identified as the most relevant comparator to ustekinumab, meaning the relevance of ustekinumab as a comparator to mirikizumab consequently identifies vedolizumab as a relevant comparator • It is anticipated that mirikizumab would be considered by clinicians as an alternative treatment to ustekinumab and vedolizumab in the proposed treatment population
Outcomes	The outcome measures to be considered include: • mortality • measures of disease activity • rates of and duration of response, relapse and remission	The outcome measures used in this submission include: • Measures of disease activity (bowel urgency, symptomatic remission) • Rates of and duration of	As is typical for the disease area, data for mortality as an efficacy outcome were not collected during the LUCENT trials. However, it is not anticipated that mortality would be a key driver within the cost comparison analysis.

	• rates of hospitalisation (including readmission) • rates of surgical intervention • endoscopic healing • mucosal healing (combines endoscopic improvement and histological remission) • corticosteroid-free remission • adverse effects of treatment • health-related quality of life.	response and remission (clinical response, clinical remission, alternate clinical remission) • Rates of hospitalisation • Rates of surgical intervention • Mucosal healing (endoscopic remission, histologic remission) • Corticosteroid-free remission • Adverse events (AEs) • HRQoL (EQ-5D-5L, IBD-Q) • Abdominal pain numeric rating scale (NRS) and Fatigue NRS	
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial	• A cost comparison analysis has been conducted to estimate the incremental costs of mirikizumab versus ustekinumab and vedolizumab. • A 10-year time horizon was set to sufficiently reflect any differences in costs between the technologies being compared. • Costs were considered from an NHS and Personal and Social Services perspective (PSS). • A patient access scheme (PAS) for mirikizumab has been included as part of the analysis.	The manufacturer believes that mirikizumab can be appropriately assessed through the NICE cost-comparison process due to the similarities in terms of both effectiveness and costs with ustekinumab and vedolizumab. As such, a cost-comparison has been submitted. The cost-comparison compares the drug acquisition and administration costs for mirikizumab versus ustekinumab and vedolizumab. A 10-year time horizon was adopted to align with the NICE health technology evaluations manual (PMG36) and, in the absence of cost-comparison precedence in UC, with ERG and Committee preferences in previous appraisals that employed cost-comparison analyses: TA596, TA521 and TA723 in moderate to-severe plaque psoriasis and TA803 in psoriatic arthritis.[4-7]

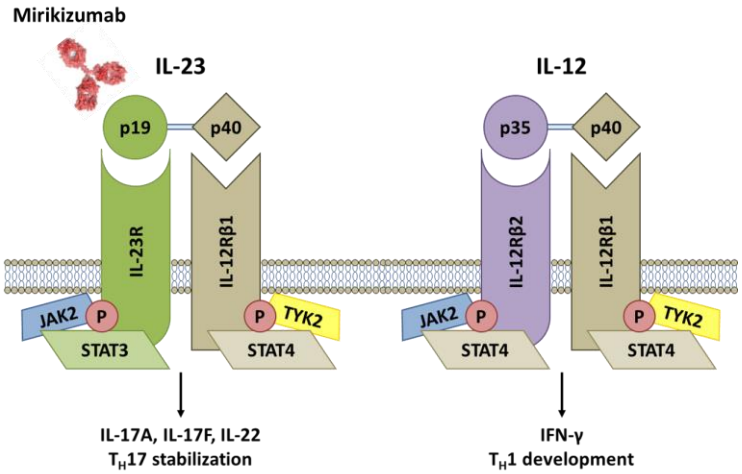
	arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.		
Subgroups to be considered	• People who have been previously treated with 1 or more biologics. • People who have not received a prior biologic.	• People who have previously failed on treatment with one or more biologics, including tofacitinib (“biologic-failed”) • People who have not received a prior biologic, including tofacitinib (“biologic- naive”)	N/A – in line with final NICE scope.

Abbreviations: AE: adverse event; ERG: evidence review group; EQ-5D-5L: European Quality of Life 5 Dimensions 5 Level; HRQoL: health-related quality of life; IBD-Q: Inflammatory Bowel Disease-Questionnaire; JAK: Janus kinase; N/A: not applicable; NICE: National Institute for Health and Care Excellence; NRS: numeric rating scale; PAS: patient access scheme; PSS: Personal and Social Services; TNF: tumour necrosis factor; UC: ulcerative colitis.

B.1.2 *Description of the technology being evaluated*

A description of the technology being appraised, mirikizumab, is presented in Table 2.

Table 2: Technology being appraised

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.[8] 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).[9] 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.[10] 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.[8, 11] As such, the inhibition of IL-23 by mirikizumab acts to reduce the inflammatory processes underlying ulcerative colitis. **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).[12]
Marketing authorisation/CE mark status	A marketing authorisation application for mirikizumab in ulcerative colitis was submitted to the European Medicines Agency (EMA) in [redacted]. CHMP positive opinion is currently anticipated in [redacted], with European marking authorisation expected in [redacted]. UK marketing authorisation is being sought [redacted]. An application to the MHRA is planned for immediately after receipt of CHMP positive opinion and marketing authorisation expected in [redacted].
Indications and any restriction(s) as described in the SmPC	The anticipated marketing authorisation for mirikizumab from the MHRA is "[redacted]"

	[redacted]".
	Mirikizumab is anticipated to have the following contraindications:[1]
	• 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 ulcerative colitis has two parts:[1] • **Induction:** 300 mg by intravenous infusion for at least 30 minutes at Weeks 0, 4 and 8. Mirikizumab 300 mg (15 m vial; 20 mg mirikizumab per mL) is available as a concentrate for solution for infusion. • **Maintenance:** 200 mg by subcutaneous injection every 4 weeks after completion of induction dosing. A full maintenance dose consists of two 100 mg pre-filled pens. After training in subcutaneous injection technique, a patient may self-inject with mirikizumab. Patients should be evaluated after the 12-week induction dosing. Those with an adequate therapeutic response should transition to maintenance dosing; those who do not achieve an adequate therapeutic response by this timepoint should continue to receive 300 mg mirikizumab by intravenous infusion at Weeks 12, 16 and 20 (extended induction therapy). If therapeutic benefit is achieved with the additional intravenous therapy, mirikizumab subcutaneous maintenance dosing (200 mg) every 4 weeks may be initiated, starting at Week 24.[1] Patients with loss of therapeutic response during maintenance treatment may receive 300 mg mirikizumab by intravenous infusion every 4 weeks, for a total of 3 doses. If clinical benefit is achieved from this additional intravenous therapy, patients may resume mirikizumab subcutaneous dosing every 4 weeks.[1]
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 ulcerative colitis.
List price and average cost of a course of treatment	List price per pack, induction dose (300 mg for IV infusion): [redacted] List price per pack, maintenance dose (200 mg for subcutaneous injection): [redacted]
Patient access scheme (if applicable)	The following patient access scheme has been submitted to PASLU: [redacted].

Abbreviations: EMA: European Medicine Agency; IgG4: immunoglobulin G4; IL: interleukin; IV: intravenous; MHRA: Medicines and Healthcare products Regulatory Agency; PASLU: Patient Access Schemes Liaison Unit; SC: subcutaneous; SmPC: summary of product characteristics.

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

B.1.3.1 Disease overview

Disease background

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterised by continuous mucosal inflammation of the colon, starting at the rectum and extending proximally.[13] The severity of inflammation varies and ulceration, oedema and haemorrhaging may be present along the length of the colon.[14] The clinical course of UC is unpredictable and consists of periods of exacerbation (flares) and remission; during flares, common symptoms include rectal bleeding, diarrhoea, abdominal pain, bowel urgency and tenesmus.[13, 15, 16]

In addition to the primary symptoms of UC, between one-third and half of patients experience a range of complications and manifestations outside of the gastrointestinal (GI) tract, known as extraintestinal manifestations (EIM).[13, 17] The risk of developing an EIM increases with duration of the disease and if a patient already has an EIM.[17] 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.[18] The most common EIM is anaemia, affecting approximately 21% of patients, followed by arthropathy (peripheral and axial) in 20% of patients.[19]

Epidemiology and diagnosis

The exact cause of the inflammation underlying UC is unclear, but factors related to genetics, the environment and the gastrointestinal microbiota have been identified as potential risk factors, with a family history of the disease representing the most common risk factor.[20] It has been estimated that 146,000 people in the UK are affected by UC, equivalent of approximately 1 in 420 people.[21] Additionally, worldwide prevalence of UC is increasing: a large study conducted across seven major countries, including the UK and US, predicted that the prevalence may rise by a further 9% in 10 years from 1.8 million in 2017 to 1.9 million in 2027.[22] This is supported by data from the Health Improvement Network (THIN) on the prevalence of IBD, which showed an increase in point prevalence from 390 per 100,000 in 200 to 570 per 100,000 in 2017, an approximate increase of 2.5% annually.[23]

UC affects both sexes relatively equally, as evidenced by the UK IBD registry which found that 48% of patients with UC in the UK were female, and by a large UK observational study in which the adjusted incidence rate ratio for females in UC was 0.87 (95% CI: 0.84, 0.90).[24, 25] Although it can present at any age, UC primarily presents during early adulthood, with a secondary peak for presentations observed after the age of 50 in some populations.[19, 24] Diagnosis of UC is typically made once other potential causes of symptoms, such as pathogens, vascular and medication-related causes, have been excluded.[19] Guidelines from the European Crohn's and Colitis Organisation (ECCO) state that no 'gold standard' for diagnosis exists and instead recommend that UC is diagnosed using clinical, laboratory and endoscopic parameters, including histopathology.[19]

Disease staging

Severity

Advancing disease severity is associated with a worsening of symptoms, with more severe disease typically leading to an increase in bloody diarrhoea and the presence of systemic symptoms such as weight loss, fever, nausea and vomiting.[13, 19] The severity of UC is typically categorised as mild, moderate or severe and is generally assessed using criteria such as stool frequency (with or without blood) and a combination of endoscopic and histological assessments and the presence of systemic symptoms.[13, 19] The ECCO and the British Society of Gastroenterology (BSG) outline several indexes by which disease severity in UC may be assessed and categorised.[19, 26, 27] A well-established scoring system is the Mayo score, which has been recommended by the BSG for use in clinical practice as a composite clinical and endoscopic tool, and which has been implemented in several clinical trials.[16, 26-28] The score consists of four variables, each scored from 0–3 and summed to a maximum of 12; a higher score corresponds to more severe disease as follows:[29]

- Remission: ≤2, with no individual subscore >1
- Mild: 3–5
- Moderate: 6–10
- Severe 11–12

Table 3: The Mayo score for ulcerative colitis

Domain	Domain score			
	0	1	2	3
Stool frequency	Normal	1–2 per day more than normal	3–4 per day more than normal	5 per day more than normal
Rectal bleeding	None	Streaks of blood <50% of the time	Obvious blood most of the time	Blood passed without stool
Mucosa (endoscopic subscore)	Normal or inactive disease	Mild disease (erythema, decreased vascular pattern, mild friability)	Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)	Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment	Normal	Mild disease	Moderate disease	Severe disease

Source: Lamb *et al*., (2019).[26]

Extent

In addition to severity, UC can be stratified depending on the extent to which the colon is involved. This is typically separated into three categories:[30]

- Proctitis: involvement limited to the rectum (extent of inflammation is distal to the rectosigmoid junction).
- Left-sided colitis (distal UC): involvement of the rectum, sigmoid colon and descending colon.
- Extensive (pancolitis): involvement of the left colon and some or all of the colon proximal to the splenic flexure.

A review of population-based studies estimated that, upon presentation, 30–60% of patients have proctitis, 16–45% have left-sided colitis and 14–35% have pancolitis.[31] A recent systematic review of studies in patients with UC found that 28–30% of patients with proctitis at diagnosis progressed to left-sided colitis and 14–16% to pancolitis; the rate of progression from left-sided colitis to pancolitis was 21–34%.[32] The severity and extent of disease affects treatment decisions, prognosis and patient outcomes, with more extensive disease at diagnosis more likely to result in surgical interventions such as removal of all or part of the colon (colectomy) or hospitalisation.[19, 26]

B.1.3.2 Burden of disease

Impact on health-related quality of life

The chronic, lifelong and progressive nature of UC results in a significant negative impact to patients' health-related quality of life (HRQoL).[33] This impact is multi-faceted and extends across patients' psychological wellbeing, education and employment, social life and daily activities.[34] In particular, the physical symptoms of the disease can result in substantial disability and significantly impacted daily life, including the ability to carry out ordinary tasks.[34, 35] Of note, patients have reported bowel urgency, stool frequency and rectal bleeding as the most bothersome symptoms of UC.[36] The additional symptoms of abdominal pain and fatigue also affect a significant number of patients, impacting their quality of life.[37, 38]

Approximately 40% of patients with UC will experience a relapse/flare each year, during which the physical symptoms are exacerbated, directly affecting HRQoL.[39, 40] In contrast to those experiencing symptoms and disease flares, patients in remission have improved HRQoL and reduced work impairment, highlighting the importance of adequate disease control. In addition to the physical burden of the disease, patients with UC experience increased incidence of anxiety and depression as compared with matched controls.[41]

Comorbidities

Aside from symptoms directly related to UC itself, the condition is associated with considerable comorbidities, with nearly half (45.6%) of patients with UC presenting with comorbidities at baseline in a recent global study.[42] The most commonly reported comorbidities were fatigue (27.7%), anxiety/depression (24.8%), sleep disorders (20.6%) and cardiac abnormalities/cardiovascular disease.[42] These findings are supported by the results of a real-world evidence (RWE) study of 208 UC patients in the UK between 2020–2021.[43] Through this disease specific programme (DSP) in UC, it was identified that [redacted] of patients suffered from comorbidities, [redacted] of which were autoimmune conditions.[43] The most common autoimmune comorbidity was psoriasis ([redacted]), but patients also reported axial spondylarthritis ([redacted]), psoriatic arthritis ([redacted]), rheumatoid arthritis ([redacted]) and coeliac disease ([redacted]).[43]

As compared with people without UC, patients with UC are also at higher risk of developing issues associated with malabsorption, as well as diabetes (5%), hypertension (11%), and irritable bowel syndrome (IBS) (10%).[43, 44] An increased risk of non-alcoholic liver disease and hepatic fibrosis, resulting from increased gut permeability, altered microbiome and chronic inflammation has also been shown to affect patients with UC.[45]

Economic burden

In addition to the considerable physical and psychological burdens for patients with UC, it is associated with an economic burden due to the increased healthcare resource utilisation required for disease management, including the potential for surgery and treatment of EIMs and flares.[46] European patients with all severities of active UC have been demonstrated to have a high cost burden, with higher costs found to be associated with more severe disease states.[47]

B.1.3.3 Clinical pathway of care

In the UK, moderately to severely active UC 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, as recommended by NICE guidance (NG130).[48] The BSG guidelines recommend that the primary treatment goal for UC should be symptomatic remission combined with mucosal healing, although treatment decisions are made based on a variety of factors, meaning that there is no single pathway of care adopted by all clinicians and patients.[26]

The current treatment pathway for patients with moderately to severely active UC in the UK is shown in Figure 2. Initially, patients receive conventional therapies, such as aminosalicylates, corticosteroids, and thiopurines. However, the effectiveness of these conventional therapies varies in between patients, with a systematic review of conventional therapies in IBD finding that some show no statistical benefit over placebo.[49] In addition, during the COVID-19 pandemic, weaning of corticosteroids for patients with IBD was recommended due to the observance that their use may increase risk of adverse outcomes of COVID-19, whereas biologics such as IL-12/23 inhibitors (ustekinumab) and TNF alpha inhibitors (TNFis), such as adalimumab and golimumab, were found to be safe to continue, and this may have accelerated patients through the conventional therapy stage.[50]

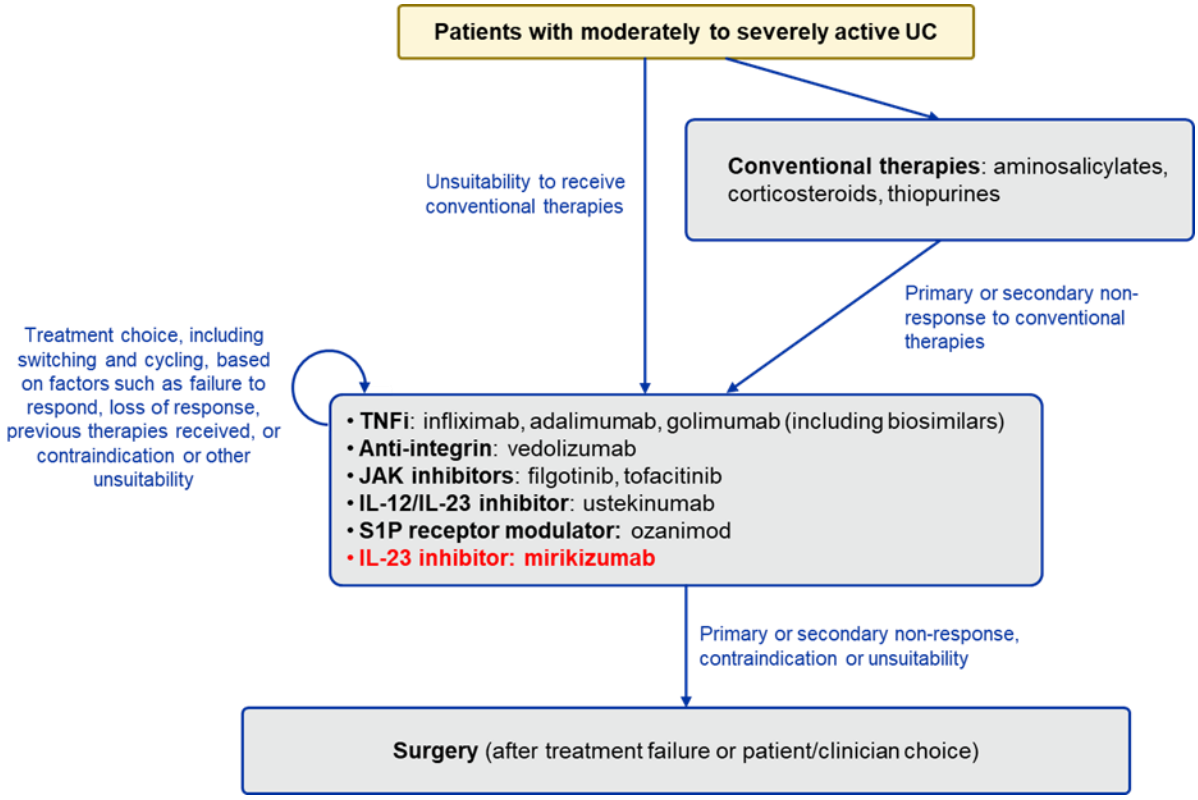
Patients who have had an inadequate response to, lose response to, or are contraindicated or otherwise unsuitable to receive conventional therapies will switch treatments, with the initiation of biologic treatments representing the next line of treatment.[51] TNFis such as infliximab, adalimumab and golimumab are considered as the first line biologic treatment for many patients, particularly since biosimilar treatment options are available for infliximab and adalimumab.[52] However, treatment options such as ustekinumab, vedolizumab, and Janus kinase (JAK) inhibitors (tofacitinib or filgotinib) may be used as a first line biologic in some circumstances, often where patients are unsuitable to receive TNFis, although the NICE recommendations for ustekinumab and ozanimod are the only treatment options for which such a restriction is specified.[3, 53-55]

Patients are treated until remission occurs, after which maintenance of the treatment with or without concomitant conventional therapies is used to maintain remission. Medication reviews are recommended to occur every 12 months to assess the suitability of the current treatment.[51] If patients lose response, treatment switching or cycling is common; therefore, a patient may be prescribed several treatments in order to induce or maintain remission.[56] Typically, patients will cycle to an alternative mechanism of action, with limited within-class switching due to typically poorer efficacy outcomes with this approach.[56]

If patients continue to experience inadequate disease control, or are unsuitable to receive these treatment options, the final stage of the treatment pathway involves surgery to remove the colon

(colectomy), although patients may 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.[48] Despite this, surgery can lead to a number of serious complications requiring further treatment, with recent clinical expert opinion received by NICE during TA828 emphasising the importance of the availability of a range of effective treatment options in order to delay or avoid surgery becoming necessary.[19, 55]

Figure 2: Current treatment pathway for moderately to severely active UC in UK clinical practice and the anticipated positioning of mirikizumab within it



Patients with a response or in remission remain on the same therapy with a 12-month review. In the biologic-naïve setting, ustekinumab is restricted for use only where a TNFi has failed (that is, the disease has responded inadequately or has lost response to treatment) or cannot be tolerated, and ozanimod is for use where conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable.
Abbreviations: IL: interleukin; JAK: Janus kinase; S1P: sphingosine-1-phosphate; TNFi: tumour necrosis factor alpha inhibitors; UC: ulcerative colitis.

Limitations of current treatments

The treatment landscape for UC currently provides several treatment options for clinicians and patients to consider. Despite this, a number of challenges are yet to be adequately addressed. Conventional therapies, typically used at first line, are associated with numerous disadvantages, including limited response, low rates of maintained remission and both short- and long-term side effects.[19, 57, 58] In addition, corticosteroid-free remission is typically sought, given that long-term corticosteroid use can be associated with development of corticosteroid-dependent disease, as well as side effects such as increased risk of infection, osteoporosis, diabetes, weight gain and cardiovascular disease amongst others.[26]

Biologic options considered following treatment failure with conventional therapies may be associated with poor initial response, loss of response over time and safety concerns. Of particular note, a substantial proportion of patients, approximately a third, show no initial

response to TNFi induction therapy (primary non-response), while it is estimated that up to 46% of patients who do respond lose response over time (secondary non-response).[59, 60] Other advanced treatments with mechanisms of action distinct from inhibition of TNF, such as vedolizumab, ustekinumab or JAK inhibitors (tofacitinib and filgotinib) may be used, and changing to other mechanisms of action has been identified as a potential solution to overcome non-response to TNFi therapy in IBD.[60] However, these treatments are also associated with several disadvantages, including the common prospect of secondary non-response and the continued experience of debilitating UC symptoms, despite ongoing biologic treatment.[61-64] Additionally, remission rates for these therapies are also suboptimal, and some currently available therapies are associated with safety concerns, such as the association of lymphoma with TNFi treatment.[65, 66]

Due to these limitations, the cycling of several treatment options is required in a significant number of patients; the primary reasons for switching include primary non-response, secondary non-response, and continued pain, and the result is suboptimal treatment for patients with UC.[67] Furthermore, it has been reported that patients who do not adequately respond to primary TNFi induction are less likely to achieve remission following subsequent treatment with a currently available biologic therapy such as another TNFi or ustekinumab.[62, 68]

Unmet need

The combination of factors described above means that there is currently an unmet need in UK clinical practice for a novel treatment for patients with UC that is effective, with a tolerable safety profile and an alternative mechanism of action. This is supported by a Delphi panel consisting of nine gastroenterologists from European countries and with a specialism in IBD, which identified an unmet need for a new treatment which improves disease control and obtains the common treatment goals of maintained long-term clinical and endoscopic remission.[69] These unmet needs clearly underscore the value that more treatment options to alleviate this situation would bring.

Additionally, a common symptom mentioned in the American and European treatment guidelines, but which has not been widely addressed with current treatment options, is bowel urgency.[19, 70] Bowel urgency is defined as the sudden and immediate need to have a bowel movement and is a distinct symptom from stool frequency. Affecting the majority of patients with UC, urgency is an impactful and disruptive symptom which can have a significant negative effect on patient quality of life, which is reflected by urgency being ranked as the most bothersome symptom in a survey of over 750 patients with UC.[36, 71] The mechanisms underlying bowel urgency are linked to rectal inflammation and a lack of mucosal healing and 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.[72, 73] 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, thereby signifying reduced disease activity.[74] However, despite being a common symptom, it 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.

Mirikizumab

Mirikizumab is positioned for use in adult patients with moderately to severely active ulcerative colitis for whom:

- Conventional treatment cannot be tolerated or is not working well enough and other biological treatment is not suitable (“biologic-naïve”), *or*
- Biologic treatment cannot be tolerated or is not working well enough (“biologic-failed”)

As outlined above, the term “biologic-failed” is used throughout this submission to encompass prior failure with anti-TNF antibodies, anti-integrin antibodies or tofacitinib. This is in line with the definition of “biologic-failed” patients within the pivotal LUCENT trials, as outlined in Section B.3.4.1.

This positioning is represented in Figure 2. Here, patients in the UK may be eligible to receive a range of biologic treatment options, such as ustekinumab, vedolizumab and ozanimod. Clinician choice is likely to depend on factors including failure to respond or loss of response, or contraindication or unsuitability. Furthermore, clinician choice often depends on prior treatment received, and for some treatment options, this restriction is explicit; for example, as per its NICE recommendation, ustekinumab may be considered a first-line biologic option only where a patient has responded inadequately or has lost response to TNFi therapy, or TNFi therapy cannot be tolerated.

The efficacy and safety of mirikizumab versus placebo have been evaluated in the LUCENT-1 and LUCENT-2 trials where it demonstrated rapid and sustained induction of clinical remission and a tolerable safety profile (the methodology and results of the LUCENT trials are presented in Section B.3.3). Given its novel mechanism of action, 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 in their armamentarium for the treatment of adult patients with moderately to severely active UC.

B.1.4 *Equality considerations*

No equality considerations have been identified.

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

B.2.1 *Clinical outcomes and measures*

The six NICE technology appraisals relating to biologic treatments for moderately to severely active UC included in the NICE final scope for this appraisal for which final NICE guidance has been published are listed below, alongside whether they followed the NICE Single Technology Appraisal (STA) route or the Multiple Technology Appraisal (MTA) route. The main comparators considered in this submission are bolded.

- Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (MTA; TA329)[51]
- **Vedolizumab for treating moderately to severely active ulcerative colitis (STA; TA342)[53]**
- Tofacitinib for moderately to severely active ulcerative colitis (STA; TA547)[75]
- **Ustekinumab for treating moderately to severely active ulcerative colitis (STA; TA633)[3]**
- Filgotinib for treating moderately to severely active ulcerative colitis (STA; TA792)[54]
- Ozanimod for treating moderately to severely active ulcerative colitis (STA; TA828)[55]

Note that upadacitinib is not considered here given that NICE are yet to published final guidance for its use in UC and therefore it is not considered to represent current clinical practice.[76]

For the six appraisals listed above, the economic models typically consisted of two phases, reflecting the design of the clinical trials informing them: a short-term induction phase and a longer-term maintenance phase. The induction phase has been modelled using two-week tunnel states in order to permit the varying lengths of induction for different treatment options to be modelled as per their respective SmPC.[3, 55]

For all six appraisals, the definitions of clinical remission and response were based on the Mayo scoring system to assess patients' disease activity after the induction period and during the maintenance phase. Surgery and post-surgery were included in all economic analyses although variations are present in their categorisation in the different appraisals. For example, in the appraisal of tofacitinib (TA547), surgery was modelled as a transient event rather than as a health state, whereas the Committee-accepted approach in TA329, TA342, TA633 and TA828 modelled surgery as a distinct health state.[3, 51, 53, 55] In addition, the TA329 appraisal modelled a single post-surgery state which captured all patients who did had not moved to the 'death' state, regardless of whether they experienced post-surgery complications or not, whereas each of the other five appraisals modelled separate post-surgery health states dependent upon whether patients experienced post-surgery complications or not.[3, 51, 53-55, 75]

The health state utility values (HSUVs) considered in these appraisals have typically been sourced from the literature, with values derived from Woehl *et al*, variously supplemented by values from Arsenau *et al* or Swinburn *et al*, being accepted for use in several appraisals.[3, 51, 53, 55, 75] Committees have accepted the use of HSUVs from the literature based on the source study being UK-specific or including a reasonably large number of patients, and EQ-5D utility values

being reported for most health states.[51] However, utility values derived from the key pivotal trial have also been considered.[3, 54]

Consistent with the ustekinumab appraisal (TA633), the filgotinib (TA792) and ozanimod (TA828) appraisals assumed 30% of patients received an escalated dose in the maintenance period at any one time, and the corresponding higher drug acquisition costs were applied to these patients.[3, 54, 55] A constant risk of discontinuation in the maintenance phase was assumed, but scenario analyses were presented in which a 25% reduction in the loss of response rate after the first year or two years was implemented.[3, 54, 55] The impact of these scenarios was minimal, and in each case, the Committee accepted the constant risk as per the Company's approach, with one citing a lack of data to inform the model otherwise.[54]

Due to the high costs incurred during the management of serious infections, the associated costs were included in the model in several appraisals (TA828, TA792, TA633 and TA547).[3, 54, 55, 75] They were calculated as a weighted average of six different infections included in the National Schedule of NHS costs: sepsis, tuberculosis, pneumonia, soft tissue infections, bone and joint infections and urinary tract infections. This assumption was deemed to be appropriate for modelling adverse events in UC submissions.

Clinical outcomes and measures in each of these appraisals are discussed in Table 4.

Table 4: Clinical outcomes and measures appraised in published NICE guidance for the comparators included in the NICE final scope

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
TA329 (infliximab, adalimumab and golimumab)[51]					
Clinical response and remission	Definitions of clinical remission and clinical response without remission were based on the Mayo scoring system as per the studies identified in the Assessment Group's clinical SLR.	Results from the Assessment Group's *de novo* NMAs were used to inform the clinical remission and response rates in the cost-effectiveness model	N/A	The Committee did not revise the model efficacy inputs.	The Committee noted that the extrapolation of clinical trial data, which extended to a maximum of 54 weeks, across the lifetime horizon of the model introduced uncertainty with respect to the long-term health benefits of TNFi estimated by the model. Despite this, the Committee concluded that further analyses were not warranted given the existing evidence and their judgement that revising the model was unlikely to estimate cost effectiveness with significantly more certainty than already available.
Stopping rule for biologic treatment	Timepoint after which patients responding to treatment are assumed to receive no further biological therapy.	In the maintenance phase of the Assessment Group model, patients were assumed to continue receiving the same biologic therapy until they were no longer in remission or had a response.	N/A	The Committee concluded that modelling stopping criteria such as those for TNFi in Crohn's disease could be implemented in UC to align the treatment pathways, but acknowledged that this would be difficult to model	The Committee noted that the assumption as applied in the Assessment Group model meant that no patients were modelled to receive a TNFi for more than three years, contrary to expert input from patients who had received TNFis for longer than this. Clinical expert opinion similarly stated that a third to half of patients are expected to receive long-term TNFi therapy. Therefore, the Committee recognised that

				given the lack of efficacy data for TNFi beyond the duration of the trials.	these patients were not captured in the model.
Dose escalation	The proportion of patients who receive dose escalation due to loss of response.	In the Assessment Group's model, 27% of patients receiving adalimumab were modelled to receive dose escalation, from 40 mg every other week to 40 mg every week.	N/A	The Committee did not discuss this.	N/A
Surgery	The approach to modelling surgery states	In the ingoing adalimumab model, surgery was modelled as a health state, with four post-surgery states ('post-surgery without complication', 'transient complication', 'chronic complication', and 'surgery-related death'). The ingoing golimumab and infliximab model had health states for colectomy, post-colectomy remission, and post-colectomy late complications. In contrast, the Assessment Group modelled surgery as an event rather than as a state. A post-surgery (with or without complications) state was modelled to which patients moved following surgery if they had not moved to the 'death' state.	N/A	The Committee did not discuss the approach taken by the Assessment Group to model surgeries.	N/A
HSUVs	EQ-5D data derived from key clinical trials	The ingoing Company models for golimumab and infliximab implemented utility values	The Assessment group performed a scenario analysis in	The Committee agreed that the identified sources	The Committee noted that the Woehl *et al* source may have overestimated the utility value

	or published literature sources.	derived from key clinical trials (PERSUIT-SC and ACT1, respectively). The assessment group noted that the same source of utility values should be used for all three interventions and identified published literature values from Woehl *et al* and Swinburn *et al* as the most useful sources of utility values for the model, given that they are UK-based, have a reasonably large number of patients, and report EQ-5D data for most states in the model. The data from Woehl *et al* were implemented in the Assessment Group base case.	which data from Swinburn *et al* were implemented. This was the only scenario analysis performed by the Assessment Group that changed the overall cost-effectiveness conclusion that adalimumab, golimumab and infliximab were dominated by colectomy.	represented the most relevant evidence on the QoL of patients with UC.	for patients who had surgery. In addition, the sensitivity of the Assessment Group's model to the utility values selected was noted.
Adverse events	Adverse events considered in the model	The Assessment Group model did not include costs or disutilities associated with adverse events.	N/A	The Committee did not revise this approach.	The Committee noted that the exclusion of costs and utility decrements related to the adverse events associated with long-term corticosteroid use may have contributed to the underestimation of the cost-effectiveness of TNFis.
TA342 (vedolizumab)[53]					
Clinical response and remission	Clinical remission and clinical response without remission were defined based on the Mayo scoring system as implemented in the GEMINI I trial.	Clinical efficacy in the ITT and biologic-experienced (TNFi failure) populations was informed by the GEMINI I study. Efficacy for the TNFi-naïve population were derived from the Company NMA in which comparison was possible only versus adalimumab due to the	N/A	The Committee did not revise the model efficacy inputs.	The ERG noted that the long-term efficacy of vedolizumab is associated with some uncertainty given that data were available from the GEMINI I trial for up to 52 weeks only. They further stated a preference for random-effects model to be used given the

		lack of available data for infliximab and golimumab in this patient population.			heterogeneity in the studies include in the NMA. The NMA for the whole population included data from studies in which the patient population was mixed with respect to prior TNFi use. The Committee highlighted that this could affect results and that the relative efficacy of vedolizumab versus comparators as derived from such mixed treatment comparisons were therefore associated with some uncertainty.
Stopping rule for biological treatment	Timepoint after which patients responding to treatment are assumed to receive no further biological therapy.	For patients who continued treatment in the maintenance phase, the ingoing Company approach assumed treatment with biological therapy was at most one year, after which patients switched to receive conventional therapy. The ERG noted that the SmPC for vedolizumab and the comparators does not stipulate this.	The ERG performed a scenario analysis in which patients could continue to receive biological therapies for more than a year if they were responding or in remission. This increased the ICER.	The Committee agreed with the Company that implementing a one-year stopping rule was appropriate and likely to reflect the use of vedolizumab in typical clinical practice.	N/A
Dose escalation	The proportion of patients who receive dose escalation due to loss of response.	In the submitted model, dose escalation was not considered.	N/A	Dose escalation was not discussed by the Committee.	N/A
Surgery	Surgery was modelled as a health state	The model included a surgery health state into which patients could enter at the end of the induction phase, response-dependent. Health states for	N/A	The Committee did not discuss the approach taken to modelling surgery.	N/A

		'post-surgical remission' and 'post-surgical complications' were also included.			
HSUVs	EQ-5D data derived from key clinical trials or published literature sources.	The Company-submitted approach implemented utility values derived from EQ-5D data collected in the GEMINI I for the non-surgery states, with HSUVs related to surgery derived from Punekar and Hawkins *et al*. The ERG investigated the effect of implementing values derived from Woehl *et al* and Swinburn *et al* and highlighted that these sources permitted the utility values for the surgery and post-surgery states to be derived from the same source.	Scenario analyses by the ERG showed the model to be sensitive to the utility value inputs, with conclusions of cost effectiveness changing depending on the source.	The Committee concluded Woehl *et al* and Swinburn *et al* to be equally valid sources of HSUVs and considered both in its decision-making.	The sensitivity of the ICER to the utility values implemented was noted by the Committee. It was further noted that the Woehl *et al* and Swinburn *et al* values had been derived from abstracts, with no full texts available, and from relatively small patient numbers.
Adverse events	Adverse events considered in the model	The submitted model included costs and disutilities associated with serious infection, tuberculosis, lymphoma, hypersensitivity and injection site reactions.	N/A	The Committee did not discuss the approach to modelling adverse events.	The ERG highlighted that the estimates of adverse event rates with conventional therapy were derived from an analysis of pooled placebo arm data from several trials in which patients received placebo via transfusion or injection, and thus it was not clear whether skin reactions with conventional therapy may be resulting from placebo delivery rather than conventional therapy itself.
TA547 (tofacitinib)[75]					
Clinical response and remission	Clinical remission and clinical response without remission were defined based on the Mayo scoring	Results from the Company induction and maintenance NMAs were used to inform the proportion of patients achieving clinical response and remission	N/A	The Committee considered both the fixed- and random-effects models in its decision-making.	Where the Company used a fixed effects model, the ERG preferred the use of random-effects models given

	system as implemented in the OCTAVE trials.	in the induction and maintenance phases of the model, respectively.			heterogeneity between studies included in the network.
Loss of response in the maintenance phase	The proportion of patients who are in the 'clinical remission' or 'clinical response without remission' health states who lose response to treatment during the maintenance phase.	In their ingoing analysis, the Company assumed patients in the maintenance phase were at a constant risk of discontinuation due to loss of response.	The ERG performed a scenario in which additional costs for outpatient visits to enable treatment cessation within eight weeks of a relapse. The impact on the ICERs was marginal.	The Committee did not discuss this.	The ERG raised concerns that while discontinuation upon relapse reflects clinical practice, its implementation in the model implicitly assumed that all patients receiving maintenance treatment had fast and/or routine access to clinical assessment.
Extended induction period	Effect of patients with a delayed response modelled to undergo an extended induction period.	The Company did not model the effect of tofacitinib induction being extended from 8 weeks to 16 weeks, citing a lack of data to inform the comparator arms.	N/A	The Committee concluded that the cost-effectiveness of tofacitinib is unlikely to change if a 16-week induction period is considered.	The Committee noted that patients may receive TNFis beyond the usual time for response assessment.
Surgery	Surgery was modelled as a transient event	The model included health states for post-surgery (without complications) and post-surgery (with complications), whereas surgery was modelled as a transient event, either elective or emergency, rather than as a health state.	N/A	The Committee did not discuss this.	N/A
HSUVs	EQ-5D data derived from published literature sources.	The Company submitted approach implemented utility values derived from the literature (Woehl *et al*), in alignment with prior appraisals.	The ERG explored scenario analyses in which utility values from the OCTAVE trial and Swinburn *et al* were implemented. Both increased the ICER.	The Committee concluded the utility values from Woehl *et al* were appropriate and consistent with previous NICE TAs for UC.	The Committee noted that utility values derived from the key clinical trial are typically preferred to those sourced from the literature. However, patient expert feedback was received that the Woehl *et al* values aligned with their experience of

					the disease and issues with data interpretation from the OCTAVE trial were noted.
Adverse events	Only serious infections were included in the model.	Based on the availability of evidence for the incidence, costs and QALY impact of serious infections for all drugs, the economic analysis considered the occurrence of serious infections.	Scenario analyses were performed in which the risk of serious infection was varied from 0% to a 50% increased risk, and the utility reduction was varied from 0% to 3%. None of the scenario analyses presented altered the cost-effectiveness conclusions in the biologic-naïve or biologic-exposed subgroups.	The Committee concluded that the Company's and the ERG's analyses should both be taken into account in decision-making.	In the company submission, the increased incidence of serious infections associated with tofacitinib was explored over a range of 0–50% rather than being sourced from the NMA results for this outcome. This was due to the wider credible intervals that occurred in the NMA due to the rare occurrence of this event. The ERG used a frequentist framework to perform an alternative analysis to adjust for this lack of events.
TA633 (ustekinumab)[3]					
Clinical remission and clinical response without remission	Clinical remission and clinical response without remission were defined based on the Mayo scoring system as implemented in the UNIFI trial.	Clinical trial data relating to the proportions of patients with clinical remission or clinical response without remission were included in the economic model. It was assumed that patients with disease that did not respond or lost response to initial therapy remained in the active UC health state (i.e., assumed a 0% response rate).	N/A	The Committee considered the approach implemented by the Company to be appropriate.	The ERG noted that the relapsing and remitting nature of UC means there is a chance some patients could improve without treatment. The Committee agreed with this, but emphasised a lack of data to inform the model otherwise.
Loss of response in maintenance phase	The proportion of patients who are in the 'clinical remission' or 'clinical response without	A loss of response analysis was implemented which took clinical remission and response data directly from the individual trial arms. In the ingoing base case	The Company presented a scenario analysis implementing a one-time 25% reduction in loss of	Despite acknowledging uncertainty, the Committee preference was to	The ERG argued that the use of direct trial data was associated with bias, such as bias related to differences in baseline factors in the trials. As

	remission' health states who lose response to treatment during the maintenance phase.	economic analysis, the calculated probability of loss of response was extrapolated beyond the trial periods and a constant loss or response rate over time was assumed.	response after the first two years of treatment initiation. The impact on the ICERs was minimal.	use the ERG's maintenance-only NMA and to assume a constant risk of loss of response throughout the maintenance treatment.	such, the ERG preferred the Company's maintenance NMA as the source of maintenance phase response data to the unadjusted indirect comparison methods. The Company provided an updated base case using a one-year NMA conditional on response which aligned with the preferences of the ERG. The committee agreed that that the results of the Company's maintenance NMA were highly uncertain.
Dose escalation	The proportion of patients who receive dose escalation due to loss of response.	In the ingoing approach, the Company assumed 30% of patients receiving all included biologics except for infliximab, with the latter justified by the SmPC for infliximab not permitting dose escalation. Based on clinical feedback that infliximab dose escalation does occur in clinical practice, the ERG preferred to implement the same assumption of 30% of patients receiving the escalated dose to infliximab. This change was accepted by the Company.	N/A	The Company's revised assumption was accepted by the Committee.	The Committee recognised there was some uncertainty about this issue but noted it not to be a major driver of cost effectiveness.
Surgery	First and second surgeries were modelled as distinct health states	The model included two health states for surgery (first surgery and second surgery) and three health states for post-surgery (post-first surgery remission, post-first surgery complications, and post-second surgery remission). These health states were selected in order to reflect	N/A	The Committee concluded the model could be used for decision-making, and the appropriateness of the surgery and post-surgery health	N/A

		the natural history of UC and to align with the definitions used in the UNIFI trial as closely as possible.		states was not discussed.	
HSUVs	EQ-5D data derived from key clinical trials or published literature sources.	The Company and the ERG both used utility values sourced from Woehl *et al*.	The Company explored scenario analyses in which utility values derived from the UNIFI trial were implemented for all non-surgery health states, and in which utility values related to surgery health states from Swinburn *et al* were implemented. Both increased the ICERs; the UNIFI scenario considerably, the Swinburn *et al* scenario modestly.	The Committee concluded that utility values derived from Woehl *et al* and the UNIFI trial were equally appropriate, and thus considered both in its decision-making.	The Committee acknowledged the use of values derived from Woehl *et al* in previous appraisals, but highlighted its limited sample size as compared with the UNIFI trial, and that assessment of its appropriateness was challenging due to it being an abstract rather than a full publication. However, limitations of the UNIFI trial utility data, such as potential placebo effects and the limited time period over which they were collected, were also acknowledged.
Adverse events	Only serious infection adverse events were modelled.	Serious infection rates were informed by a real-world study in psoriasis patients. Rates were applied in the induction and maintenance phases of the model as one-time events, and patients were assumed to be at constant risk of experiencing the adverse event.	The ICERs were not sensitive to scenarios explored by the company or ERG, including a scenario in which all treatments were assumed to have the same rate of serious infection as ustekinumab.	This was not discussed by the Committee.	The ERG noted uncertainty regarding the use of the literature data in psoriasis patients; however, it was agreed that this was the most appropriate source of data available.

Delayed response	Delayed response was assessed using clinical remission or clinical response without remission.	Patients who did not respond after the initial induction period for vedolizumab, golimumab, ustekinumab, infliximab or tofacitinib remained on treatment for an additional cycle, based on the respective SmPCs, to allow for a delayed response. In the base case, delayed response data were assumed to be the same as early responders as reported in clinical trials.	Scenario analyses in which delayed responder efficacy was derived from individual trials and in which delayed responders were excluded from the analysis both resulted in lower ICERs.	This was not discussed by the Committee.	The ERG noted that maintenance efficacy may differ between initial and delayed responders; however, a paucity of evidence is available to inform this was acknowledged.
TA792 (filgotinib)[54]					
Clinical remission and clinical response without remission	Definitions of clinical remission and clinical response without remission were based on the Mayo scoring system as per the SELECTION trial.	The proportions of patients with clinical remission or with clinical response without remission in the economic model were derived from the Company's induction and maintenance NMAs for filgotinib and all comparators.	N/A	This was not discussed by the Committee.	N/A
Loss of response in maintenance phase	The proportion of patients who are in the clinical remission or clinical response without remission health states who lose response to treatment during the maintenance phase.	In the Company base case, a constant risk of loss of response was applied.	The Company presented a scenario analysis implementing a 25% reduction in the loss of response rate after the first year of maintenance, which had a minimal effect on the ICER.	The Committee considered the Company's scenario analysis in its decision-making.	Clinical experts confirmed the Company scenario to be appropriate. However, the ERG still raised concerns that the model was not accurately capturing the effectiveness of filgotinib versus comparators over time. The Company noted that this is due to a lack of long-term data to inform the model, and that this issue had been raised by the ERGs in TA633

					and TA547, where a constant rate of loss of response was thus accepted. The Committee agreed that the lack of long-term data meant it was unclear if loss of response would be constant over time.
Dose escalation	The proportion of patients who receive dose escalation due to loss of response.	Dose escalation was modelled for some comparators but not for filgotinib. It was assumed that 30% of patients would require dose escalation.	The Company presented scenario analyses in which the proportion of patients assumed to receive dose escalation was varied to 10% or 50%.	The Committee agreed with the ERG that if the cost of dose escalation is included, its clinical benefit should also be included.	The ERG noted uncertainty in the proportion of patients who would undergo dose escalation in clinical practice. In addition, the ERG highlighted that the Company modelled the additional costs associated with dose escalation with no additional benefit accounted for, which they did not deem appropriate.
Surgery	Elective and emergency surgeries were modelled as distinct, transient health states	Surgery was incorporated as two transient states: emergency surgery, and elective surgery. Patients who undergo either surgery move on to the post-surgery states (post-surgery with or without long-term complications).	N/A	The Committee and ERG agreed that the company's model was appropriate for decision-making.	N/A
HSUVs	EQ-5D data derived from the key clinical trial.	The Company and the ERG both used utility values sourced from the SELECTION trial. The Company implemented utility values collected at baseline for active UC; the ERG preferred for the active UC HSUV to be derived from data collected at Week 10, in alignment with the timepoint used to derive the	N/A	In the absence of other scenarios, the Committee concluded that the ERG approach to deriving utility values was most appropriate.	The ERG noted that the utility values provided were not specific to biologic-naïve and biologic-experienced patients, nor to the induction or maintenance phases. The Company did not provide these. The Committee noted that the utility values for active UC were

		response without remission and remission health states.			considerably lower than those used in previous NICE appraisals (TA547 and TA633) and recognised uncertainty in the estimations provided.
Adverse events	Only serious infection adverse events were modelled.	The company's safety NMA was used as the source of rates of serious infections in the base case and the results were converted to 10-weekly probabilities. All other adverse events were excluded from consideration.	N/A	The Committee agreed that the approach to include serious infections only for all comparators was appropriate but noted that cardiovascular adverse events should have been included in the model for filgotinib.	The Committee noted uncertainty as to whether patients with UC who received filgotinib may experience cardiovascular adverse events. Clinical experts highlighted that patients with UC are younger than those with rheumatoid arthritis, and therefore have a different risk profile.

TA828 (ozanimod)[55]					
Clinical remission and clinical response without remission	Definitions of clinical remission and clinical response without remission were based on the Mayo scoring system as per the TRUENORTH trial.	The proportions of patients with clinical remission or with clinical response without remission in the economic model were derived from the Company's induction and maintenance NMAs for ozanimod and all comparators.	The scenario analysis performed by the ERG in which revised modelled efficacy estimates for BSC in the post-active treatment phase were implemented had a negligible impact on the ICERs.	The Committee concluded that efficacy estimates for best supportive care in the post-active treatment phase should be informed by subgroup-specific data, although noted that the difference in the ICERs between the scenarios implementing the two approaches was modest.	The Company modelled efficacy estimates for best supportive care in the post-active treatment phase and made use of data from the TNFi-experienced subgroup to inform the transition probabilities for the TNFi-naïve subgroup. However, the ERG raised concerns with the use of data from the TNFi-experienced cohort to inform efficacy in the TNFi-naïve population, and instead considered that that loss of response and loss of response (no remission) should be based on both the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-experienced estimates.
Loss of response in maintenance phase	The proportion of patients who are in the clinical remission or clinical response without remission health states who lose response to treatment during the maintenance phase.	Loss of response rates were derived from the company's maintenance NMA with a constant loss of response assumed within and beyond the trial duration of one year.	In line with TA547, a scenario analyses was explored in which a 25% treatment waning effect after two years was implemented.	This was not discussed by the Committee.	N/A
Dose escalation	The proportion of patients who receive dose escalation due to loss of response.	Dose escalation was modelled in the maintenance period for ozanimod and several comparators, as per the relevant SmPCs. In alignment with the Committee-preferred approach	The Company performed scenario analyses in which dose escalation was assumed for 0% or 50% of patients.	This was not discussed by the Committee.	N/A

		in TA633 and clinical opinion, dose escalation was modelled for infliximab despite this being off-label. Dose escalation was modelled as per the approach taken in TA633: 30% of patients were assumed to receive an escalated dose in the maintenance period at any one time, and the corresponding higher drug acquisition costs were applied to these patients.	Respectively, these scenarios generally reduced and increased the NHB of ozanimod compared to relevant comparators.		
Surgery	First and second surgeries were modelled as distinct health states	The model included two health states for surgery (first surgery and second surgery) and three health states for post-surgery (post-first surgery remission, post-first surgery complications, and post-second surgery remission).	N/A	The ERG and Committee agreed that the company's model captured all relevant health states and was appropriate for decision-making.	N/A
HSUVs	EQ-5D data derived from key clinical trials or published literature sources.	The Company and the ERG both used utility values sourced from Woehl *et al*.	The Company explored scenario analyses in which utility values were derived from the TRUENORTH trial, or aligned with those used in TA342 or TA547. These analyses generally resulted in higher ICERs.	This was not discussed by the Committee.	N/A
Adverse events	Only serious infection adverse	Incidences of serious infections were obtained from the relevant trials and converted to two-week	N/A	This was not discussed by the Committee.	N/A

	events were modelled.	probabilities. Patients were assumed to be at constant risk of experiencing adverse events throughout the model time horizon.			

Abbreviations: ERG: Evidence Review Group; EQ-5D: European Quality of Life 5 Dimensions; HSUV: health state utility value; ICER: incremental cost-effectiveness analysis; ITT: intent-to-treat; NICE: National Institute of Health and Care Excellence; NMA: network meta-analysis; SAE: serious adverse event; SLR: systematic literature review; SmPC: summary of product characteristics; TA: technology appraisal; TNFi: tumour necrosis factor alpha inhibitor; QoL: quality of life; UC: ulcerative colitis.

B.2.2 *Resource use assumptions*

The resource use and cost elements included in previous NICE technology appraisals in adults with moderately to severely active UC (TA342 and TA633) that are most relevant to the current appraisal were:

- Drug acquisition costs
- Drug administration costs
- Health-state costs
- Costs of surgery
- Costs associated with the management of AEs (discussed in Section B.2.1)

These costs categories are broadly in line with those included in the cost-effectiveness models of the previous technology appraisals mentioned in Section B.2.1. Disease-related monitoring costs are captured within the health state costs, and except for ozanimod, existing products have minimal to no treatment-specific monitoring requirements outlined in their SmPCs, so costs related to treatment-specific monitoring have not been included in their respective models.[55]

A summary of the healthcare resource use and related cost assumptions and Committee comments on these assumptions are presented below.

Drug acquisition costs

Drug acquisition costs for active and concomitant treatments were included in the cost-effectiveness analyses in TA547, TA792 and TA828.[54, 55, 75] In TA633, the costs for concomitant therapies were not included in the company base case, which did not align with ERG preferences.[3] Prior appraisals have derived unit costs from standard sources including the British National Formulary (BNF), the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT), Monthly Index of Medical Specialities (MIMS), previous NICE submissions and published literature. Costs were also modelled separately during the induction phase and maintenance phase of the treatment cycles in TA342, TA633 and TA828.[3, 53, 55] This approach was deemed reasonable by the ERG for each appraisal.

Dose escalation

The ERG considered the modelling of a 30% dose escalation in the maintenance phase as being a reasonable assumption in TA828, particularly given that this was in line with the assumptions for dose escalation accepted in TA633.[3, 55] In addition, this assumption is supported by a multi-national chart review conducted in Europe and Canada of patients with IBD who received treatment with TNFi which found that 25.8% of patients with UC needed dose escalation.[77]

Conventional therapy costs

In prior appraisals, patients on active treatment were expected to receive concomitant treatment, which may include treatments typically considered under the term ‘conventional therapy’ such as corticosteroids.[53, 54] Upon discontinuation of active treatment, patients were modelled to proceed to conventional therapy.[3, 53, 54] As such, prior appraisals applied costs of conventional therapy to patients both in the “active treatment” and “post-active treatment” states of the model.[53, 54]

In prior appraisals, the proportion of patients modelled to be receiving conventional therapy have been derived from TA342 (such as TA633), or from TA547 (such as TA792).[3, 53, 54, 75] In the most recent appraisal, TA828, the ERG and Committee considered that the proportions derived from TA342 were more appropriate for use, in line with those accepted in TA633.[55]

Administration costs

Successive Committees have acknowledged that the costs incurred during drug administration are reliant upon the method of administration.[3, 54, 55, 75] Orally administered drugs have been assumed to not incur any costs to the NHS (TA792).[54] Additionally, in TA633 and TA828, the Committees concluded that it is appropriate for drugs administered subcutaneously to be assumed as having no cost to the NHS, besides the initial cost associated with a nurse training the patient in how to self-administer treatment, due to the possibility of self-administration.[3, 55] In the case of TA828, the ERG noted that approximately 2% of patients may require assistance when using subcutaneous therapy, but it was considered that the inclusion of administration costs for such a small proportion of patients would not have a meaningful impact on results. As such, the Company's base case assumption was deemed to be acceptable.[55] Drugs requiring IV administration have been assumed to incur the cost of an outpatient visit, based on a weighted average of the NHS reference costs for consultant-led non-admitted, face-to-face follow-up appointments and non-consultant led non-admitted, face-to-face follow-up appointments (TA633, TA792 and TA828).[3, 54, 55]

Health state costs

Various health states were modelled in previous technology appraisals in UC (TA828, TA792, TA633, TA547 and TA342), including: Active UC, Response without remission, Remission, first surgery, Post-first surgery, Post-first surgery complications, Second surgery, and Post-second surgery. Differences between appraisals in how surgery was modelled are outlined in Section B.2.1, but across all appraisals outlined (TA329, TA342, TA547, TA633, TA792 and TA828), a UK cost-effectiveness study by Tsai *et al* (2008) has represented the accepted source of health care resource use and costs for all non-surgery health states, for which no costs were reported. [3, 51, 53-55, 75, 78] The assumption in TA633 that the resource use for first and second surgery health states would be equivalent to the active UC health state was deemed appropriate by the ERG.[3] Modelled costs were also validated by clinical expert opinion in TA828 which elicited costs that were broadly in line with those reported in TA633.[55]

B.3 Clinical effectiveness

Summary of clinical effectiveness evidence

The LUCENT trials

- The efficacy and safety data for mirikizumab versus placebo are derived from two randomised, double-blind, placebo-controlled Phase III trials (LUCENT-1 and LUCENT-2).
- Baseline characteristics of patients in both trials were well-balanced across treatment groups, and in the mITT study population, biologic-naïve patients constituted [redacted] and [redacted] of the mirikizumab and placebo arms in LUCENT-1, respectively, and [redacted] in the primary analysis cohort (mirikizumab induction responders) in LUCENT-2.

Efficacy data from LUCENT-1 (induction)

- Treatment with mirikizumab in the LUCENT-1 trial showed improvements in all efficacy outcomes at Week 12 compared to treatment with placebo.
- In the mITT cohort, a significantly higher proportion of patients receiving mirikizumab achieved clinical remission at Week 12 as compared with those receiving placebo ([redacted]), and clinical response at the same timepoint was similarly statistically significantly improved ([redacted]).
- Bowel urgency, an endpoint noted as being of importance to patients, was significantly improved in mITT patients receiving mirikizumab as compared with those receiving placebo at Week 12 ([redacted]), with statistically significant improvements in urgency observed consistently from as early as Week 2 ([redacted]).
- Consistent efficacy results were observed for patients in the biologic-naïve and biologic-failed subgroups.

Efficacy data from LUCENT-2 (maintenance)

- As in LUCENT-1, treatment with mirikizumab in the LUCENT-2 trial demonstrated improvements in all efficacy outcomes at Week 40 compared to treatment with placebo amongst mirikizumab induction responders.
- In the cohort of mirikizumab induction responders, significantly higher rates of clinical remission were observed at Week 40 in patients re-randomised to receive mirikizumab as compared with those re-randomised to receive placebo ([redacted]), and mirikizumab was additionally associated with a statistically significant benefit over placebo in maintaining response in those who have previously responded to mirikizumab induction therapy ([redacted]).
- At Week 40, histologic endoscopic mucosal remission rates and improvements in bowel urgency were both statistically significantly higher for patients receiving mirikizumab than those receiving placebo (both [redacted]).
- The rates of corticosteroid-free remission without surgery, at Week 40, were also significantly improved among mirikizumab induction responders when compared to placebo ([redacted]), and this improvement held true across both of the subgroups analysed (both [redacted]).
- In alignment with LUCENT-1, efficacy results from subgroup analyses by prior biologic exposure status were broadly consistent with the mITT population.
- Mirikizumab re-induction, for patients who achieved a response in LUCENT-1 but subsequently lost it during LUCENT-2, and open-label extended mirikizumab induction therapy, for patients who did not achieve a response (regardless of treatment allocation) in LUCENT-1, also evidenced mirikizumab efficacy.

Safety data from LUCENT-1 and LUCENT-2

- The frequencies of adverse events (AEs) in the mirikizumab-treated patients of LUCENT-2

compared to those receiving placebo were similar, with the majority of TEAEs observed being mild to moderate in nature in both treatment arms.

- In both trials, frequencies of serious adverse events (SAEs) and treatment discontinuation due to an AE were broadly comparable between arms, although in LUCENT-2, rates were marginally higher in the group of mirikizumab induction responders receiving placebo than in those receiving mirikizumab ([redacted] versus [redacted] and [redacted] versus [redacted], respectively).
- [redacted] occurred throughout either study, which was in the placebo group of LUCENT-2.

Efficacy data from the network meta-analyses (NMAs)

- In the absence of direct head-to-head data for the efficacy of mirikizumab versus relevant comparators in UC, indirect efficacy analyses were performed for induction and maintenance timepoints for the biologic-naïve and biologic-failed populations
- The results of the analyses found that regardless of biologic exposure, mirikizumab offered similar efficacy to most treatments at induction, and clinical benefits in terms of clinical response, clinical remission and mucosal healing versus all other comparators in the maintenance phase.

Conclusion

- In summary, the introduction of mirikizumab to UK clinical practice would provide clinicians with an additional, effective option with a tolerable safety profile in their armamentarium of biologic therapies to treat patients with moderately to severely active UC in the UK.

B.3.1 *Identification and selection of relevant studies*

A *de novo* systematic literature review (SLR) was conducted in November 2018 to identify relevant clinical evidence from randomised controlled trials (RCTs) describing the clinical efficacy and safety of biologic treatments (including JAK inhibitors) for patients with moderately to severely active UC. The SLR was updated in July 2020, April 2021, October 2021, May 2022 and June 2022 using identical methodology to ensure recently published evidence was included.

In total, the overall SLR, including all updates, included 94 publications reporting on 68 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 two randomised, double-blind, placebo-controlled Phase III trials (LUCENT-1 and LUCENT-2) for mirikizumab in UC. The results of these trials are presented from the final clinical study reports (CSRs).[79, 80] A summary of the clinical effectiveness evidence from LUCENT-1 and LUCENT-2 are presented in Table 5.

Table 5: Clinical effectiveness evidence

Study	LUCENT-1[79]	LUCENT-2[80]
Study design	A Phase III, multicentre, randomised, double-blind, parallel, placebo-controlled induction study of mirikizumab.	A Phase III, multicentre, randomised, double-blind, parallel-arm, placebo-controlled maintenance study of mirikizumab.
Population	Adult patients with an established diagnosis of UC at least 3 months prior to baseline, including endoscopic evidence. Patients had	Patients who completed LUCENT-1, received at least 1 dose of mirikizumab and had all necessary evaluations to assess the modified

Study	LUCENT-1[79]	LUCENT-2[80]
	moderately to severely active UC with a modified Mayo score of 4–9 and endoscopic subscore of ≥2. Patients were also required to have failed prior medication with conventional therapy ("conventional failed" or with biologic therapy ("biologic-failed"). Conventional-failed patients had: • An inadequate response to, loss of response to, or intolerance to corticosteroids or immunomodulators. • Never failed nor demonstrated an intolerance to a biologic medication indicated for the treatment of UC. Biologic-failed patients had: • An inadequate response to, loss of response to, or intolerance to biologic or tofacitinib therapy.	Mayo score. The trial included patients who achieved clinical response in LUCENT-1, as well as patients who did not achieve clinical response with mirikizumab or placebo.
Intervention(s)	300 mg mirikizumab administered intravenously at Weeks 0, 4 and 8.	• 200 mg mirikizumab administered subcutaneously every 4 weeks (Q4W). • Open-label 300 mg mirikizumab administered intravenously Q4W.
Comparator(s)	Placebo administered intravenously at Week 0, 4 and 8.	Placebo administered subcutaneously Q4W.
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes
Reported outcomes specified in the decision problem	The outcome measures used in this submission include: • Rates of and duration of response and remission (clinical response, clinical remission) • Measures of disease activity (symptomatic remission, bowel urgency) • Mucosal healing (endoscopic remission, histologic remission) • Corticosteroid-free remission • AEs	

Abbreviations: AE: adverse event; CRP: C-reactive protein; Q4W: every 4 weeks; UC: ulcerative colitis.

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

B.3.3.1 Trial design and methodology

Two Phase III studies, LUCENT-1 and LUCENT-2, were conducted to evaluate the clinical effectiveness and safety of mirikizumab in UC. LUCENT-1 was a 12-week induction study, after which patients could enrol into the LUCENT-2 maintenance study. Further details of both studies are presented below.

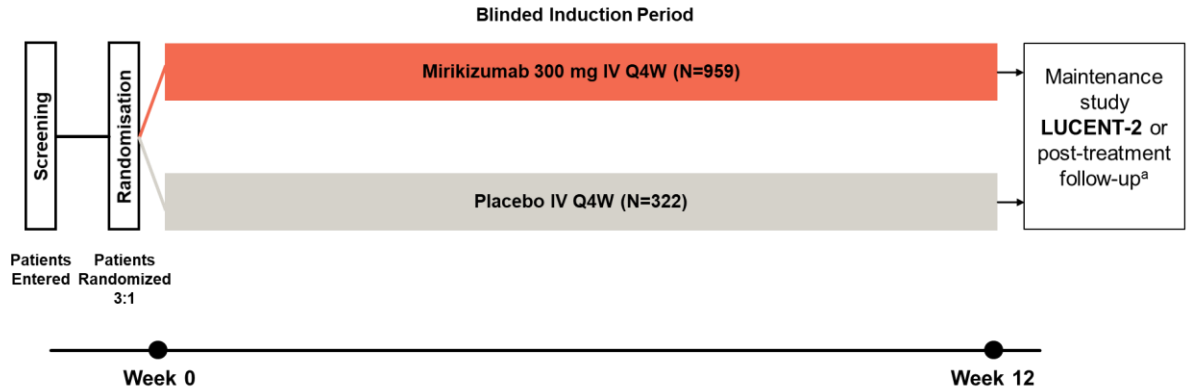
B.3.3.1.1 LUCENT-1

Trial design

The trial design of LUCENT-1 is shown in Figure 3. LUCENT-1 was a multicentre, randomised, double-blind, parallel-arm, placebo-controlled Phase III trial designed to evaluate the safety and efficacy of mirikizumab, compared with placebo, over a 12-week induction period. The trial was conducted at 163 centres that screened 2079 patients; screening lasted up to 28 days prior to trial baseline. As outlined in Section B.3.2, the study population included patients with moderately to severely active UC who had an inadequate response to, loss of response to, or intolerance to conventional therapy for UC ("conventional-failed"), and those who had an inadequate response to, loss of response to, or intolerance to biologic therapy for UC ("biologic-failed").

After screening, patients were randomised 3:1 to intravenous (IV) mirikizumab 300 mg Q4W or IV placebo Q4W, respectively, and were stratified by biologic-failed status, baseline corticosteroid use, baseline disease activity (as defined by a modified Mayo score of 4–6 or 7–9) and region. Patients received their allocated study treatment at Weeks 0, 4 and 8. Patients who completed Week 12 of LUCENT-1 were eligible to enrol into the LUCENT-2 maintenance trial, regardless of their clinical response status at Week 12 of LUCENT-1, while patients who discontinued LUCENT-1 before Week 12, or completed LUCENT-1 but did not enrol in LUCENT-2, completed a post-treatment follow-up period for 16 weeks subsequent to their last visit.

Figure 3: The trial design of LUCENT-1



[a]Patients who completed LUCENT-1 through Week 12 either completed post-treatment follow-up within the study or were eligible to participate in the maintenance study LUCENT-2.
Abbreviations: IV: intravenous; Q4W: every 4 weeks.

Trial methodology

The primary endpoint of LUCENT-1 was the proportion of patients in clinical remission at Week 12, based on the modified Mayo score. Secondary endpoints included further assessments of remission, the proportion of patients with clinical response at Week 12, the proportion of biologic-failed patients with clinical response at Week 12 and assessment of improvement in bowel urgency. A summary of the methodology of the LUCENT-1 trial is presented in Table 6.

Table 6: Summary of LUCENT-1 trial methodology

Trial name	LUCENT-1
Location	The study was conducted at 471 centres in Argentina, Australia, Austria, Belgium, Canada, China, Croatia, the Czech Republic, Denmark, France, Germany, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, the Netherlands, Poland, the Republic of South Korea, Romania, the Russian Federation, Serbia, Slovakia, Spain, Switzerland, Taiwan, Turkey, Ukraine, the United Kingdom ([redacted] patients recruited from [redacted] centres), and the United States.
Trial design	A Phase III, multicentre, randomised, double-blind, parallel-arm, placebo-controlled study designed to evaluate the safety and efficacy of mirikizumab, compared with placebo, over a 12-week induction period.
Eligibility criteria for participants	A summary of the 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 UC at least 3 months prior to baseline • Endoscopic evidence of UC • A histopathology report that supports a UC diagnosis • A modified Mayo Score of 4–9 with an endoscopic subscore of ≥2 within 14 days of baseline • UC extending beyond the rectum **Prior medication failure inclusion criteria:** • Conventional-failed patients must have had inadequate response to, loss of response to, or intolerance to corticosteroids or immunomodulators AND never failed nor demonstrated an intolerance to a biologic medication. • Biologic-failed patients must have had inadequate response to, loss of response to, or intolerance to TNFis, anti-integrins, or tofacitinib. **Exclusion criteria:** • UC limited to the rectum (proctitis) • Any other forms of IBD • An immunodeficiency syndrome that would cause UC-like colonic inflammation • Extensive colonic resection • Stricture/stenosis within the small bowel or colon • Toxic megacolon • Colonic adenoma that had not been removed • Dysplasia of colonic mucosa • Gastrointestinal cancer • Received or failed ≥3 biologic therapies (excluding tofacitinib) for UC
Study drugs	**Study drug:** 300 mg mirikizumab, administered intravenously at Weeks 0, 4 and 8 **Comparator:** Placebo administered intravenously at Weeks 0, 4 and 8 to match mirikizumab.
Permitted and disallowed concomitant medication	Stable doses of the following drugs were permitted: • Oral 5-aminosalicylic acid therapy • Oral corticosteroids • Azathioprine • Mercaptopurine • Methotrexate Disallowed medications included:

	• TNFi • Anti-integrin antibodies • Immunomodulators such as cyclosporine, although stable doses of some immunomodulators such as azathioprine were permitted as outlined above • JAK inhibitors
Primary outcome	The primary outcome was to evaluate the proportion of patients in clinical remission at Week 12 defined using the modified Mayo score (see Section B.3.3.3).
Secondary outcomes	Major secondary endpoints are listed below; for definitions, see Section B.3.3.3. • Alternate clinical remission at Week 12 • Clinical response at Week 12 • Endoscopic remission at Week 12 • Symptomatic remission at Week 4 • Symptomatic remission at Week 12 • Clinical response in the biologic-failed population at Week 12 • Bowel movement urgency improvement at Week 12 • Histologic-endoscopic mucosal improvement at Week 12 Additional secondary outcomes can be found in Appendix M and the CSR.[79]
Pre-specified subgroups	Subgroup analyses for all primary and major secondary endpoints were conducted for the following: • Previous systemic therapy • Previous biologic therapy • Demographics • Geographic region • Baseline disease severity and activity • Duration and location of disease • Concomitant therapy for UC

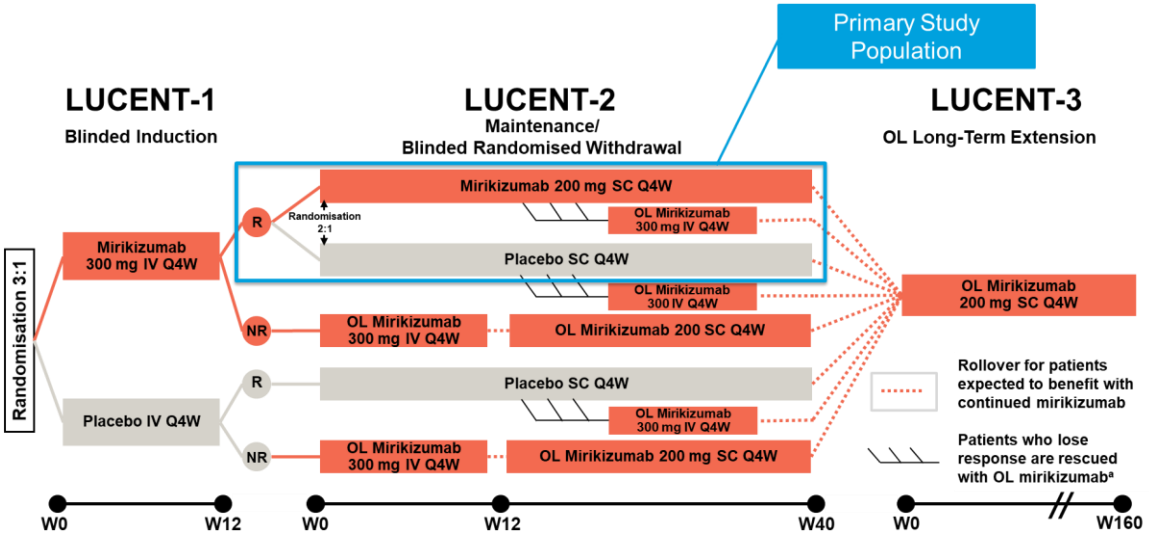
Abbreviations: CSR: clinical study report; IBD: inflammatory bowel disease; JAK: Janus kinase; TNFi: tumour necrosis factor alpha inhibitor; UC: ulcerative colitis.

B.3.3.1.2 LUCENT-2

Trial design

LUCENT-2 was a multicentre, randomised, double-blind, parallel-arm, placebo-controlled Phase III maintenance study which followed LUCENT-1 and evaluated the safety and efficacy of mirikizumab in maintaining treatment response at Week 40 (after 52 weeks of continuous study drug treatment). The trial was conducted at 368 centres with 1178 patients and comprised five treatment arms. The treatment received in LUCENT-2 was dependent on the treatment arm patients were initially randomised to at Week 0 of LUCENT-1, and the achievement of clinical response at Week 12 of LUCENT-1. The LUCENT-2 study design is shown in Figure 4. Patients who completed LUCENT-2 could be enrolled into an open-label extension (LUCENT-3).

Figure 4: The trial design of LUCENT-2



[a]Patients for whom re-induction ("rescue therapy") with open-label mirikizumab was not deemed to demonstrate clinical benefit discontinued treatment and were not eligible to enter the open-label extension.
Abbreviations: IV: intravenous; NR: non-responder OL: open-label; Q4W: every 4 weeks; R: responder; SC: subcutaneous; W: week.

Mirikizumab responders from LUCENT-1 (primary study population)

The primary study population comprised patients, randomised to the mirikizumab arm of LUCENT-1, who showed a clinical response at Week 12 (for definition see Section B.3.3.3). These patients were re-randomised 2:1 to subcutaneous mirikizumab 200 mg Q4W (maintenance therapy) or subcutaneous placebo Q4W, respectively. Randomisation was stratified based on biologic-failed status, induction remission status, baseline corticosteroid use, and region. Patients continued their treatment assignment throughout the LUCENT-2 trial unless they developed secondary loss of response (for definition, see Section B.3.3.3).

If a loss of response was confirmed (including the use of endoscopy results), patients received three doses of open-label IV mirikizumab 300 mg Q4W re-induction therapy. If patients were deemed to have achieved clinical benefit from the re-induction therapy after the three doses, the patients were considered for enrolment into LUCENT-3 but could not continue in LUCENT-2.

Placebo responders from LUCENT-1

Patients randomised to placebo in LUCENT-1 who achieved clinical response at Week 12 continued to receive placebo in LUCENT-2. If a loss of response was confirmed, patients followed the same procedures as for the mirikizumab responders, described above.

Mirikizumab and placebo non-responders from LUCENT-1

Patients who did not achieve clinical response to IV mirikizumab 300 mg Q4W or placebo during LUCENT-1 received open-label extended induction therapy (IV mirikizumab 300 mg Q4W) at Weeks 0, 4 and 8 of LUCENT-2. At Week 12, following extended induction, these patients underwent delayed clinical response assessment. Patients who achieved delayed clinical response, as compared with LUCENT-1 baseline, after extended induction therapy could subsequently receive open-label subcutaneous mirikizumab 200 mg Q4W from Week 12. Patients continued this treatment and underwent clinical response evaluation via endoscopy at Week 40 unless they discontinued from the study. If patients were deemed to have achieved

clinical benefit at Week 40, they were considered for enrolment into LUCENT-3 to continue subcutaneous maintenance therapy. Patients who did not achieve clinical response after extended induction therapy at Week 12 of LUCENT-2 discontinued the study.

Post-treatment follow-up period

Patients underwent a maximum 16-week post-treatment follow-up period. Patients who discontinued the study having last received IV mirikizumab returned for post-treatment follow-up visits at 4 and 16 weeks after the end-of-treatment visit. Patients who discontinued the study having received subcutaneous mirikizumab returned for post-treatment follow-up at 4 and 12 weeks after the end-of-treatment visit. Patients who subsequently entered the open-label extension study did not need complete the post-treatment follow-up period.

Trial methodology

The primary endpoint of LUCENT-2 was the proportion of patients in clinical remission at Week 40, based on the modified Mayo score. Secondary endpoints included further assessments of remission, maintenance of remission from Week 12 of LUCENT-1 to Week 40 of LUCENT 2 and assessment of improvement and remission in bowel urgency. A summary of the methodology of the LUCENT-2 trial is presented in Table 7.

Table 7: Summary of LUCENT-2 trial methodology

Trial name	LUCENT-2
Location	The study was conducted at 368 centres in Argentina, Australia, Austria, Belgium, Canada, China, the Czech Republic, Denmark, France, Germany, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, the Netherlands, Poland, the Republic of South Korea, Romania, the Russian Federation, Serbia, Slovakia, Spain, Switzerland, Taiwan, Turkey, Ukraine, the United Kingdom ([redacted] patients enrolled from [redacted] centres), and the United States.
Trial design	A Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-arm study evaluating the safety and efficacy of mirikizumab in maintaining treatment response at Week 40 (Week 52 of continuous study treatment).
Eligibility criteria for participants	A summary of the inclusion and exclusion criteria is provided below. Full details of the eligibility criteria are presented in Appendix K. **Inclusion criteria:** • Completion of LUCENT-1 having received at least 1 dose of study drug and had all necessary evaluations to assess the modified Mayo score at the end of the study • Patients must have been willing and able to complete the scheduled study assessments, including endoscopy and daily diary entry **Exclusion criteria:** • Diagnosed with Crohn's disease or IBD-Unclassified during LUCENT-1 • Had bowel resection or other surgery for the treatment of UC during LUCENT-1, or are likely to require surgery for the treatment of UC during LUCENT-2 • Evidence of colonic dysplasia at maintenance baseline (Week 12 of LUCENT-1) or diagnosis of cancer of the gastrointestinal tract during LUCENT-1. • Current adenomatous polyps that have not been removed - patient may be eligible for study after removal and confirmation of no dysplasia or malignancy on local histology report

	• Initiation of a new prohibited medication during LUCENT-1 • Presence of a hepatic or hematologic laboratory abnormality prior to Week 0 that would require permanent discontinuation from study drug
Study drugs	**Maintenance therapy:** blinded 200 mg mirikizumab, administered subcutaneously Q4W **Extended induction/re-induction therapy:** open-label 300 mg mirikizumab, administered intravenously Q4W Comparator (in primary study population and for LUCENT-1 placebo responders): blinded placebo administered subcutaneously Q4W
Permitted and disallowed concomitant medication	Stable doses of the following drugs were permitted: • Oral 5-aminosalicylic acid therapy • Oral corticosteroids • Azathioprine • Mercaptopurine • Methotrexate Disallowed medications included: • TNFi • Anti-integrin antibodies • Immunomodulators such as cyclosporine, although stable doses of some immunomodulators such as azathioprine were permitted as outlined above • JAK inhibitors
Primary outcome	The proportion of patients in clinical remission at Week 40, using the modified Mayo score (see Section B.3.3.3).
Secondary outcomes	Major secondary endpoints are listed below; for definitions, see Section B.3.3.3. • Alternate clinical remission at Week 40 • Endoscopic remission at Week 40 • Histologic-endoscopic mucosal remission at Week 40 • Change from LUCENT-1 baseline in Urgency Numerical Rating Scale • Corticosteroid-free remission without surgery at Week 40 • Urgency remission at Week 40 • Maintenance of clinical remission (from Week 12 of LUCENT-1 to Week 40 of LUCENT-2) Additional secondary outcomes can be found in Appendix N and the CSR.[80]
Pre-specified subgroups	Subgroup analyses for all primary and major secondary endpoints were conducted for the following: • Previous systemic therapy • Previous biologic therapy • Demographics • Geographic region • Baseline disease severity and activity • Duration and location of disease • Concomitant therapy for UC • Induction remission status

Abbreviations: IBD: inflammatory bowel disease; JAK: Janus kinase; Q4W: every 4 weeks; TNFi: tumour necrosis factor alpha inhibitor; UC: ulcerative colitis.

B.3.3.2 Baseline characteristics

B.3.3.2.1 LUCENT-1

Summaries of the demographic characteristics and baseline disease characteristics for patients included in the LUCENT-1 trial are provided below in Table 8 and Table 9, respectively.

Overall, baseline characteristics were well-balanced across treatment groups. Respectively, patients in the mITT population receiving mirikizumab and placebo had a mean age of [redacted] years and [redacted] years, and [redacted] and [redacted] were male. A similar proportion of patients in each arm had severe disease at baseline as per their modified Mayo score category (7–9) ([redacted] for the mirikizumab arm, [redacted] for the placebo arm) and the mean total Mayo score was [redacted] in both arms. Additionally, in line with the decision problem, biologic-naïve and biologic-failed patients were included, with biologic-naïve patients constituting [redacted] and [redacted] of the mirikizumab and placebo arms, respectively.

Table 8: Baseline demographic characteristics for patients in the mITT population of the LUCENT-1 trial

Characteristics	PBO (N=[redacted])	Miri 300 mg IV (N=[redacted])
Age (years), mean (SD)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]
BMI category, n (%)		
Underweight (<18.5 kg/m^2)	[redacted]	[redacted]
Normal (≥18.5 and <25 kg/m^2)	[redacted]	[redacted]
Overweight (≥25 and <30 kg/m^2)	[redacted]	[redacted]
Obese or extreme obese (≥30 kg/m^2)	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Geographical region, n (%)		
North America	[redacted]	[redacted]
Europe	[redacted]	[redacted]
Western Europe	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]
Other	[redacted]	[redacted]
Asia	[redacted]	[redacted]
Central America/South America	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]

Abbreviations: BMI: body mass index; IV: intravenous; Miri: mirikizumab; mITT: modified intent-to-treat; PBO: placebo; SD: standard deviation.
Source: Eli Lilly and Company (data on file): LUCENT-1 Clinical Study Report Table AMAN 8.3 (page 108)[79]

Table 9: Baseline disease characteristics and prior therapies of patients in the mITT population of the LUCENT-1 trial

Characteristics	PBO (N=[redacted])	Miri 300 mg IV (N=[redacted])
Duration of ulcerative colitis (years), mean (SD)	[redacted]	[redacted]
Disease location, n (%)		
Proctitis	[redacted]	[redacted]
Left-side colitis	[redacted]	[redacted]
Pancolitis	[redacted]	[redacted]
Baseline modified Mayo score category, n (%)		
Mild (1-3)	[redacted]	[redacted]
Moderate (4-6)	[redacted]	[redacted]
Severe (7-9)	[redacted]	[redacted]
Total Mayo score, mean (SD)	[redacted]	[redacted]
Severe disease (endoscopic Mayo subscore=3), n (%)	[redacted]	[redacted]
Fecal calprotectin (µg/g), mean (SD)	[redacted]	[redacted]
Baseline corticosteroid use, n (%)	[redacted]	[redacted]
Baseline immunomodulator use, n (%)	[redacted]	[redacted]
Prior biologic or tofacitinib failure, n (%)	[redacted]	[redacted]
Prior TNFi failure, n (%)	[redacted]	[redacted]
Prior vedolizumab failure, n (%)	[redacted]	[redacted]
Prior tofacitinib failure, n (%)	[redacted]	[redacted]
Number of failed biologics or tofacitinib, n (%)		
None	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]

Abbreviations: IV: intravenous; Miri: mirikizumab; mITT: modified intent-to-treat; PBO: placebo; SD: standard deviation; TNFi: tumour necrosis factor inhibitor.
Source: Eli Lilly and Company (data on file): LUCENT-1 Clinical Study Report Table AMAN 8.3 (page 108)[79]

B.3.3.2.1 LUCENT-2

Summaries of the demographic characteristics and baseline disease characteristics for patients included in the LUCENT-2 trial and grouped by their response status at the end of the LUCENT-1 trial are provided below in Table 10 and Table 11, respectively.

As in LUCENT-1, baseline demographic and disease characteristics were well-balanced across all treatment arms. The mean age of all study patients in the mITT population was [redacted] years, ranging from [redacted] years to [redacted] years across treatment groups, and just over half of patients were male in all groups (mean: [redacted]). Disease severity at baseline was similarly consistent between groups, with [redacted] to [redacted] (mean: [redacted]) with modified Mayo score of 7–9, and a mean total Mayo score of between [redacted] and [redacted] (mean: [redacted]). Of all patients in the mITT study population, [redacted] were biologic-naïve and [redacted] were biologic-failed.

Table 10: Baseline demographic characteristics for patients in the mITT population of the LUCENT-2 trial

Characteristics	Miri induction responders		PBO induction Responder (PBO SC, N=[redacted])	Miri induction non-responder (OL Miri 300 IV N=[redacted])	PBO induction non-responder (OL Miri 300 IV N=[redacted])	All study patients (N=[redacted])
	PBO (N=[redacted])	Miri 300 mg SC (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 category, n (%)						
Underweight (<18.5 kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal (≥18.5 and <25 kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overweight (≥25 and <30 kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obese or extreme obese (≥30 kg/m^2)	[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]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region, n (%)						
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Western Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Central or South America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; IV: intravenous; Miri: mirikizumab; mITT: modified intent-to-treat; PBO: placebo; SD: standard deviation.
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.6 (page 23).[81]

Table 11: Baseline disease characteristics and prior therapies of patients in the mITT population of the LUCENT-2 trial

Characteristics	Miri induction responders		PBO induction Responder (PBO SC, N=[redacted])	Miri induction non-responder (OL Miri 300 IV N=[redacted])	PBO induction non-responder (OL Miri 300 IV N=[redacted])	All study patients (N=[redacted])
	PBO (N=[redacted])	Miri 300 mg SC (N=[redacted])				
Duration of ulcerative colitis (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease location, n (%)						
Proctitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Left-side colitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancolitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Modified Mayo Score category, n (%)						
Mild (1-3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Moderate (4-6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe (7-9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Mayo Score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic Mayo Subscore, Severe disease (3) , n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urgency NRS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fecal calprotectin (µg/g), median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C-Reactive protein (µg/g), median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline corticosteroid use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline immunomodulator use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior biologic or tofacitinib failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior TNFi failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Vedolizumab failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Tofacitinib failure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of failed biologics or tofacitinib, n (%)						
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]All Study Patients pooling together LUCENT-1 responders and non-responders.
Abbreviations: IV: intravenous; Miri: mirikizumab; OL: open-label; PBO: placebo; SC: subcutaneous; SD: standard deviation; TNFi: tumour necrosis factor inhibitor.
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.6 (page 23).[81]

B.3.3.3 Outcome definitions

Definitions for the modified Mayo score and clinical effectiveness outcomes used in the LUCENT-1 and LUCENT-2 trials are presented in Table 12.

Table 12: Definitions of clinical effectiveness outcomes used in the LUCENT-1 and LUCENT-2 trials

Outcome	Definition
LUCENT-1 and LUCENT-2	
Modified Mayo score	A modified version of the full Mayo score for UC (Table 3).[26, 27] The modified Mayo score does not include the Physician's global assessment subscore but has been shown to correlate well with the full Mayo score.[29] Includes the following subscores, with a total possible score of 9: • Stool frequency subscore (0–3) • Rectal bleeding subscore (0–3) • Endoscopic subscore (0–3) The exclusion of the Physician's Global Assessment subscore is in line with guidance published by the FDA that patient-reported outcomes are better able to measure the signs and symptoms of UC than this clinician-reported outcome.[82]
Clinical remission	• Stool frequency subscore = 0 or 1, with ≥1-point decrease from baseline • Rectal bleeding subscore = 0 • Endoscopic subscore = 0 or 1 (excluding friability)
Alternate clinical remission	• Stool frequency subscore = 0 or 1 • Rectal bleeding subscore = 0 • Endoscopic subscore = 0 or 1 (excluding friability)
Clinical response	• ≥2-point and ≥30% decrease in the modified Mayo score from baseline • Rectal bleeding subscore = 0 or 1, or ≥1-point decrease from baseline
Endoscopic remission	• Endoscopic subscore = 0 or 1 (excluding friability)
Symptomatic remission	• Stool frequency subscore = 0 or 1, with ≥1-point decrease from baseline • Rectal bleeding subscore = 0
Histologic-endoscopic mucosal improvement	• LUCENT-1: Histologic improvement, defined using Geboes scoring system[83] with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue, and an endoscopic subscore = 0 or 1 (excluding friability) • LUCENT-2: Histologic remission with resolution of mucosal neutrophils (defined using Geboes scoring system[83] with subscores of 0 for grades: 2b [lamina propria neutrophils], 3 [neutrophils in epithelium], 4 [crypt destruction] and 5 [erosion or ulceration]) and endoscopic remission (defined as an endoscopic subscore of 0 or 1, excluding friability).
Health outcomes endpoints	Change from baseline in: • IBDQ score at Week 12 (LUCENT-1) and Week 40 (LUCENT-2) • EQ-5D 5L index at Week 12 (LUCENT-1) and Week 40 (LUCENT-2) • WPAI:UC score at Week 12 (LUCENT-1) and Week 40 (LUCENT-2) • SF-36, Version 2 physical and mental component and domain scores at Week 12 (LUCENT-1) and Week 40 (LUCENT-2)
LUCENT-2 only	

Corticosteroid-free remission without surgery	• Clinical remission at Week 40 • Symptomatic remission at Week 28 • No corticosteroid use for ≥12 weeks prior to Week 40
Urgency remission	• Urgency NRS score at week 40 = 0 or 1
Loss of response	Loss of response was defined as: • ≥2-point increase in the combined stool frequency and rectal bleeding subscores (relative to LUCENT-1 baseline) • ≥4 points combined stool frequency and rectal bleeding subscores on 2 consecutive visits • Confirmation of negative *Clostridium difficile* testing (from Week 8) And • Confirmed by a centrally read endoscopic subscore of 2 or 3 from Week 12 and no later than Week 28

Abbreviations: EQ-5D 5L: European Quality of Life 5 Dimensions 5 Level index; IBDQ: Inflammatory Bowel Disease Questionnaire; NRS: numerical rating scale; SF-36: Medical Outcomes Study 36-Item Short Form Health Survey UC: ulcerative colitis; WPAI:UC: Work Productivity and Activity Impairment Questionnaire ulcerative Colitis.

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

B.3.4.1 Trial populations

LUCENT-1 and LUCENT-2

The description and number of patients in each analysis population for the LUCENT-1 and LUCENT-2 trials are presented in Table 13. The modified intention-to-treat (mITT) population was used in the analysis of efficacy and health outcomes. The safety population was used for safety-related analysis.

Table 13: Trial populations used for the analysis of outcomes in the LUCENT-1 and LUCENT-2 trials

Analysis set		LUCENT-1	LUCENT-2
Screening population (LUCENT-1)/All entered patients (LUCENT-2)	N	2079	1178
	Description	All patients who signed informed consent.	
Intention-to-treat (ITT) population	N	1281	1177
	Description	All randomised patients. Patients were analysed according to the treatment to which they were assigned.	
Modified intention-to-treat (mITT) population	N	1162	1073
	Description	All randomised patients who received any amount of study treatment, excluding patients impacted by the electronic clinical outcome assessment (eCOA) transcription error in Poland and Turkey[a] (regardless of whether the patient did not receive the correct treatment, or otherwise did not follow the protocol).	
	Use	For all efficacy and health outcome analyses	

Safety population	N	1279	1177
	Description	All randomised patients who received any amount of study treatment (regardless of whether the patient did not receive the correct treatment, or otherwise did not follow the protocol).	
	Use	For all safety-related analyses	
Per-protocol population (PP)	N	955	897
	Description	All mITT patients who were not deemed non-compliant with treatment, who did not have significant protocol deviations, and whose investigator site did not have significant good clinical practice deviations that required a report to regulatory agencies (regardless of study period).	

[a]For details of the eCOA transcription error, see Section 3.1.2.2 of the LUCENT-1 and LUCENT-2 CSRs.[79, 80]
Abbreviations: CSR: clinical study report; eCOA: electronic outcome assessment; ITT: intention-to-treat; mITT: modified intention-to-treat; PP; per-protocol.

LUCENT-2

In addition to the populations described above, LUCENT-2 comprised additional cohorts which were based on the clinical response at Week 12 of LUCENT-1 and the subsequent treatment received in LUCENT-2. These analysis cohorts are presented in Table 14. The mirikizumab induction responder cohort was used for inferential comparisons in the analysis of LUCENT-2 trial data. Data reported for all other cohorts were descriptive.

Table 14: Analysis cohorts used in LUCENT-2, dependent on clinical response at Week 12 of LUCENT-1

Cohort	Description	Treatment groups in LUCENT-2
Mirikizumab induction responders (primary analysis cohort)	Patients who responded to mirikizumab induction dosing at Week 12 of LUCENT-1 and were then re-randomised to subcutaneous mirikizumab 200 mg Q4W or placebo.	Subcutaneous placebo
		Subcutaneous mirikizumab 200 mg Q4W
Mirikizumab induction remitters (sub-population of mirikizumab induction responders)	Patients classified as clinical remitters at Week 12 of LUCENT-1 and were re-randomised to subcutaneous mirikizumab 200 mg Q4W mirikizumab or placebo.	Subcutaneous placebo
		Subcutaneous mirikizumab 200 mg Q4W
Induction responders	Patients enrolled into LUCENT-2 who were classified as clinical responders at Week 12 of LUCENT-1.	Subcutaneous placebo (placebo induction responders)
		Subcutaneous placebo (mirikizumab induction responders)
		Subcutaneous mirikizumab 200 mg Q4W (mirikizumab induction responders)
Induction non-responders	Patients enrolled into LUCENT-2 who were classified as clinical non-responders at Week 12 of LUCENT-1.	IV mirikizumab 300 mg Q4W (mirikizumab induction non-responders)
		IV mirikizumab 300 mg Q4W (placebo induction non-responders)
Loss of response cohort	Patients who responded to induction dosing at Week 12 of LUCENT-1,	Subcutaneous placebo (placebo induction responders)

	lost response during LUCENT-2, and received at least 1 dose of open-label IV mirikizumab re-induction. Note that in the LUCENT trial materials, re-induction therapy is referred to as "rescue therapy".	Subcutaneous placebo (mirikizumab induction responders)
		Subcutaneous mirikizumab 200 mg Q4W (mirikizumab induction responders)
Delayed clinical responders	Subset of induction non-responders who achieved delayed clinical response, entered the open-label maintenance period and received at least 1 dose of subcutaneous mirikizumab dosing.	Subcutaneous mirikizumab 200 mg Q4W (mirikizumab induction non-responders)
		Subcutaneous mirikizumab 200 mg Q4W (placebo induction non-responders)

Abbreviations: IV: intravenous; Q4W: every 4 weeks.

Subgroup definitions

In line with the NICE final scope, subgroup analyses based on prior biological agent use were performed. The trial definition of conventional-failed patients, henceforth referred to as "biologic-naïve", included patients who had an inadequate response to, loss of response to, or were intolerant to conventional therapy. The trial definition of biologic-failed patients, referred to as "biologic-failed", included patients who had failed and thus discontinued prior biologic therapy, including tofacitinib, due to loss of response, inadequate response, or intolerance. An additional 5 patients on placebo and 15 patients on mirikizumab were previously exposed to but did not fail a biologic or JAK inhibitor.

B.3.4.2 Patient disposition

Patient flow diagrams for LUCENT-1 and LUCENT-2 are presented in Appendix D.2.

B.3.4.3 Statistical methods

The statistical methods employed for the LUCENT-1 and LUCENT-2 trials are presented in Table 15.

Table 15: Summary of the statistical methods employed in the LUCENT-1 and LUCENT-2 trials

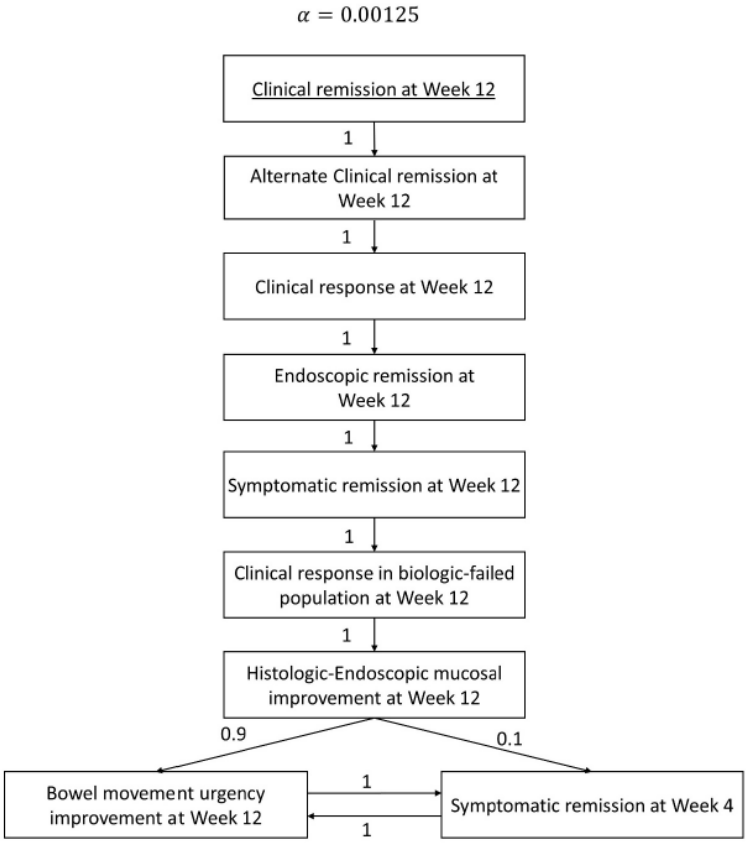
	LUCENT-1[84]	LUCENT-2[85]
Hypothesis objective	To test the hypothesis that mirikizumab is superior to placebo at inducing clinical remission (for definition see Table 12) at Week 12 in patients with moderately to severely active colitis (UC).	To test the hypothesis that mirikizumab is superior to placebo in achieving clinical remission at Week 40 (Week 52 of continuous therapy) among patients induced into clinical response with mirikizumab in LUCENT-1.
Multiple comparisons and multiplicity	A prespecified graphical multiple testing approach was implemented to control the overall Type I error rate at two-sided alpha of 0.00125, for all primary and major secondary endpoints (Figure 5).[86, 87] The graphical approach is a closed testing procedure; hence, it strongly controlled the family-wise error rate across all endpoints.[86-88]	A prespecified graphical multiple testing approach was implemented to control the overall Type I error rate at two-sided alpha of 0.05, for all primary and major secondary endpoints (Figure 6).[86, 87] The graphical approach is a closed testing procedure; hence, it strongly controlled the family-wise error rate across all endpoints.[86-88]

Statistical analysis	• Primary endpoint and other binary efficacy endpoints: the Cochran–Mantel–Haenszel (CMH) chi-square test was used to compare the two treatment groups with the following stratification factors: (a) previous biologic therapy failure status, (b) baseline corticosteroid use, (c) baseline disease activity, and (d) region. • Continuous endpoints: treatment comparisons were made using mixed-effects model for repeated measures (MMRM) analysis. When the MMRM was used, it included: (a) treatment group, (b) previous biologic therapy failure status, (c) baseline corticosteroid use, (d) baseline disease activity, (e) region, (f) baseline value in the model, (g) visit, and (h) the interactions of treatment-by-visit and baseline-by-visit as fixed factors. • Continuous endpoints with a single post-baseline timepoints: treatment comparisons were made using analysis of covariance (ANCOVA) with: (a) treatment group, (b) previous biologic therapy failure status, (c) corticosteroid use, (d) baseline disease activity, (e) region, and (f) baseline value in the model.	• Primary endpoint and other categorical efficacy endpoints: the CMH chi-square test was used to compare mirikizumab and placebo with stratification factors: (a) previous biologic therapy failure, (b) corticosteroid use, (c) region, and (d) LUCENT-1 clinical remission status. • Continuous endpoints: treatment comparisons were made using MMRM analysis. When the MMRM was used, it included: (a) treatment group, (b) previous biologic therapy failure status, (c) baseline corticosteroid use, (d) LUCENT-1 clinical remission status, (e) region, (f) baseline value in the model, (g) visit, and (h) the interactions of treatment-by-visit and baseline-by-visit as fixed factors. • Continuous endpoints with a single post-baseline timepoints: treatment comparisons were made using ANCOVA with: (a) treatment group, (b) previous biologic therapy failure status, (c) corticosteroid use, (d) LUCENT-1 clinical remission status, (e) region, and (f) baseline value in the model.
Sample size, power calculation	The study was planned to randomise approximately 1160 patients in a 3:1 ratio of IV mirikizumab 300 mg Q4W to IV placebo, assuming that approximately 1044 patients would complete the study. The power calculations assumed the following: • The randomised study population would include approximately 50% biologic-failed patients and approximately 50% conventional-failed patients. • The predicted clinical remission rates at Week 12 for mirikizumab versus placebo were expected to be 23% versus 7.8% (biologic-failed patients: 16% versus 3.5%; conventional-failed patients: 30% versus 12%). Given the assumptions, a sample size of 1160 patients was expected to provide >90% power to demonstrate	It was assumed that 90% of patients would complete LUCENT-1 and that approximately 470 would enter LUCENT-2 as clinical responders, randomised 2:1 to subcutaneous mirikizumab 200 mg Q4W (313 patients) and subcutaneous placebo (157 patients). Among the approximately 470 mirikizumab clinical responders, approximately 180 were assumed to be clinical remitters. It was assumed that: • The induction study (LUCENT-1, which has a mixed population with approximately 50% biologic-failed patients) was expected to have an overall clinical remission rate of 23% and response rate of 60% with mirikizumab. • 75% of induction patients would receive treatment with mirikizumab, based on a 3:1 randomisation ratio for the induction study. • A 10% dropout rate from induction

	that mirikizumab is superior to placebo in achieving the primary endpoint.	to maintenance. Assuming mirikizumab and placebo clinical remission rates of 47% and 27%, respectively, the study based on the 470 mirikizumab induction responders was expected to have >95% power to demonstrate that mirikizumab is superior to placebo by using a chi-square test with a 2-sided significance level of 0.05. In addition, the sample size was expected to provide adequate power (>80%) to demonstrate that mirikizumab is superior to placebo for endoscopic remission and corticosteroid-free remission at Week 40, among responders to mirikizumab induction treatment by using a chi-square test with a 2-sided significance level of 0.05.
Data management, patient withdrawals	Dropouts and missing data were handled as follows: • Binary endpoints: missing data were imputed using non-responder imputation (NRI).[a] • Continuous endpoints: primary analysis was MMRM using the missing at random assumption for handling missing data. • Patients discontinuing due to an AE: the baseline observation carried forward (mBOCF) method was used. The baseline observation for the endpoint was carried forward to the corresponding visit for all missing observations after the patient discontinued study treatment. • Patients discontinuing for any other reason: mBOCF was used; the last non-missing post-baseline observation before discontinuation was carried forward to the corresponding visit for all missing observations after the patient discontinued. • Patients with sporadically missing observations prior to discontinuation: mBOCF was used; the last non-missing observation before the sporadically missing observation was carried forward to the corresponding visit.	

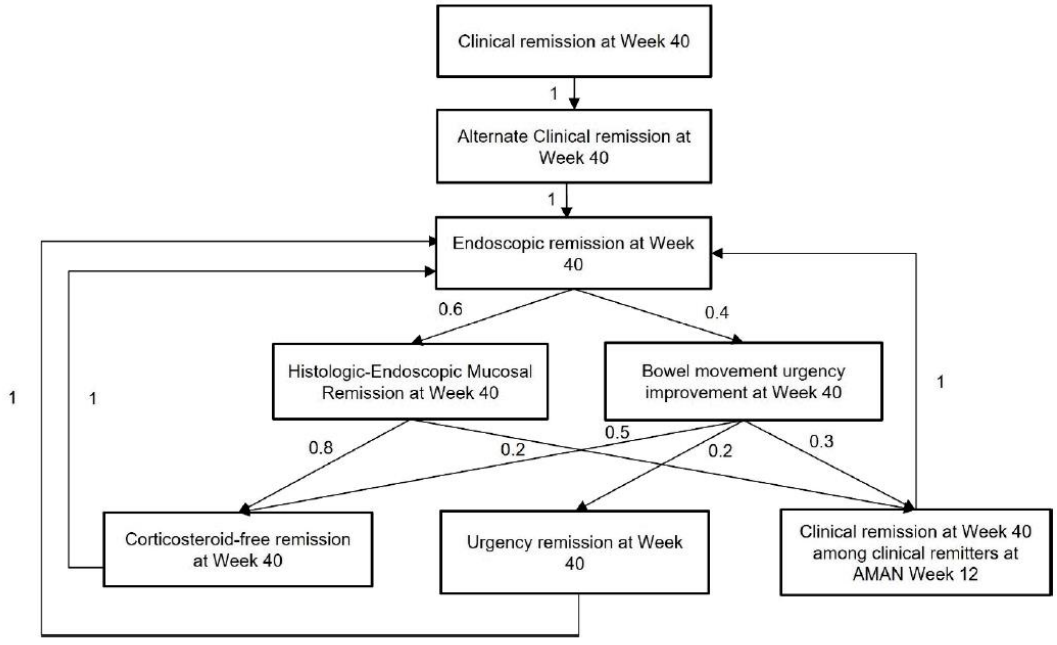
[a]For patients impacted by the eCOA transcription error, modified NRI was used; for more details see Section 5.3.4 of the LUCENT-1 SAP and LUCENT-2 SAP.[84, 85]
Abbreviations: ANCOVA: analysis of covariance; CMH: Cochran–Mantel–Haenszel; eCOA: electronic outcome assessment; mBOCF: modified baseline observation carried forward; MMRM: mixed-effects model for repeated measures; NRI: non-responder imputation; SAP: statistical analysis plan.
Source: Eli Lilly (Data on File): LUCENT-1 Statistical Analysis Plan;[84] Eli Lilly (Data on File): LUCENT-2 Statistical Analysis Plan.[85]

Figure 5: Graphical approach to controlling Type I error rate in LUCENT-1



Source: Eli Lilly (Data on File): LUCENT-1 Statistical Analysis Plan.[84]

Figure 6: Graphical approach to controlling Type I error rate in LUCENT-2



Source: Eli Lilly (Data on File): LUCENT-2 Statistical Analysis Plan.[89]

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 LUCENT-1 and LUCENT-2 is presented in Table 16.

Table 16: Quality assessment results for the LUCENT-1 and LUCENT-2 trials

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

B.3.6 *Clinical effectiveness results of the relevant studies*

Summary of key efficacy outcomes from the LUCENT-1 and LUCENT-2 trials

LUCENT-1:[79]

- Treatment with mirikizumab in the LUCENT-1 trial was associated with improvements in all efficacy outcomes at Week 12 as compared with receipt of placebo.
- Clinical remission at Week 12 was a primary endpoint in LUCENT-1 and in the mITT cohort, a significantly higher proportion of patients receiving mirikizumab achieved clinical remission as compared with those receiving placebo: [redacted]% versus [redacted] %, respectively (99.875% CI: [redacted]). A higher rate of clinical remission was similarly observed in the biologic-naïve and biologic-failed subgroups, although only the former reached statistical significance ([redacted] and [redacted], respectively).
- Similarly, for a major secondary endpoint of clinical response, a significantly greater proportion of patients receiving mirikizumab achieved clinical response at Week 12 as compared with those receiving placebo ([redacted]% versus [redacted], respectively; RD: [redacted]; 98.785% CI: [redacted]) in the mITT cohort. This result remained consistent in the biologic-naïve and biologic-failed subgroups (both [redacted]).
- Bowel urgency was another key secondary endpoint; after 12 weeks of treatment, patients receiving mirikizumab showed significant improvement in bowel urgency as compared with those receiving placebo in the mITT ([redacted]), biologic-naïve ([redacted]) and biologic-failed ([redacted]) groups.
- Furthermore, the statistically significant improvement in bowel urgency associated with mirikizumab treatment as compared with placebo treatment was observed as early as Week 2 in the mITT cohort ([redacted]) and the biologic-failed subgroup ([redacted]), and at

Week 8 in the biologic-naïve subgroup ([redacted]).

LUCENT-2:[80]

- The primary analysis cohort for LUCENT-2 was mirikizumab induction responders: patients who responded to mirikizumab induction dosing at Week 12 of the LUCENT-1 trial who were subsequently re-randomised to mirikizumab 200 mg Q4W or placebo.
- In alignment with the efficacy results observed in the LUCENT-1 trial, treatment with mirikizumab in the LUCENT-2 trial in this cohort demonstrated improvements in all efficacy outcomes at Week 40 compared to those re-randomised to receive placebo.
- At Week 40, mirikizumab induction responders showed significantly greater clinical remission rates ([redacted] versus [redacted]; RD: [redacted]; [redacted]), and this was observed regardless of prior exposure to biologic therapy (biologic-naïve and biologic-failed both [redacted]).
- In patients who had achieved clinical remission with mirikizumab induction therapy in LUCENT-1, a significantly higher proportion maintained clinical remission to Week 40 with mirikizumab treatment as compared with those receiving placebo in the LUCENT-2 study ([redacted] versus [redacted], respectively; RD: [redacted]; 95% CI: [redacted]). In alignment with this, the proportion of patients in receipt of mirikizumab who maintained response was higher than those receiving placebo in both the biologic-naïve and biologic-failed subgroups, although this reached statistical significance only in the latter ([redacted] and [redacted], respectively)
- As compared to placebo, mirikizumab treatment in LUCENT-2 was associated with statistically significant improvements at Week 40 of corticosteroid-free remission in the full mirikizumab induction responder population ([redacted] versus [redacted] respectively; RD: [redacted]; [redacted]). This was similarly observed in both the biologic-naïve and biologic-failed subgroups (both [redacted]).
- Similarly to LUCENT-1, bowel urgency was statistically significantly improved in mirikizumab induction responders receiving mirikizumab as compared with those receiving placebo in the full mirikizumab induction responder population ([redacted]), as well as in the biologic-naïve ([redacted]) and biologic-failed subgroups([redacted]), with improvements maintained to Week 40 ([redacted]).

The Phase III LUCENT-1 and LUCENT-2 trials provide the key source of efficacy and safety data for mirikizumab versus placebo. Efficacy results in this submission are presented for the modified ITT population, the biologic-naïve and biologic-failed populations, as defined in Section B.3.4, from these trials. Presented efficacy results for LUCENT-2 are for the primary study population as defined in Section B.3.4.1: mirikizumab responders from LUCENT-1 who were re-randomised 2:1 to receive mirikizumab or placebo, respectively, throughout LUCENT-2.

The primary and key secondary outcomes for both trials are presented below.[79, 80] Additional secondary outcomes from LUCENT-1 and LUCENT-2 can be found in Appendix M and Appendix N, respectively.

Phase II efficacy and safety results for mirikizumab are not considered in this submission due to the availability of Phase III data but are presented in Sandborn *et al* (2020).[9]

B.3.6.1 LUCENT-1

B.3.6.1.1 Clinical remission at Week 12

Clinical remission rates at Week 12 for patients receiving mirikizumab or placebo in the LUCENT-1 trial are presented in Figure 7. These results show that a higher proportion of patients receiving mirikizumab achieved clinical remission at Week 12 as compared with those receiving

placebo: [redacted] versus [redacted], respectively. This translated to a common risk difference (RD) of [redacted] (99.875% CI: [redacted]) which was statistically significant ([redacted]).

In the biologic-naïve subgroup, the proportion of patients who achieved clinical remission was similarly higher in those treated with mirikizumab compared to the placebo group (RD: [redacted]; 95% CI: [redacted]; [redacted]). Similarly, in the biologic-failed subgroup, a higher rate of clinical remission was achieved by patients receiving mirikizumab than those receiving placebo (RD: [redacted]; 95% CI: [redacted]; [redacted]).

Figure 7: Clinical remission rates at Week 12 (NRI)

Abbreviations: CI: confidence interval; Miri: mirikizumab; NRI: non-responder imputation; PBO: placebo.
Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN.5.1 and AMAN.5.2 (pages 52–53).[79]

B.3.6.1.2 Alternate clinical remission at Week 12

As outlined in Section B.3.3.3, an alternative definition of clinical remission was considered based on feedback from the FDA on the mirikizumab paediatric programme proposal. In LUCENT-1, [redacted] of the mITT population receiving mirikizumab achieved alternate clinical remission at Week 12, as compared with [redacted] patients receiving placebo. The associated RD was [redacted], identical to the RD observed with the primary outcome, which remained statistically significant ([redacted]) (Table 17). Statistically significantly higher rates of alternate clinical remission at Week 12 were also observed with mirikizumab as compared with placebo in the biologic-naïve subgroup (RD: [redacted]; 95% CI: [redacted]; [redacted]) whereas statistical significance was not achieved in the biologic-failed subgroup (RD: [redacted]; 95% CI: [redacted]; [redacted]).

Table 17: Alternative clinical remission rates at Week 12 (NRI)

Population	Response, n/N (%)		Common risk difference vs placebo (CI) [p-value]
	Placebo IV Q4W	Miri 300 mg IV Q4W	
mITT	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

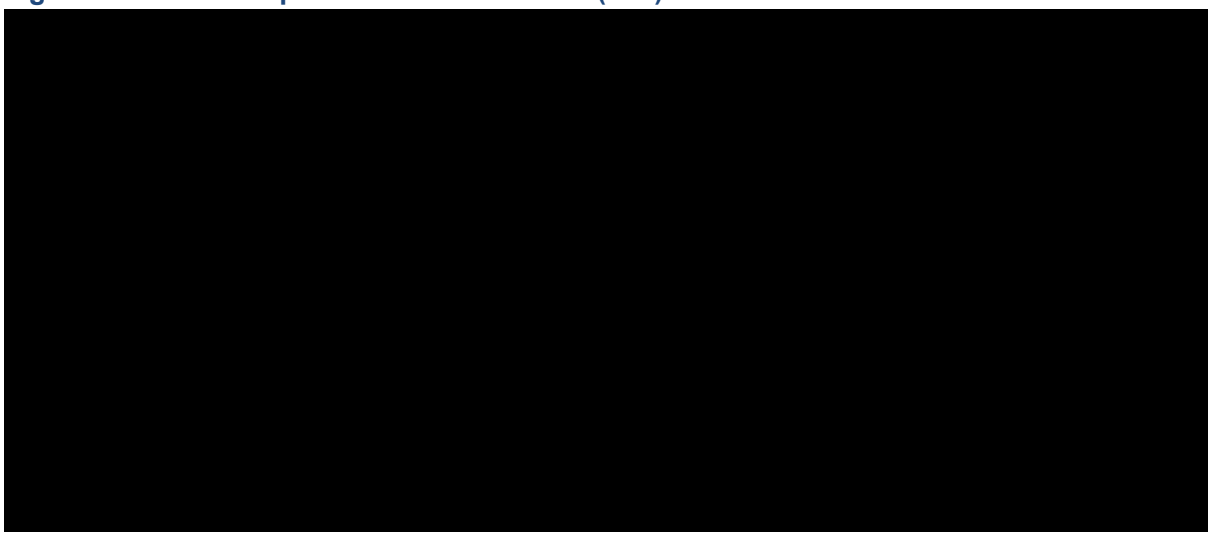
[a] 99.875% CI reported. [b] 95% CI reported.
Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; mITT: modified intent-to-treat; NRI: non-responder imputation; Q4W: every 4 weeks.

Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN.5.3 and AMAN.5.4 (pages 54–55).[79]

B.3.6.1.3 Clinical response at Week 12

At Week 12 of the LUCENT-1 trial, a greater proportion of patients receiving mirikizumab than placebo achieved clinical response: [redacted] versus [redacted] respectively (RD: [redacted]; 98.785% CI: [redacted]), which translated to a statistically significant effect ([redacted]) (Figure 8). Similarly, in both the biologic-naïve and biologic-failed subgroups, a significantly higher proportion of patients achieved clinical response at Week 12 in the group receiving mirikizumab as compared with placebo (both [redacted]).

Figure 8: Clinical response rates at Week 12 (NRI)



Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PBO: placebo.
Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN.5.5 and AMAN.5.6 (pages 55–56).[79]

B.3.6.1.4 Endoscopic remission at Week 12

Endoscopic remission at Week 12, as defined in Section B.3.3.3, was measured in patients receiving mirikizumab or placebo at the end of Week 12 of the LUCENT-1 trial. The results are summarised in Table 18.

Patients in the mITT population receiving mirikizumab showed significantly higher rates of endoscopic remission at Week 12 when compared to those receiving placebo ([redacted] versus [redacted]). The associated RD ([redacted]) was statistically significant (99.875% CI: [redacted]), and remained statistically significant in the subgroups by prior treatment: in the biologic-naïve subgroup, [redacted] of patients receiving mirikizumab achieved endoscopic remission at Week 12 as compared with [redacted] receiving placebo (RD: [redacted]; [redacted]), and in the biologic-failed subgroup, [redacted] of patients in the mirikizumab arm achieved this outcome as compared with [redacted] in the placebo arm (RD: [redacted]; [redacted]).

Table 18: Endoscopic remission rates at Week 12 (NRI)

Population	Response, n/N (%)		Common risk difference vs placebo (CI) [p-value]
	Placebo IV Q4W	Miri 300 mg IV Q4W	
mITT	[redacted]	[redacted]	[redacted]

Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

[a]99.875% CI reported. [b] 95% CI reported.
Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; mITT: modified intent-to-treat; NRI: non-responder imputation; Q4W: every 4 weeks
Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN.5.7 and AMAN.5.8 (pages 57–58).[79]

B.3.6.1.5 Symptomatic remission at Week 12

Considering symptomatic remission, a significantly greater proportion of patients in the mITT population achieved symptomatic remission at Week 12 following mirikizumab treatment as compared with placebo ([redacted] versus [redacted]). This RD was statistically significant (RD: [redacted], [redacted]), as presented in Table 19. This result remained consistent in the prior treatment subgroups, both [redacted].

Table 19: Symptomatic remission rates at Week 12 (NRI)

Population	Response, n/N (%)		Common risk difference vs placebo (CI) [p-value]
	Placebo IV Q4W	Miri 300 mg IV Q4W	
mITT	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

[a] 99.875% CI reported. [b] 95% CI reported
Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; mITT: modified intent-to-treat; NRI: non-responder imputation; Q4W: every 4 weeks
Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN.5.9 and AMAN.5.10 (page 58–59).[79]

B.3.6.1.6 Bowel urgency NRS at Week 12

As presented in Table 20, bowel urgency at Week 12 was found to be statistically significantly improved in patients in the mITT population receiving mirikizumab as compared with those receiving placebo, as assessed by improvements in the Numeric Rating Scale (NRS) from baseline. Patients receiving mirikizumab demonstrated a greater least squares mean (LSM) change from baseline when compared to the corresponding group receiving placebo ([redacted] versus [redacted], respectively). This LSM difference of [redacted] was statistically significant at [redacted]. Similar statistically significant improvements in bowel urgency associated with mirikizumab treatment as compared with placebo were observed in the biologic-naïve subgroup (LSM change from baseline [redacted]; [redacted]) and in the biologic-failed subgroup ([redacted]; [redacted]) at the same timepoint.

As demonstrated in Figure 9, the statistically significant improvement in bowel urgency associated with mirikizumab treatment as compared with placebo treatment was observed as early as Week 2 in the mITT cohort ([redacted]) and the biologic-failed subgroup ([redacted]), and at Week 8 in the biologic-naïve subgroup ([redacted]).

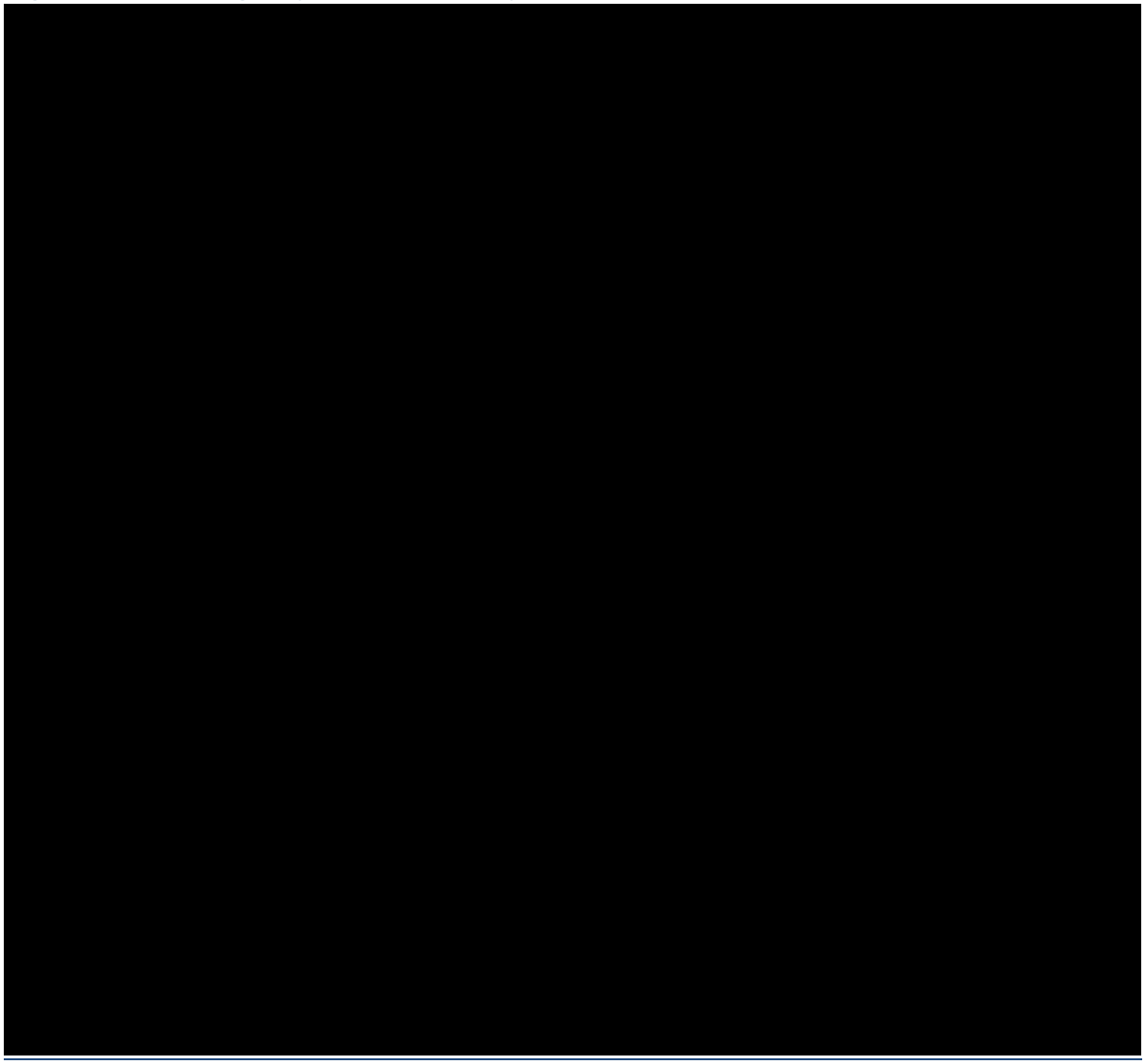
Table 20: Bowel movement urgency NRS change from baseline at Week 12 (MMRM)

Population	LSM change from baseline		LSM change vs placebo (CI) [p-value]
	Placebo IV Q4W	Miri 300 mg IV Q4W	

mITT	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

[a] 99.875% CI reported. [b] 95% CI reported.
Abbreviations: CI: confidence interval; IV: intravenous; LSM: least squares mean; Miri: mirikizumab; mITT: modified intent-to-treat; NRS: numeric rating scale; MMRM: mixed model for repeated measures; Q4W: every 4 weeks; SE: standard error.
Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN.5.11 and AMAN.5.12 (pages 60–61).[79]

Figure 9: Bowel urgency improvement by treatment week (MMRM)



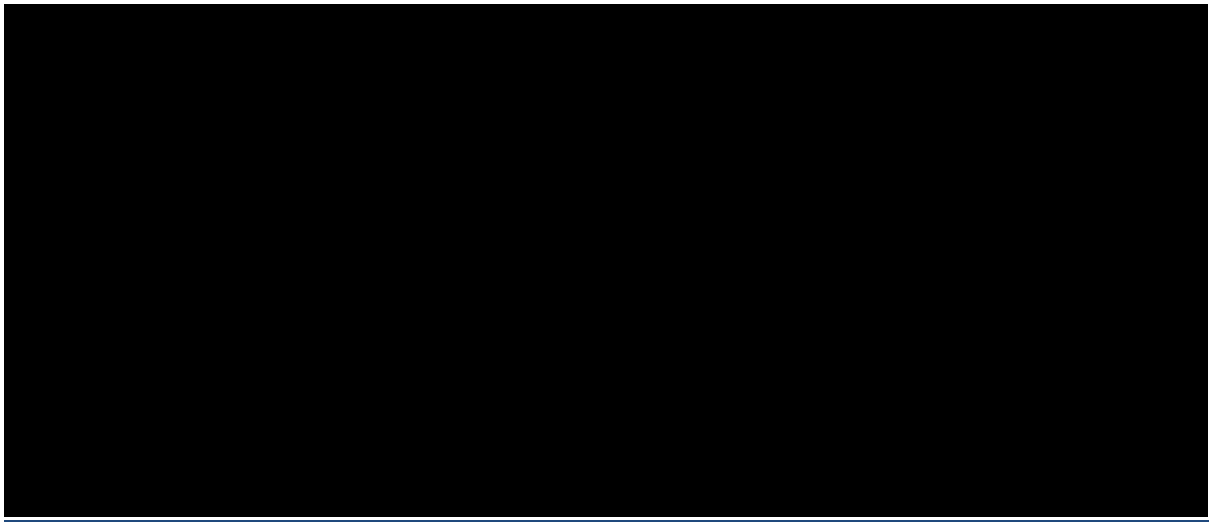
*p≤0.05; **p≤0.01; ***p≤0.001. MMRM analysis performed only for data at scheduled visits ie, Week 2, Week 4, Week 8, and Week 12.
Abbreviations: CI: confidence interval; IV: intravenous; LSM: least squares mean; Miri: mirikizumab; MMRM: mixed-effects model for repeated measures; NRI: non-responder imputation; PBO: placebo.
Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN 8.26 and 8.27 (pages 323 and 326) .[79]

B.3.6.1.7 Histologic-endoscopic mucosal improvement at Week 12

Histological-endoscopic mucosal improvement at Week 12 was compared in the group of mITT patients receiving mirikizumab and the group receiving placebo. Histologic-endoscopic mucosal improvement was defined as having achieved both histological improvement and endoscopic remission, as outlined in Section B.3.3.3.

Results for histologic-endoscopic mucosal improvements at Week 12 of the LUCENT-1 trial are presented in Figure 10. In the mITT population, a statistically significantly greater proportion of patients receiving mirikizumab achieved histological-endoscopic mucosal improvement at Week 12 ([redacted]) as compared to those receiving placebo ([redacted]) (RD: [redacted]; [redacted]). This statistical significance was similarly observed in the biologic-naïve subgroup (RD: [redacted]; [redacted]) and the biologic-failed subgroup (RD: [redacted]; [redacted]).

Figure 10: Histologic-endoscopic mucosal improvement rates at Week 12 (NRI)



Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; PBO: placebo.
Source: Eli Lilly (data on file): LUCENT-1 Clinical Study Report, Tables AMAN.5.13 and AMAN.5.14 (pages 61–62).[79]

B.3.6.2 LUCENT-2

B.3.6.2.1 Clinical remission at Week 40

The proportion of patients who responded to mirikizumab in the LUCENT-1 trial, and were subsequently re-randomised to receive mirikizumab or placebo (mirikizumab induction responders), who achieved clinical remission at Week 40 of the LUCENT-2 trial are presented in Figure 11. In the group receiving mirikizumab, [redacted] of patients achieved clinical remission at Week 40; by comparison, [redacted] of patients receiving placebo achieved clinical remission at the same time point. This translated to a statistically significant benefit for mirikizumab over placebo (RD: [redacted]; [redacted]). This result remained consistent for the biologic-naïve (RD: [redacted]) and the biologic-failed subgroups (RD: [redacted]) (both [redacted]).

Figure 11: Clinical remission rates at Week 40 (NRI)

[a]Including tofacitinib-failed patients.
Abbreviations: CI: confidence interval; NRI: non-responder imputation; SC: subcutaneous.
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.1 and AMBG.5.2 (pages 70 and 71).[80]

B.3.6.2.2 Alternate clinical remission at Week 40

Rates of clinical remission defined using an alternate definition (see Section B.3.3.3) for mirikizumab induction responders at Week 40 of the LUCENT-2 trial are presented in Table 21. In the full mirikizumab induction responder population, [redacted] of patients achieved alternate clinical remission at Week 40, which was significantly higher than the proportion of patients achieving this response following receipt of placebo ([redacted]). This RD ([redacted]) was statistically significant at [redacted]). Additionally, patients receiving mirikizumab were found to have significantly higher rates of alternate clinical response at Week 40 in both the biologic-naïve and biologic-failed subgroups when compared with those receiving placebo (both [redacted]).

Table 21: Alternate clinical remission rates at Week 40 in a randomised withdrawal maintenance period

Population	Mirikizumab induction responders, n/N (%)		Common risk difference vs placebo (95% CI) [p-value]
	Placebo SC Q4W	Miri 200 mg SC Q4W	
Mirikizumab induction responders	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; Miri: mirikizumab; Q4W: every 4 weeks; SC: subcutaneous
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.3 and AMBG.5.4 (pages 72 and 73).[80]

B.3.6.2.3 Maintenance of clinical remission rates at Week 40

In addition to achievement of clinical remission at Week 40 (see Section B.3.6.2.1), the efficacy of mirikizumab versus placebo in maintaining the clinical remission to Week 40 of patients in the LUCENT-2 trial who had achieved clinical remission in LUCENT-1, was measured in the LUCENT-2 study (Figure 12). In the full mirikizumab induction responder population, more patients achieved maintenance of clinical remission at Week 40 in the mirikizumab group as

compared with the group who received placebo ([redacted] versus [redacted], respectively; RD: [redacted]; 95% CI: [redacted]). This translated to a statistically significant benefit for mirikizumab over placebo in maintaining remission in those who have previously responded to treatment ([redacted]). Similarly, the number of patients achieving maintenance of clinical remission at Week 40 were higher in both the biologic-naïve and biologic-failed subgroups. However, this improvement was statistically significant in the biologic-failed subgroup only ([redacted] and [redacted], respectively).

Figure 12: Maintenance of clinical remission at Week 40 (NRI) in a randomised withdrawal maintenance period

Abbreviations: CI: confidence interval; IV: intravenous; Miri: mirikizumab; NRI: non-responder imputation; SC: subcutaneous.
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.7 and AMBG.5.8 (pages 75 and 77).[80]

B.3.6.2.4 Endoscopic remission at Week 40

As compared with those receiving placebo, a statistically significantly greater proportion of mirikizumab induction responders receiving mirikizumab in LUCENT-2 achieved endoscopic remission at Week 40 regardless of previous treatments received (all [redacted]; Table 22). In the full mirikizumab induction responder population, [redacted] and [redacted] of patients receiving mirikizumab and placebo achieved endoscopic remission, respectively (RD: [redacted]). Similarly, in the biologic-naïve and biologic-failed subgroups respectively, [redacted] and [redacted] of patients receiving mirikizumab achieved endoscopic remission as compared with [redacted] and [redacted] patients receiving placebo (RDs: [redacted] and [redacted], respectively; both [redacted]).

Table 22: Endoscopic remission rates at Week 40 (NRI) in a randomised withdrawal maintenance period

Population	Mirikizumab induction responders, n/N (%)		Common risk difference vs placebo (95% CI) [p-value]
	Placebo SC Q4W	Miri 200 mg SC Q4W	
Mirikizumab induction responders	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; Miri: mirikizumab; NRI: non-responder imputation; Q4W: every 4 weeks; SC: subcutaneous

Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.5 and AMBG.5.6 (pages 74 and 75).[80]

B.3.6.2.5 Corticosteroid-free remission without surgery at Week 40

Corticosteroid-free remission without surgery at Week 40 was measured among mirikizumab induction responders. As shown in Table 23, a significantly greater proportion of patients in the full mirikizumab induction responder population achieved corticosteroid-free remission without surgery at Week 40 in the mirikizumab-treatment group as compared with the placebo group ([redacted] versus [redacted], respectively. The resulting RD of [redacted] (95% CI: [redacted]) was statistically significant at [redacted]. This was similarly observed in both the biologic-naïve and biologic-failed subgroups, where statistically significantly more patients attained corticosteroid-free remission without surgery at Week 40 following mirikizumab treatment than placebo treatment (both [redacted]).

Table 23: Corticosteroid-free remission without surgery rates at Week 40 (NRI) in a randomised withdrawal maintenance period

Population	Mirikizumab induction responders, n/N (%)		Common risk difference vs placebo (95% CI) [p-value]
	Placebo SC Q4W	Miri 200 mg SC Q4W	
Mirikizumab induction responders	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; Miri: mirikizumab; NRI: non-responder imputation; Q4W: every 4 weeks; SC: subcutaneous
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.9 and AMBG.5.10 (pages 78 and 79).[80]

B.3.6.2.6 Histologic-endoscopic mucosal remission rates at Week 40

At Week 40, a significantly greater proportion of mirikizumab induction responders who received mirikizumab in LUCENT-2 achieved histologic-endoscopic mucosal remission as compared with those receiving placebo: [redacted] of patients in the mirikizumab arm as compared with just [redacted] in the placebo group (RD: [redacted]; [redacted]) (Figure 13). The same result was observed when considering the biologic-naïve and biologic-failed subgroups: the RDs of [redacted] and [redacted], respectively, were both statistically significant at [redacted].

Figure 13: Histologic-endoscopic mucosal remission rates at Week 40 (NRI) in a randomised withdrawal maintenance period

Abbreviations: CI: confidence interval; Miri: mirikizumab; NRI: non-responder imputation; PBO: placebo; SC: subcutaneous.
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.11 and AMBG.5.12 (pages 80 and 81).[80]

B.3.6.2.7 Bowel urgency NRS improvement at Week 40

Bowel movement urgency numeric rating scale (NRS) improvement was measured among mirikizumab induction responders in LUCENT-2. At Week 40, patients in the full mirikizumab induction responder population receiving mirikizumab had a significantly greater reduction in bowel movement urgency when compared to those receiving placebo (LSM change: [redacted]; [redacted]) (Table 24). At the same timepoint, similar improvements in bowel movement urgency were observed with mirikizumab treatment in the biologic-naïve (LSM change: [redacted]) and biologic-failed (LSM change: [redacted]), with both reaching statistical significance ([redacted] and [redacted], respectively).

As demonstrated in Figure 14, the statistically significant improvement in bowel urgency associated with mirikizumab treatment as compared with placebo treatment in the full mirikizumab induction responder population was observed to Week 40 ([redacted]).

Table 24: Bowel movement urgency NRS improvement (change from induction baseline) at Week 40

Population	LSM change from baseline (SE)		LSM change vs placebo (95% CI) [p-value]
	Placebo SC Q4W	Miri 200 mg SC Q4W	
Mirikizumab induction responders	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; LSM: least squares mean; Miri: mirikizumab; NRS: numeric rating scale; Q4W: every 4 weeks; SC: subcutaneous; SE: standard error
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.13 and AMBG.5.14 (pages 82 and 83).[80]

Figure 14: Bowel urgency improvement by treatment week in induction responders (MMRM, full mirikizumab induction responder population)

*p<0.05; **p<0.01; ***p≤0.001.
Abbreviations: CI: confidence interval; LSM: least squares mean; Miri: mirikizumab; MMRM: mixed-effects model for repeated measures; NRI: non-responder imputation; PBO: placebo; SC: subcutaneous.
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.33, page 377.[81]

B.3.6.2.8 Bowel urgency remission at Week 40 among clinical responders with urgency NRS ≥3 at induction baseline

Bowel urgency remission at Week 40, defined as a score of 0 or 1 in the urgency NRS, was measured amongst clinical responders who had an urgency NRS of ≥3 at induction baseline. As shown in Table 25, a statistically greater proportion of patients in the full mirikizumab induction responder mirikizumab group achieved urgency remission at Week 40 as compared with those in the placebo group ([redacted] versus [redacted], respectively; RD: [redacted]; [redacted]). Similar results were observed when considering the biologic-naïve and biologic-failed subgroups, with mirikizumab showing higher rates of urgency remission at Week 40 compared with placebo in both populations (RD: [redacted] and [redacted], respectively). In line with the full mirikizumab induction responder population, this result was statistically significant for both subgroups ([redacted] and [redacted], respectively).

Table 25: Urgency remission (urgency NRS=0 or 1) at Week 40 (NRI) in a randomised withdrawal maintenance period in patients with urgency NRS ≥3 at induction baseline

Population	Mirikizumab induction responders, n/N (%)		Common risk difference vs placebo (95% CI) [p-value]
	Placebo SC Q4W	Miri 200 mg SC Q4W	
Mirikizumab induction responders	[redacted]	[redacted]	[redacted]
Biologic-naïve	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; Miri: mirikizumab: NRI: non-responder imputation; NRS: numeric rating scale; Q4W: every 4 weeks; SC: subcutaneous
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report, Tables AMBG.5.15 and AMBG.5.16 (pages 84 and 85).[80]

B.3.6.2.9 Efficacy in patients with loss of response Symptomatic response and remission rates through the re-induction period

As an additional analysis, patients who achieved a clinical response in the LUCENT-1 trial, regardless of treatment allocation, but subsequently lost clinical response during the LUCENT-2 trial entered the Loss of Response (LOR) rescue period where they received open-label re-induction therapy: three doses of 300 mg intravenous mirikizumab (Q4W). This period is referred to throughout this document as the "re-induction" period, but, as noted in Section B.3.4.1, is referred to as "rescue therapy" throughout the LUCENT-2 CSR.

Among the mirikizumab induction responders, [redacted] patients in the placebo group lost response during the Maintenance Period and entered the re-induction period. After receiving at least one dose of open-label IV mirikizumab re-induction, by Week 12 of the re-induction period, [redacted] ([redacted]%) regained symptomatic response (Table 26) and [redacted] ([redacted]%) achieved symptomatic remission (Figure 15).

Additionally, [redacted] patients in the mirikizumab-treatment group lost response during the Maintenance Period and entered the re-induction period. After receiving at least one dose of open-label IV mirikizumab re-induction, by Week 12 of the re-induction period, [redacted] ([redacted]%) regained symptomatic response (Table 26) and [redacted] ([redacted]%) achieved symptomatic remission (Figure 15).

Table 26: Symptomatic response rates through the re-induction (NRI)

	Response, n (%) [95% CI]			
	Placebo responder Placebo SC (N=[redacted])	Mirikizumab responder Placebo SC (N=[redacted])	Mirikizumab responder 200 mg Miri SC (N=[redacted])	Mirikizumab responder, total (N=[redacted])
LOR Week 4	[redacted]	[redacted]	[redacted]	[redacted]
LOR Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; Miri: mirikizumab; SC: subcutaneous.
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.102. (page 1106).[81]

Figure 15: Symptomatic remission rates through the re-induction period (NRI)

Abbreviations: NRI: non-responder imputation; SC: subcutaneous.
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG 8.101. (page 1101).[81]

B.3.6.2.10 Efficacy in mirikizumab induction non-responders

As an additional analysis, patients who did not achieve clinical response to blinded mirikizumab or blinded placebo in LUCENT-1 were entered into LUCENT-2 and received open-label extended induction therapy with 300 mg mirikizumab IV at Weeks 0, 4, and 8, and underwent delayed clinical response assessment via endoscopy at Week 12 of LUCENT-2. The results from these additional analyses are presented below.

Clinical remission

Clinical remission for LUCENT-1 non-responders in the mITT population was measured at Week 12 of the LUCENT-2 trial (Table 27). At this timepoint, following three initial doses of 300 mg, open-label IV mirikizumab therapy in LUCENT-2, [redacted]% of patients previously treated with placebo in LUCENT-1 achieved clinical remission, while [redacted]% of patients previously treated with mirikizumab demonstrated clinical remission.

Table 27: Clinical remission at 12 Weeks (NRI) in an open-label extended induction period (mITT population)

	Mirikizumab 300 mg IV Q4W	
	Placebo induction non-responders, N=133	Mirikizumab induction non-responders, N=272
Response, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IV: intravenous; mITT: modified intent-to-treat; n: number of patients responding within each specific category; N: total number of patients in the population; NRI: non-responder imputation; Q4W: every 4 weeks
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.94 (page 1084).[81]

Clinical response

Clinical response rates for LUCENT-1 non-responders in the mITT population was measured at Week 12 of the LUCENT-2 trial (Table 28). At this timepoint, following 3 initial doses of 300 mg, open-label IV mirikizumab therapy in LUCENT-2, [redacted]% of patients treated with placebo in

LUCENT-1 achieved a clinical response and [redacted]% of patients previously treated with mirikizumab.

Table 28: Clinical response rates at 12 Weeks (NRI) in an open-label extended induction period (mITT population)

	Mirikizumab 300 mg IV Q4W	
	Placebo induction non-responders, N=133	Mirikizumab induction non-responders, N=272
Response, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IV: intravenous; mITT: modified intent-to-treat; n: number of patients responding within each specific category; N: total number of patients in the population; NRI: non-responder imputation; Q4W: every 4 weeks
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.93 (page 1082).[81]

Endoscopic remission

Endoscopic remission for LUCENT-1 non-responders in the mITT population was measured at Week 12 in the LUCENT-2 trial (Table 29). At this timepoint, following 3 initial doses of 300 mg, open-label IV mirikizumab therapy in LUCENT-2, [redacted]% of patients treated with placebo in LUCENT-1 achieved endoscopic remission as compare with [redacted]% of patients previously treated with mirikizumab.

Table 29: Endoscopic remission at 12 Weeks (NRI) in an open-label extended induction period (mITT population)

	Mirikizumab 300 mg IV Q4W	
	Placebo induction non-responders, N=133	Mirikizumab induction non-responders, N=272
Response, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IV: intravenous; mITT: modified intent-to-treat; n: number of patients responding within each specific category; N: total number of patients in the population; NRI: non-responder imputation; Q4W: every 4 weeks
Source: Eli Lilly (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.95 (page 1086).[81]

B.3.7 *Subgroup analysis*

The pre-specified subgroup analyses relevant to the decision problem (previous systemic therapy and previous biologic therapy) are presented in Section B.3.6. No additional subgroup analyses are considered.

B.3.8 *Meta-analysis*

The pre-planned analyses of clinical efficacy from the LUCENT-1 and LUCENT-2 trials are presented in Section B.3.6. A meta-analysis was not conducted as there was no head-to-head comparison between mirikizumab and the comparators within the scope of this submission. A network meta-analysis was conducted and is presented in Section B.3.9.6.

B.3.9 *Indirect and mixed treatment comparisons*

In the absence of RCTs providing direct head-to-head data, network meta-analyses (NMAs) to compare the efficacy and safety of mirikizumab with comparators were performed and are presented below. As outlined in Section B.1.1, ustekinumab and vedolizumab have been selected as the reference comparators for the cost-comparison analysis. However, indirect efficacy and safety data for mirikizumab versus a range of comparators are provided for completeness, with the relative efficacy data for ustekinumab and vedolizumab discussed in Section B.3.9.6 and considered further in the subsequent economic analysis presented in Section B.4.

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 the two populations of interest (biologic-naïve and biologic-failed) and analyses of safety outcomes were performed for the overall trial population regardless of prior exposure to biologic therapy for reasons described in Section B.3.9.3.1). In alignment with the approach outlined in Section B.1.1 and with the definition of "biologic-failed" patients within the pivotal LUCENT trials, the "biologic-failed" subgroup considered in these NMA analyses encompassed prior failed with JAKi as well as with a biologic therapy such as a TNFi.

B.3.9.1 Identification and selection of relevant studies

The basis for the NMA was an SLR originally conducted on 12th November 2018 which has since been continuously updated to identify newly published studies of interest; the most recent update was conducted in June 2022. Full details on the methodology and results of the SLR, including a full list of search dates, are presented in Appendix D. The onrolling SLR periodically updates the evidence base to account for new studies and changes in approved treatment regimens and dosages.

The objectives of the SLR were to identify all eligible RCT evidence on relevant treatments for patients with moderately to severely active UC to inform the NMA of mirikizumab versus the respective treatment comparators. The scope of the SLR included RCT evidence for adult patients with moderately or severely active disease as defined by the Mayo score or by UC-DAI (further details of the study eligibility criteria are presented in Appendix D.1.3).

To date, a total of 68 unique studies have been included. A summary of the overall SLR search results alongside a PRISMA flow diagram is presented in Appendix D.1.4.1. In addition, while Phase II data for mirikizumab were identified in the SLR, data for the Phase III LUCENT-1 and LUCENT-2 trials were not published at the time of the latest SLR searches and were therefore provided by Lilly as data on file. Further, the PURSUIT-SC study of golimumab identified in the SLR as one study reported on two separate Phase II and Phase III studies and was therefore considered as two studies for the purpose of the NMA feasibility assessment. Thus, a total of 71 studies were considered for inclusion in the NMA and were investigated in the feasibility assessment presented below.

B.3.9.2 Feasibility assessment

The comparability of the evidence identified from the 71 studies included in the SLR was investigated extensively through a NMA feasibility assessment prior to the conduct of the analyses. Heterogeneity with respect to patient characteristics, interventions, outcomes, and

study design were assessed and the potential implications of identified differences is summarised in sections below, and further details for each section are provided in Appendix D.1.6.1.

B.3.9.2.1 Population

As the patient population eligibility criteria for the SLR stipulated that patients must have moderately to severely active UC, as defined by the Mayo score or by UC-DAI, all studies included in the SLR have a patient population relevant for inclusion in the NMA.

A summary of the key baseline characteristics (such as age, the proportion of males, disease duration, baseline Mayo score and the proportion receiving concomitant glucocorticoids and/or immunosuppressants) of studies included in the NMA, by population (biologic-naïve or failed) and timepoint (induction or maintenance), are presented in Section 1.3 of the NMA report appendices, as provided in the reference pack. In addition, Section 1.4 of the NMA report appendices presents a summary of the reported imputation methods used by study.

A number of population and trial characteristics have previously been shown to impact placebo response rates (or baseline risk) within trials of patients with ulcerative colitis, including study location (European versus non-European) and duration of the induction phase, disease status, disease duration, and prior exposure to biologic therapy at enrolment.[90-93] To reduce heterogeneity observed across population characteristics discussed above, and aligning with the LUCENT trial populations, subgroup populations were considered for the NMA and were evaluated where the evidence base allowed as described in Section B.3.9.3.1. In addition, placebo response rates across trials identified for inclusion in the NMA were explored as is further described in Appendix D.1.6.2.

B.3.9.2.2 Study design

Induction

Of the 68 studies identified in the SLR, 28 compared an EMA or FDA approved dosing regimen (see Section B.3.9.2.3 and Appendix D.1.6.1) with another approved dosing regimen or placebo over the induction period. In addition, data for LUCENT are not yet published and thus were not identified by the SLR but were provided by Lilly as data on file and were also included in the feasibility assessment. Further, the study PURSUIT SC was considered as two separate studies (Phase II and Phase III) for the purpose of the feasibility assessment. Thus, a total of 30 induction studies were considered for inclusion in the NMA.

Most studies were multi-regional, with only 5 single-centre studies identified, 4 of which were conducted in Japan (3) and China (1). All included studies were double-blinded, however, substantial differences in sample size were observed ranging from 20 (Probert et al., 2003) to [redacted] patients (LUCENT). In addition, differences in length of induction periods varied across studies from 6 to 14 weeks, as presented in Appendix D.1.5.

Maintenance

Of the 68 studies identified in the SLR, 21 compared an EMA or FDA approved dosing regimen (see Section B.3.9.2.3 and Appendix D.1.6.1) with another approved dosing regimen or placebo over the maintenance period. Again, LUCENT was also included in the feasibility assessment, thus, a total of 22 maintenance studies were considered for inclusion in the NMA.

Most studies were multinational, with 6 single-centre studies identified, all of which were conducted in Japan (5) and China (1). All included studies were double-blinded, however, again substantial differences in sample size were observed ranging from 31 (PURSUIT-J) to 386 patients (VARSITY).

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 such as those of infliximab (ACT 1) and adalimumab (ULTRA 2) are randomised at baseline and outcomes are measured after induction and maintenance treatment phases. Patients in re-randomised responder trials on the other hand, continue to maintenance only if they had responded to induction treatment. The induction phase responders are re-randomised to the intervention or placebo/active comparator at maintenance doses. This trial design is more commonly used to evaluate newer treatments such as vedolizumab (GEMINI 1), tofacitinib (OCTAVE sustain), golimumab (PURSUIT), ustekinumab (UNIFI), upadacitinib (U-ACHIEVE), ozanimod (TRUE NORTH), filgotinib (SELECTION) and mirikizumab (LUCENT).

A summary of the included studies and the timepoint of assessment is provided in Appendix D.1.5. The approach to account for heterogeneity arising from these alternative trial designs, and from the timepoint of assessment in the maintenance phase, is discussed in Appendix D.1.6.1.

B.3.9.2.3 Approved doses and regimens for treatment and comparators

All EMA and FDA approved doses and regimens of targeted therapies for the treatment of moderately to severely active UC were included in the NMA. Different dosing arms of the same drug were treated as individual comparators within the NMA, and 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 27 in Appendix D.1.6.1, and a list of all excluded studies, alongside reasons for exclusion, is provided in Table 26 in Appendix D.1.5.

B.3.9.2.4 Outcomes of interest

The primary goal of treatment for UC is to induce and maintain remission. Rates of clinical response and clinical remission are the most consistently reported outcomes across studies and are the most relevant efficacy parameter in UC to allow comparative analysis. Therefore, the NMA evaluated clinical response and remission for both induction and maintenance phase. Based on the previous HTA submissions and more recently published trials mucosal healing/endoscopic remission emerged as relevant outcome to assess efficacy.[3, 54, 61, 94, 95] To capture and compare the safety profiles of approved regimens to mirikizumab, all cause discontinuation and incidence of severe adverse events (SAEs) during the induction phase were analysed. The definition of the efficacy and safety endpoints are as per the clinical trials. Across the included trials the definitions were deemed as heterogenous. An overview of the trial definitions per outcome is presented in sections below.

Efficacy Outcomes

Clinical response (induction and maintenance)

In total, 30 induction studies and 15 maintenance studies reported clinical response. The most commonly reported definition of clinical response in both the induction and maintenance networks was a total Mayo score decrease of ≥3 points and ≥30% from baseline accompanied by

a decrease in the rectal bleeding subscore of ≥1 point or an absolute score of 0 or 1. The definitions of clinical response implemented in trials in the induction and maintenance networks are presented in Table 28 (induction) and Table 29 (maintenance) in Appendix D.1.6.1.

Clinical remission (induction and maintenance)

In total, 31 studies reported clinical remission for the induction phase and 24 studies reported clinical response for the maintenance phase. The most commonly reported definition of clinical remission in both networks, reported by 17 studies in the induction NMA and by 15 studies in the maintenance NMA, was a total Mayo score of ≤2 points with no individual subscore >1. The definitions of clinical remission implemented in trials in the induction and maintenance networks are presented in Table 30 (induction) and Table 31 (maintenance) in Appendix D.1.6.1.

Mucosal healing (induction and maintenance)

Terminology around mucosal healing and endoscopic improvement are often used interchangeably across studies. In addition, definitions of mucosal healing may differ. For the purpose of the NMA, the definition of mucosal healing was aligned with the definition used in the LUCENT trials: “Endoscopic subscore of 0 or 1”. In total, 13 induction studies used this definition when reporting on mucosal healing while 7 induction studies used this definition when reporting on endoscopic improvement. For the maintenance phase, mucosal healing was uniformly reported by 12 studies.

Safety outcomes

Due to different trial designs for the maintenance phase (outlined in Section B.3.9.2.2), patients with UC can be assigned to placebo or active treatment for the full length of the trial (treat-through trials) and patients responding to active treatment after induction are re-randomised to active treatment, or placebo (withdrawal). In order to limit the exposure to inactive placebo in re-randomised response-based trials, there are variations in the maintenance treatment received following induction with placebo:

- Placebo induction responders are continued on placebo (UNIFI and PURSUIT studies)
- Placebo induction responders are re-randomised and placebo induction non-responders are treated separately (OCTAVE Sustain)
- Placebo induction responders and non-responders continue on placebo (GEMINI)

As a result, the ‘placebo’ safety population of these trials consist of various ‘placebo’ patients which differ due to the trial designs mentioned above. Therefore, for the safety outcomes, only all cause discontinuation (lack of efficacy, DAEs) and SAEs (adverse events grade 3–4) during the induction phase were considered to be of relevance.

B.3.9.2.5 Summary of trials included in the NMA

Included studies

In total, the NMA included 37 studies from the total of 71 identified in the SLR. For the induction study period, 21 and 13 studies reported data for at least one efficacy outcome for the biologic-naïve and biologic-failed populations, respectively. Further, 21 studies reported data for at least one safety outcome for the overall population (regardless of prior biologic exposure). For the

maintenance study period, 15 and 11 studies reported data for at least one efficacy outcome for the biologic-naïve and biologic-failed populations, respectively.

The studies included in the induction and maintenance NMAs, and their full publication references, are provided in Tables 21 and 22 in Appendix D.1.5, respectively, and an overview of these included studies by population and outcome of interest is presented in Table 23 (induction) and Table 24 (maintenance) in Appendix D.1.5. A summary of the prior biologic therapy population definitions included in the NMA, where reported in the study publications, is presented in Table 25 in Appendix D.1.5.

Excluded studies

Following the NMA feasibility assessment, 34 studies were excluded from the NMA. Most (32 studies) were excluded because they evaluated an intervention and/or comparator which was not an EMA or FDA approved dosing regimen. Other reasons for exclusion from the NMA were relating to population: the RIVETING study (Vermeire et al., 2020) recruited patients who had received tofacitinib for two years and were in stable remission for six months prior to study entry, and the TOUCHSTONE study (Sandborn et al., 2016) did not present outcome data by subgroups for prior exposure to biologic treatment. A list of excluded studies, including further details of reasons for exclusion by study, is presented in Table 26 in Appendix D.1.5.

B.3.9.3 Methodology

All NMAs were conducted under a Bayesian framework. NMAs of clinical response and remission were performed using a multinomial model with probit link, and a binomial model with logit link was used for NMAs of mucosal healing, all cause discontinuations, and serious adverse events. For each analysis (summarised in Table 30 and presented in full in Appendix D.1.7.1) both fixed effect and random-effects models were considered and are presented in Section B.3.9.4 below, Appendix D.1.10 and Section 2 of the NMA report appendices provided as part of the reference pack (additional results) and Section 3 of the NMA report approaches (supplementary analyses). Results from the best fitting model are reported for each outcome, population and timepoint combination.

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.1.7.6.

In addition to the base case analyses, for NMAs of maintenance of clinical response and remission, sensitivity analyses were performed restricting the evidence base of re-randomised studies only (i.e., excluding treat-through studies). Exploratory analyses for baseline risk adjustment using meta-regression models were also conducted in recognition of differences in placebo response observed across trials of UC. Results from the best fitting model for each outcome, population and timepoint combination are reported throughout this section and Appendix D.1.10. Additional sensitivity analyses are presented in Sections 3.1 and 3.2 of the NMA report appendices provided in the reference pack.

Table 30: NMA models used in the base case analysis

Population	Timepoint	Outcome	Statistical model
Biologic naïve	Induction	Clinical response and remission	Multinomial model with ordered categories

		Mucosal healing	Binomial model
	Maintenance	Clinical response and remission	Multinomial model with ordered categories
		Mucosal healing	Binomial model
Biologic failed[a]	Induction	Clinical response and remission	Multinomial model with ordered categories
		Mucosal healing	Binomial model
	Maintenance	Clinical response and remission	Multinomial model with ordered categories
		Mucosal healing	Binomial model
Overall/mixed[b] population	Induction	All cause discontinuations	Binomial model
		SAEs	Binomial model

[a] Reported definitions "Biologic/JAKi experienced", "Biologic/JAKi non-failure" and "Biologic/JAKi failure" were grouped as "biologic-failed", as outlined in Section B.3.9.3.1.
[b] Mixed population with regards to prior medication
Abbreviations: NMA: network meta-analysis; SAE: serious adverse event.

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: biologic-naïve and biologic-failed. These subgroups were defined as follows:

- Biologic-naïve: patients who had not received any prior biologic, including a JAKi. This could be the overall trial population (if trial eligibility specified) or a subgroup of the overall trial population.
- Biologic-failed: patients who had failed previous biologic therapy, including with a JAKi. This could be the overall trial population (if trial eligibility specified) or a subgroup of the overall trial population.

Subgroup analyses were also considered to stratify patients according to number of prior biologics used (e.g., patients who failed at least one biologic or JAK-inhibitor versus patients who failed more than one biologic or JAKi), but such subgroup data were only identified for trials of filgotinib. Thus, NMAs for this subgroup were not feasible. In addition to the NMA assessing efficacy outcomes, a NMA of safety outcomes was also conducted. However, as per CONSORT recommendations, these outcomes are most commonly reported for the intention-to-treat (ITT) population, rather than separately by prior therapy, hindering the analyses to account for prior biologic exposure. As such, the safety NMA considered overall trial population (e.g., mixed biologic-naïve and biologic-failed patients) in a single analysis. Further, as described in Section B.3.9.2.4, safety outcomes were assessed at the end of the induction period only, due to heterogeneity in the definition of 'placebo' safety population within maintenance trials.

B.3.9.3.2 Explorative analysis for baseline risk adjustment

Several studies have presented the importance of investigating, and when appropriate, analytically accounting for between-study heterogeneity.[96-99] Differences in placebo response rates (or baseline risk) across UC trials have been reported previously.[90-93, 100] Placebo event rates for additional outcomes of interest across included studies for induction and maintenance by population (biologic-naïve and biologic-failed) are presented in Appendix D.1.6.2. Additional

placebo event rates are presented in Section 1.2 of the NMA report appendices provided in the reference pack.

B.3.9.4 Results

The results of the NMAs are presented in the subsections which follow, further broken down 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 (fixed effects and random effects) are presented in Appendix D.1.10.1 (efficacy outcomes, biologic-naïve population), D.1.10.2 (efficacy outcomes, biologic-failed population) and D.1.10.3 (safety outcomes, overall population). Results from all sensitivity and exploratory analyses are presented in Sections 3.1 and 3.2 of the NMA report appendices in the reference pack.

Abbreviated treatment labelling was used in all figures presented in the NMA, a summary of which is presented in Table 33 in Appendix D.1.10.

B.3.9.4.1 Efficacy outcomes (biologic-naïve population)

Induction

Clinical response and remission

The network diagram, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the induction period of the biologic-naïve population are presented in Appendix D.1.10.1. Model fit statistics can be found in Section 2.1.1.1 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.1, primary results for clinical response and remission during the induction period for the biologic-naïve population described in this section were derived from the random effects model (**without** baseline risk adjustment); the complementary results with baseline risk adjustment are presented in Section 3.1.1 of the NMA report appendices, as provided in the reference pack.

[redacted] (see Figure 16 and Figure 17).

Figure 16: All pairwise odds ratios with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: clinical response, induction, biologic-naïve 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 17: All pairwise odds ratios with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: clinical remission, induction, biologic-naïve population

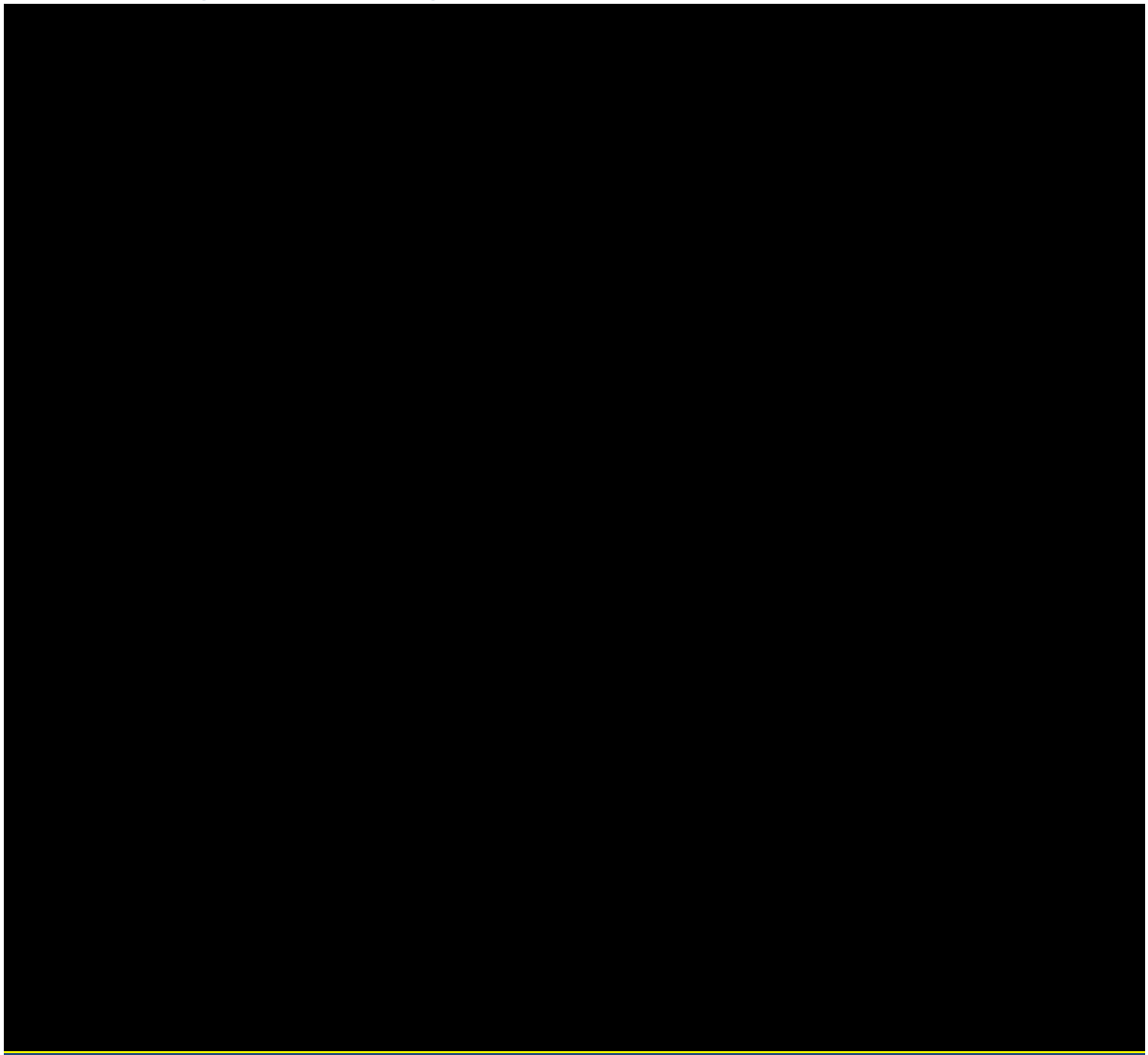
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and ORs for all active treatments, including mirikizumab, versus placebo for mucosal healing during the induction period of the biologic-naïve population are presented in Appendix D.1.10.1. Model fit statistics can be found in Section 2.1.1.2 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.1, primary results for mucosal healing during the induction period for the biologic-naïve population described in this section were derived from the random effects model (**with** baseline risk adjustment).

[redacted] (Figure 18).

Figure 18: Odds ratios with random treatment effects with baseline risk meta-regression and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: mucosal healing, induction, biologic-naïve 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Maintenance

Clinical response and remission

The network diagram, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the maintenance period of the biologic-naïve population are presented in Appendix D.1.10.1. Model fit statistics can be found in Section 2.1.2.1 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.1, primary results for clinical response and remission during the maintenance period for the biologic-naïve population described in this section were derived from the fixed effect model (**with** baseline risk adjustment); the complementary results without baseline risk adjustment are presented in Section 3.2.1 of the NMA report appendices, as provided in the reference pack.

[redacted] (Figure 19 and Figure 20).

Complete results for the sensitivity analysis of clinical response and remission including only re-randomised studies of the biologic-naïve population at maintenance are also provided in Section 2.1.2.2 of the NMA report appendices, provided in the reference pack.

Figure 19: Odds ratios with fixed treatment effects with baseline risk meta-regression: clinical response, maintenance, biologic-naïve 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 20: Odds ratios with fixed treatment effects with baseline risk meta-regression: clinical remission, maintenance, biologic-naïve 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for mucosal healing during the maintenance period of the biologic-naïve population are presented in Appendix D.1.10.1. Model fit statistics can be found in Section 2.1.2.3 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.1, primary results for mucosal healing during the maintenance period for the biologic-naïve population described in this section were derived from the fixed effects model (**with** baseline risk adjustment).

As shown in Figure 21, [redacted].

Figure 21: All pairwise odds ratios with fixed treatment effects with baseline risk meta-regression: mucosal healing, maintenance, biologic naïve 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

B.3.9.4.2 Efficacy outcomes (biologic-failed population)

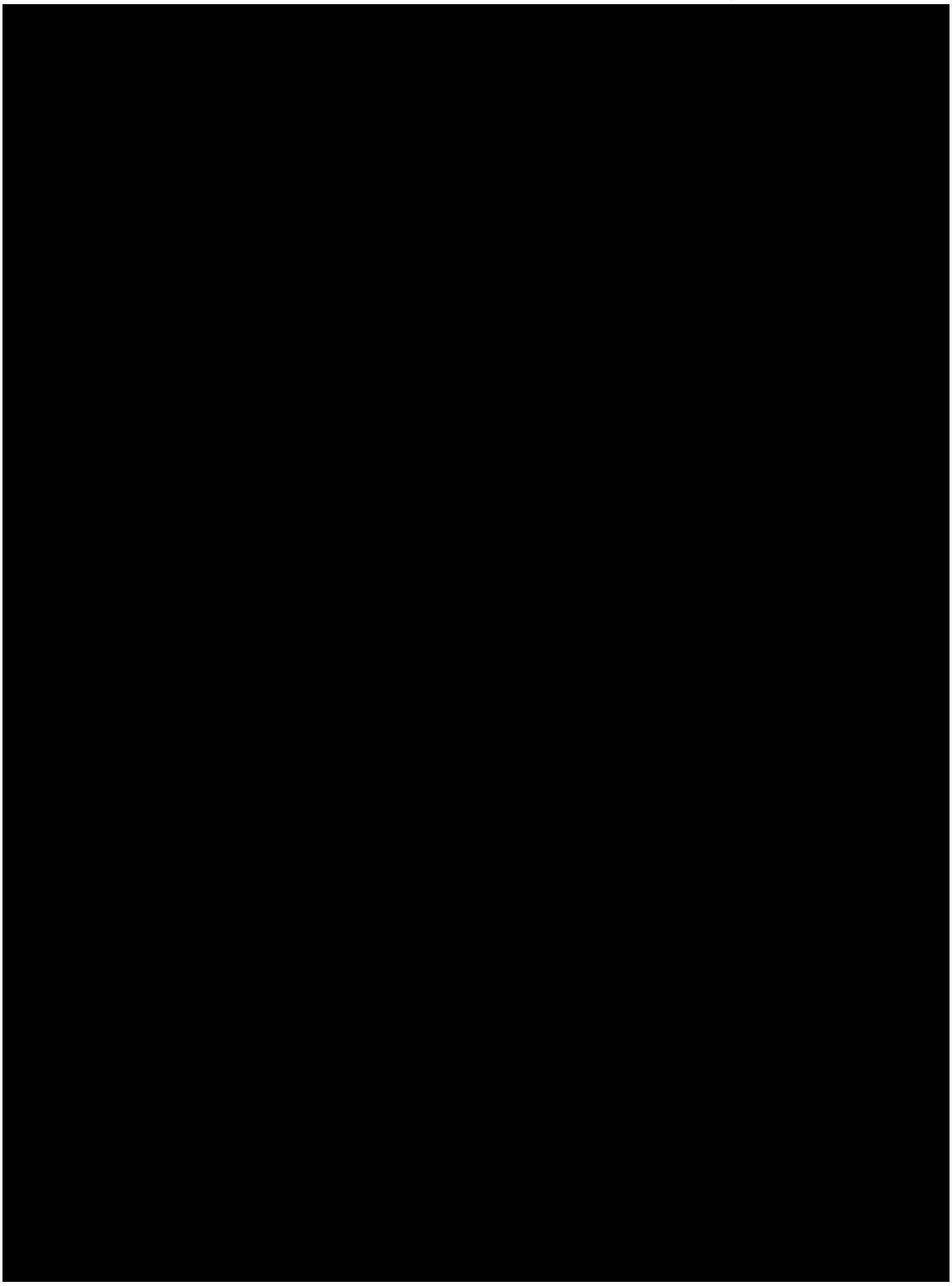
Induction

Clinical response and remission

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the induction period of the biologic-failed population are presented in Appendix D.1.10.2. Model fit statistics can be found in Section 2.2.1.1 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.2, primary results for clinical response and remission during the induction period for the biologic-failed population described in this section were derived from the fixed effect model (**without** baseline risk adjustment); the complementary results with baseline risk adjustment are presented in Section 3.1.2 of the NMA report appendices, as provided in the reference pack.

[redacted] (Figure 22).

Figure 22: All pairwise odds ratios with fixed treatment effects (response and response with remission): clinical response and remission, induction, biologic-failed population



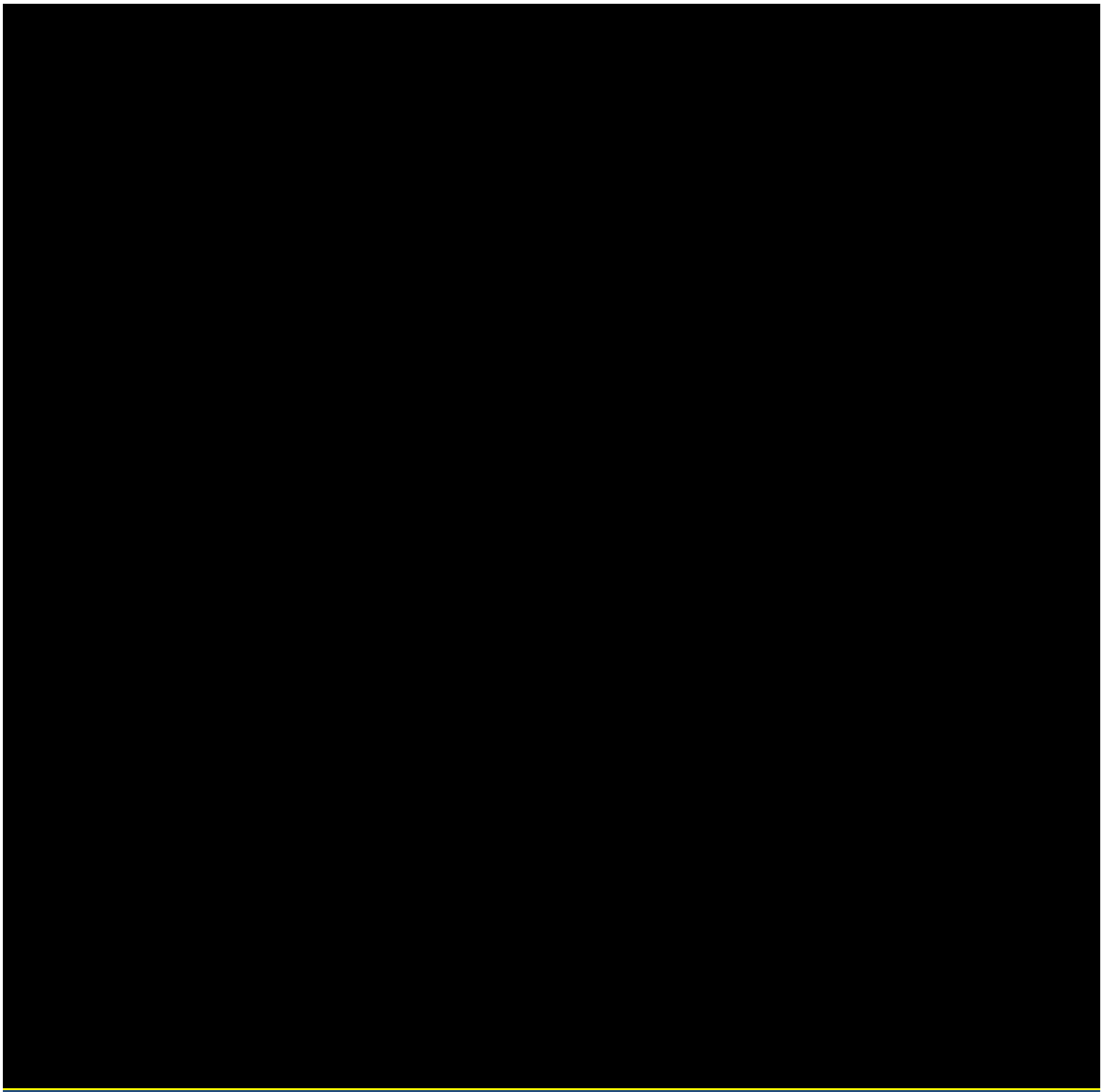
ORs and 95% CrIs (and associated colour shading) correspond to the comparison of row treatment versus column treatment i.e., an OR>1 illustrates a result in favour of the row treatment.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for mucosal healing during the maintenance period of the biologic-naïve population are presented in Appendix D.1.10.2. Model fit statistics can be found in Section 2.2.1.2 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.2, primary results for mucosal healing during the induction period for the biologic-failed population described in this section were derived from the fixed effects model (**with** baseline risk adjustment).

[redacted] (Figure 23).

Figure 23: All pairwise odds ratios with fixed treatment effects: mucosal healing, induction, biologic-failed 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

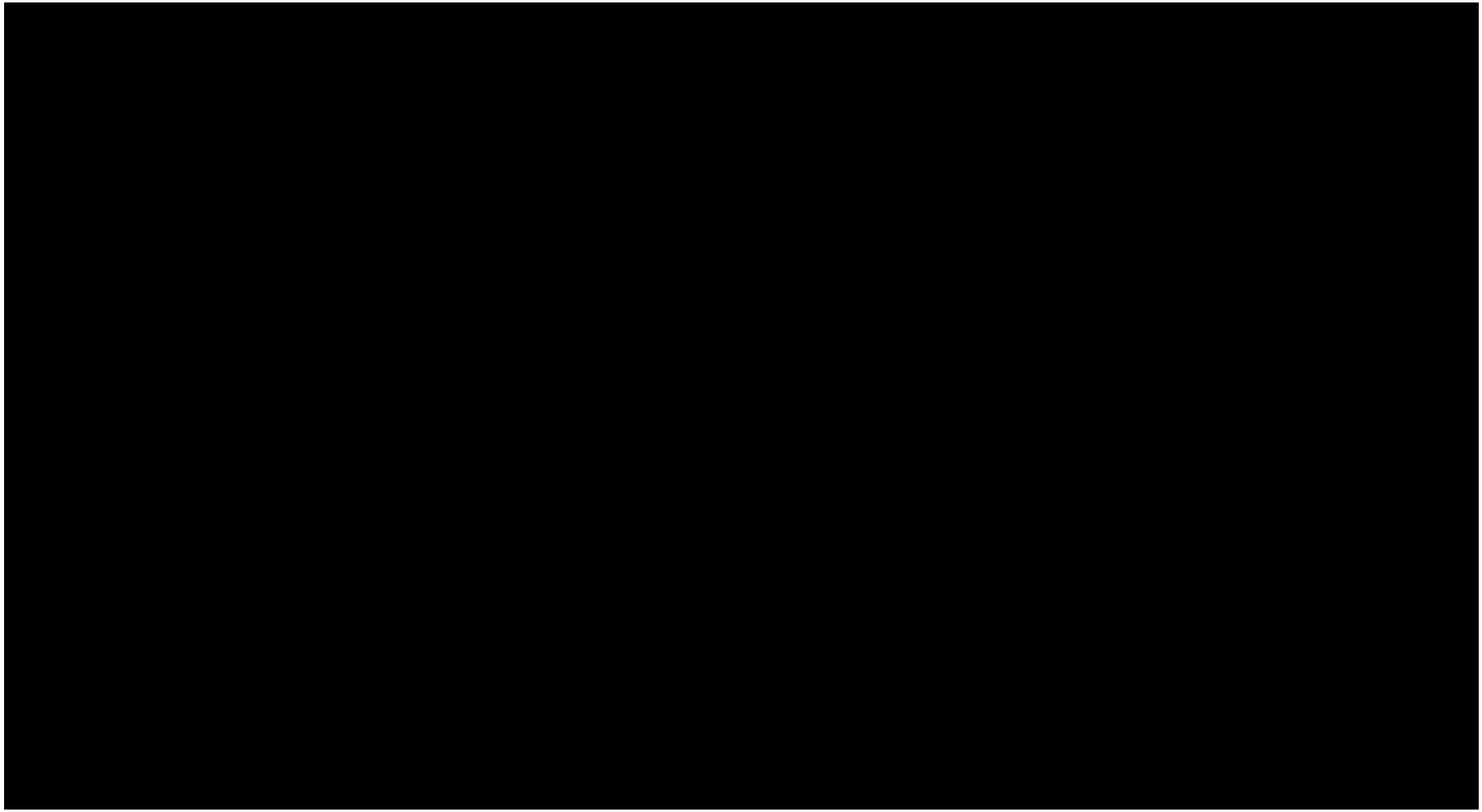
Maintenance

Clinical response and remission

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the maintenance period of the biologic-failed population are presented in Appendix D.1.10.2. Model fit statistics can be found in Section 2.2.2.1 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.2, primary results for clinical response and remission during the maintenance period for the biologic-failed population described in this section were derived from the fixed effects model (**with** baseline risk adjustment); the complementary results without baseline risk adjustment are presented in Section 3.2.2 of the NMA report appendices, as provided in the reference pack. Complete results for the sensitivity analysis of clinical response and remission including only re-randomised studies of the biologic-failed population at maintenance are provided in Section 2.2.2.2 of the NMA report appendices, as provided in the reference pack.

[redacted] (Figure 24 and Figure 25).

Figure 24: Odds ratios with fixed treatment effects with baseline risk meta-regression: clinical response, maintenance, biologic-failed 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 25: Odds ratios with fixed treatment effects with baseline risk meta-regression: clinical remission, maintenance, biologic-failed 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for mucosal healing during the maintenance period of the biologic-failed population are presented in Appendix D.1.10.2. Model fit statistics can be found in Section 2.2.2.3 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.2, primary results for mucosal healing during the maintenance period for the biologic-failed population described in this section were derived from the fixed effects model (**with** baseline risk adjustment).

[redacted] (Figure 26).

Figure 26: All pairwise odds ratios with fixed treatment effects with baseline risk meta-regression: mucosal healing, maintenance, biologic-failed 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

B.3.9.4.3 Safety outcomes (overall mixed population)

Induction

All cause discontinuation

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for all cause discontinuation in the overall population are presented in Appendix D.1.10.3. Model fit statistics can be found in Section 2.3.1.1 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.3, the random effects model using a half-Normal prior demonstrated better fit as compared with the fixed effects model.

The results of the random effect NMA demonstrated high uncertainty in the estimates, this is reflected in the large CrIs (Figure 27). The likely uncertainty probably arises from the low number of discontinuations occurring across some studies.
[redacted].

Figure 27: All pairwise odds ratios with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: 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.
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Serious adverse events

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for SAEs in the overall population are presented in Appendix D.1.10.3. Model fit statistics can be found in Section 2.3.1.2 of the NMA report appendices, as provided in the reference pack. As described further in Appendix D.1.10.3, the random effects model seems most appropriate for inference as this better captures the uncertainty in the estimates.

The results of the random effects NMA are presented with Figure 28 depicting the pairwise ORs.

[redacted]

Figure 28: All pairwise odds ratios with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: serious adverse events, 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: Placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons

Most uncertainty associated with this analysis are related to heterogeneity. Whilst outcome definitions were mostly consistent across trials, differing definitions of clinical response and remission were observed for some studies, and in some cases a definition was not provided.

However, the approach to assessing mucosal healing was strengthened through use of a consistently applied definition in line with LUCENT studies, regardless of terminology used to describe the outcome. In addition, while the designs of the induction phase studies were consistent, the length of the induction period varied from 6 to 12 weeks. Further, it should be noted that comparisons across maintenance trials in UC are extremely challenging due to the differences in study designs, and the comparisons made in this NMA were only possible after substantial data manipulation, as has been done in previous NMAs. These results should therefore be interpreted with caution.

Another source of heterogeneity was that the inclusion criteria for biologic-naïve and biologic-failed populations varied across studies. In the biologic-naïve population, most studies recruited or analysed patients who had failed conventional therapy, such as corticosteroids or immunomodulators like azathioprine, 6-MP, or methotrexate, but had not yet been treated with a biologic or small molecule, such as in the LUCENT trials. Similarly, in the biologic-failed population, studies varied with respect to whether they recruited only failure with a biologic such as TNF, and/or vedolizumab, and/or ustekinumab, or if they also recruited patients who had failed a small molecule such as a JAKi. In addition, trials varied in their approach to permitting concomitant medication during the trial, with some trials, such as the TRUE NORTH study of ozanimod, excluding immunomodulators, where other trials, such as the LUCENT trials and the ACT 1 and ACT 2 trials of infliximab, permitted these.

Despite these sources of heterogeneity, the very thorough feasibility assessment performed as part of this analysis and the approaches undertaken with the aim of harmonising the data to allow for robust like-for-like comparisons are considered considerable strengths which address key limiting factors in previous NMAs in this area. Indeed, previous NICE appraisals have identified and accepted that trials in UC are heterogeneous, but that data obtained from rigorous NMAs nonetheless represent the best available estimates of relative efficacy and are appropriate to inform decision-making.[3, 55] After this extensive assessment, it was concluded that the baseline populations of the studies included in the analyses were sufficiently comparable to provide meaningful indirect clinical data.

B.3.9.6 Conclusions

Overall, these NMAs demonstrated that at induction, mirikizumab offered similar efficacy to most treatment regardless of biologic exposure. At maintenance, irrespective of prior biologic therapy exposure, after adjusting for differences in study design, baseline risk adjusted models suggested mirikizumab demonstrated clinical benefits in terms of clinical response, clinical remission and mucosal healing versus all other comparators, which aligns with the primary treatment goal (as outlined in Section B.1.3.3) of symptomatic remission combined with mucosal healing. 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 ustekinumab and vedolizumab, in both the induction and maintenance phases.

B.3.10 *Adverse reactions*

Trial results relating to adverse events in this submission are presented for the mirikizumab induction responders cohort of LUCENT-2: patients from LUCENT-1 who were re-randomised in

a 2:1 ratio at Week 12 to receive mirikizumab or placebo throughout LUCENT-2. The key safety results from this induction responder population of the LUCENT-2 trial are presented below. Data from other cohorts of the LUCENT-2 trial are available in the CSR.[80, 81, 101] Safety data from the LUCENT-1 trial are presented in Appendix F and are available in the CSR.[79]

B.3.10.1 Overview of adverse events

As shown in Table 31, the frequencies of adverse events (AEs) in the mirikizumab-treated patients compared to those receiving placebo were similar. The proportion of patients receiving placebo who experienced one or more treatment emergent adverse event (TEAE) was [redacted], as compared with [redacted] of those receiving mirikizumab, and the majority of TEAEs were mild to moderate in nature in both treatment arms. Frequencies of serious adverse events (SAEs) and treatment discontinuation due to an AE were broadly comparable between arms, albeit marginally higher in the group receiving placebo than in those receiving mirikizumab ([redacted] versus [redacted] and [redacted] versus [redacted], respectively). [redacted] occurred in LUCENT-2, in the placebo group of the study.

Table 31: Overview of adverse events (LUCENT-2)

Adverse event, n (%)	Mirikizumab induction responders, n (%)	
	PBO SC (N=[redacted])	Miri 200 SC (N=[redacted])
Patients with ≥1 TEAE	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Death	[redacted]	[redacted]
Serious adverse event	[redacted]	[redacted]
Treatment discontinuation due to AE[a]	[redacted]	[redacted]

[a]Including death
Abbreviations: AE: adverse event; Miri: mirikizumab; PBO: placebo; SC: subcutaneous; TEAE: treatment-emergent adverse event
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1), Table AMBG.8.103 (page 1112).[81]

B.3.10.2 Treatment-emergent adverse events

TEAEs occurring in ≥2% of patients in either arm of the mirikizumab induction responders cohort of the LUCENT-2 trial are presented in Table 32. Nasopharyngitis was the most frequently reported TEAE in the mirikizumab treatment group ([redacted]), while ulcerative colitis was the most frequent in the placebo group ([redacted]). Arthralgia was the only other TEAE reported in [redacted] of patients in either treatment arm.

Table 32: TEAEs occurring in ≥2% of patients in the mirikizumab induction responders cohort of LUCENT-2

TEAE, n (%)	Mirikizumab induction responders	
	PBO SC (N=[redacted])	Miri 200 SC (N=[redacted])
Patients with ≥1 TEAE	[redacted]	[redacted]

Ulcerative colitis	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gastroesophageal reflux disease	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]

Abbreviations: AE: adverse event; n: number of patients reporting the adverse event within each specific category; Miri: mirikizumab; PBO: placebo; SC: subcutaneous; TEAE: treatment-emergent adverse event.
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1) Table AMBG.8.108 (page 1125).[81]

B.3.10.3 Serious adverse events

Serious adverse events (SAEs) for mirikizumab induction responders in LUCENT-2 are presented in Table 33 below. Ulcerative colitis was the only SAE reported in more than one patient in any treatment group and was reported more frequently in the placebo group than in the mirikizumab treatment group ([redacted] versus [redacted], respectively). In the mirikizumab treatment group, no single SAE was reported in >1 patient.

Table 33: SAEs in patients in the mirikizumab induction responders cohort of LUCENT-2

SAE, n (%)	Mirikizumab induction responders	
	PBO SC (N=[redacted])	Miri 200 SC (N=[redacted])
Any SAE	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]
Rectocele[a]	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]
Asthma	[redacted]	[redacted]

Autoimmune thyroiditis	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]
Large intestine infection	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]
Rectal polyp	[redacted]	[redacted]
Subcutaneous abscess	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Depression suicidal	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]
Gastric cancer	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Inguinal hernia	[redacted]	[redacted]
Lipoma	[redacted]	[redacted]
Migraine	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]
Retinopexy	[redacted]	[redacted]
Spinal compression fracture	[redacted]	[redacted]

[a]Denominator adjusted because gender-specific event for females: N=78 (Miri responder placebo SC), N=160 (Miri responder 200 miri SC).
Abbreviations: Miri: mirikizumab; PBO: placebo; SAE: serious adverse event; SC: subcutaneous.
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1) Table AMBG.8.125 (page 1517).[81]

B.3.10.3.1 Serious infections

Treatment-emergent serious infection events in LUCENT-2 are summarised in Table 34. The frequency of patients who reported at least 1 SAE in the infections system organ class was [redacted] in the placebo group and [redacted] in the mirikizumab-treatment group. In the group of placebo induction responders, [redacted] reported at least one serious infection.

[redacted] from the placebo group discontinued due to a SAE of COVID-19 infection. [redacted] were discontinued from the mirikizumab treatment group due to a serious infection.

Table 34: Treatment-emergent serious infection events experienced by patients in LUCENT-2

Serious infection, n (%)	PBO induction responders	Mirikizumab induction responders	
	PBO SC (N=[redacted])	PBO SC (N=[redacted])	Miri 200 SC (N=[redacted])
Gastroenteritis	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]

COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Cytomegalovirus colitis	[redacted]	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]	[redacted]
Large intestine infection	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Subcutaneous abscess	[redacted]	[redacted]	[redacted]

Abbreviations: Miri: mirikizumab; PBO: placebo; SAE: serious adverse event; SC: subcutaneous.
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 2) Table AMBG.8.140 (page 38).[101]

B.3.10.4 Adverse events of special interest

The adverse events listed in Table 35 were predetermined as adverse events of special interest (AESI) in LUCENT-2 for mirikizumab induction responders. Overall, serious infections, cerebrocardiovascular events, major cardiac events and malignancies occurred more frequently in patients receiving placebo throughout LUCENT-2 as compared with those treated with mirikizumab.

Table 35: AESIs in patients in the mirikizumab induction responders cohort of LUCENT-2

AESI, n (%)	Mirikizumab induction responders	
	PBO SC (N=[redacted])	Miri 200 SC (N=[redacted])
Infection	[redacted]	[redacted]
Serious infection	[redacted]	[redacted]
Opportunistic infection (narrow)	[redacted]	[redacted]
Injection-site reaction (high-level term)	[redacted]	[redacted]
Hepatic event (narrow)	[redacted]	[redacted]
Immediate hypersensitivity reactions (narrow)	[redacted]	[redacted]
Depression excluding suicide and self-injury (narrow)	[redacted]	[redacted]
Cerebro-cardiovascular (CCV) event (adjudicated and confirmed)	[redacted]	[redacted]
Major adverse cardiac event (MACE)	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]
Suicide/self-injury (narrow)	[redacted]	[redacted]

Abbreviations: AESI: adverse events of special interest; Miri: mirikizumab; PBO: placebo; SC: subcutaneous.
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 2) Tables AMBG.8.134, 8.138, 8.139, 8.140, 8.150, 8.160, 8.163, 8.164, 8.170, 8.177 (Pages 3 – 156).[101]

B.3.10.5 Discontinuations due to adverse events

Adverse events which led to treatment discontinuation in mirikizumab induction responders are presented in Table 36. Overall, a higher proportion of treatment discontinuations due to AEs occurred in patients receiving placebo as compared with patients receiving mirikizumab treatment ([redacted] versus [redacted], respectively). In both treatment groups, ulcerative colitis was the

only AE causing discontinuation in more than one patient: [redacted] ([redacted]) in the placebo arm and [redacted] ([redacted]) in the mirikizumab arm.

Table 36: Discontinuations due to adverse events in patients in the mirikizumab induction responders cohort of LUCENT-2

Adverse event, n (%)	Mirikizumab induction responders	
	PBO SC (N=[redacted])	Miri 200 SC (N=[redacted])
Treatment discontinuation due to AE	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]
Autoimmune hepatitis	[redacted]	[redacted]
Gastric cancer	[redacted]	[redacted]
Injection site hypersensitivity	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]

Abbreviations: Miri: mirikizumab; PBO: placebo; SC: subcutaneous.
Source: Eli Lilly and Company (data on file): LUCENT-2 Clinical Study Report (Additional Analyses 1): AMBG 8.3.5 – Table AMBG.8.130 (page 1546).[81]

B.3.11 *Conclusions about comparable health benefits and safety*

Mirikizumab has demonstrated clinical efficacy and tolerability in patients with moderately to severely active UC. Results from both the LUCENT-1 induction trial and the LUCENT-2 maintenance trial showed mirikizumab to be statistically significantly superior to placebo for the key outcomes of clinical remission, clinical response, mucosal healing and bowel urgency. In addition, the efficacy of mirikizumab was demonstrated across both biologic-naïve and biologic-failed 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.[56]

The LUCENT-1 trial met its primary endpoint of clinical remission at Week 12; [redacted] of patients receiving mirikizumab achieved clinical remission, compared with [redacted] of those receiving placebo. Similarly, clinical response at Week 12 was a major secondary endpoint and was achieved by [redacted] of patients receiving mirikizumab versus [redacted] receiving placebo. Bowel urgency, assessed using the bowel urgency NRS, was also significantly improved for patients receiving mirikizumab, as compared with those receiving placebo; statistically significant improvements were observed as early as Week 2 in the mITT cohort. Consistent efficacy results were demonstrated across both biologic-naïve and biologic-failed subgroups.

In the LUCENT-2 study, the primary analysis was conducted on patients who responded to mirikizumab induction treatment at Week 12 of LUCENT-1. These patients were re-randomised to 2:1 to mirikizumab maintenance treatment or placebo for the blinded randomised withdrawal period. In alignment with the efficacy results observed in the LUCENT-1 trial, treatment with mirikizumab in this cohort demonstrated improvements in all efficacy outcomes at Week 40 compared to those re-randomised to receive placebo. At Week 40, [redacted] of patients receiving

mirikizumab achieved clinical remission versus [redacted] of those re-randomised to placebo. In addition, rates of maintenance were high on mirikizumab with [redacted] of patients maintaining remission while on mirikizumab, compared with [redacted] of those who were re-randomised to placebo. Importantly, mirikizumab treatment was associated with higher proportions of patients in corticosteroid-free remission at Week 40, versus those on placebo ([redacted] versus [redacted], respectively). This result is of importance to both clinicians and patients, particularly given the aim of reducing corticosteroid use due to associated side effects and detriment to patients with long-term use. As in LUCENT-1, bowel urgency was also statistically significantly improved in mirikizumab-treated patients compared with those who received placebo. In alignment with LUCENT-1, efficacy results from subgroup analyses by prior biologic exposure status were broadly consistent with the mITT population.

In addition, mirikizumab demonstrated high efficacy amongst patients who achieved a clinical response to mirikizumab induction therapy in LUCENT-1 but subsequently lost clinical response during the LUCENT-2 trial and received open-label re-induction therapy for 12weeks. Of these patients, [redacted]% of patients regained symptomatic response, with [redacted]% achieving symptomatic remission at the end of the re-induction period. Similarly, amongst patients who did not achieve clinical response in LUCENT-1 and who went on to receive open-label extended induction therapy with 300 mg mirikizumab IV in LUCENT-2, [redacted]% of patients previously treated with mirikizumab in LUCENT-1 achieved a clinical response at the delayed clinical response assessment, as compared with [redacted]% of patients who received placebo in LUCENT-1. These results demonstrate that mirikizumab has a high efficacy when used as an extended induction or re-induction treatment.

Across both studies, mirikizumab was well-tolerated and the frequencies of AEs were similar in both mirikizumab-treated patients and patients who received placebo. The proportion of patients receiving placebo who experienced one or more treatment emergent adverse event (TEAE) was [redacted], as compared with [redacted] of those receiving mirikizumab, and the majority of TEAEs were mild to moderate in nature in both treatment arms.

The direct evidence available from both the induction and maintenance trials show mirikizumab to be an effective and tolerable treatment for inducing clinical response and clinical remission in patients with moderately to severely active UC, 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. At maintenance, irrespective of prior biologic therapy exposure, after adjusting for differences in study design, baseline risk adjusted models suggested mirikizumab demonstrated clinical benefits in terms of clinical response, clinical remission and mucosal healing versus the majority of other comparators, including both of the comparators of relevance in the decision problem, 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 ustekinumab and vedolizumab, as outlined in Section B.1.1, and suggest that mirikizumab would provide a valuable new treatment option for patients with UC in the UK.

B.3.12 *Ongoing studies*

One trial of mirikizumab in moderately to severely active UC, the LUCENT-3 open-label long-term extension study (NCT03519945), is currently ongoing and results are expected to become available in [redacted].

B.4 Cost-comparison analysis

B.4.1 *Changes in service provision and management*

Mirikizumab is administered intravenously at Weeks 0, 4 and 8 during the induction period, followed by a subcutaneous injection every 4 weeks thereafter (the maintenance period). For patients who do not show clinical response after the initial induction period, or who lose response to the maintenance dose, intravenous re-induction therapy may be administered. 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 subcutaneous injection technique, patients may 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, the re-induction period, and the initial subcutaneous dose.

As described in Section B.1.1, mirikizumab is positioned for use as an alternative to ustekinumab and vedolizumab. As such, the cost-comparison analysis presented herein focuses on the comparison of cost outcomes associated with mirikizumab, ustekinumab and vedolizumab only. Since ustekinumab and vedolizumab share a similar method of administration to mirikizumab, 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 clinical practice as compared to ustekinumab and vedolizumab in relevant patient subgroups under the assumption that the treatments have the same efficacy and safety. Ustekinumab and vedolizumab were considered appropriate comparisons for the reasons outlined in Section B.1.1.

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 UC for whom:

- Conventional treatment cannot be tolerated or is not working well enough and other biological treatment is not suitable (“biologic-naïve”), *or*
- Biologic treatment cannot be tolerated or is not working well enough (“biologic-failed”)

The population characteristics in the model are based on the Phase III LUCENT clinical trials. The efficacy of all treatments was set as equal to the efficacy of mirikizumab as obtained from the NMA presented in Section B.3.9. The model allows for analysis of subgroup populations by prior biologic exposure, as clinical efficacy and patient characteristics, such as weight, vary by subgroup.

The model structure is informed by both previous cost-effectiveness analyses in UC, as identified by the economic SLR (see Appendix I), simplified where possible for the purposes of a cost comparison analysis and previous cost comparison models used in NICE appraisals for the treatment of autoimmune inflammatory disorders – in particular the manufacturer models

submitted to NICE as part of the technology appraisals (TAs) for bimekizumab (TA723), guselkumab (TA521) and risankizumab (TA596) in psoriasis, and risankizumab in psoriatic arthritis (TA803).[4-7]

The model, developed in Microsoft Excel, has a full Markov model structure and consists of four components: an induction period of up to 26 weeks comprising two-week tunnel states, an on-treatment maintenance state, an off-treatment state, and a death state.

Although in clinical practice patients are treated with a succession of therapies, including surgery, the assumption of similar efficacy between treatments implies that these down-stream costs would be similar for all treatments. Therefore, they are not formally modelled. Instead, patients incur no costs in the off-treatment state.

The base case time horizon was set to 10 years in line with recent cost comparison models in autoimmune inflammatory disorders submitted to NICE.[6, 7] A shorter time horizon of five years was tested in a scenario analysis. In the base case, discounting was not applied, as recommended by NICE in the user guide applicable to cost comparison models, with costs discounted at rates of 3.5% and 5% per annum in scenario analyses.[2] The model was populated with UK data, and the analysis was based on the UK National Health Service and the Patient Support (NHS & PSS) perspective.

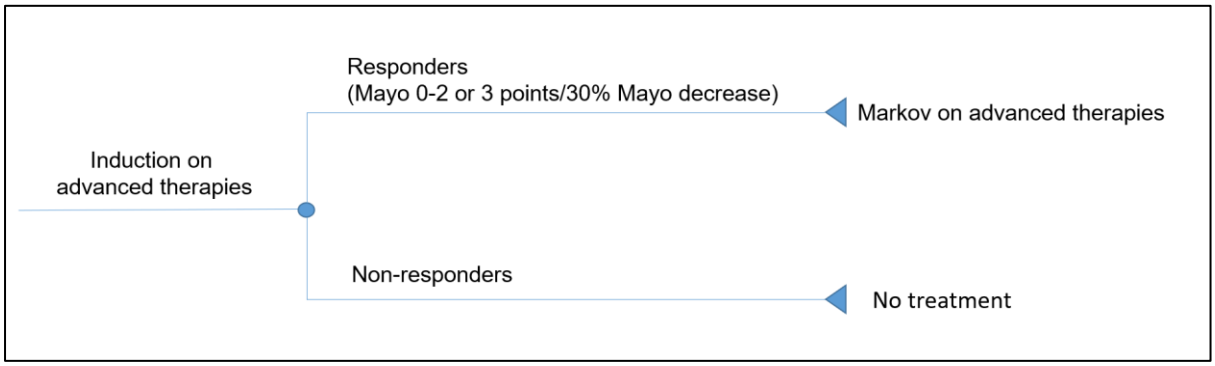
B.4.2.1.1 Induction phase model structure

All patients entered the model with moderately to severely active UC and receive induction treatment. Variable and treatment-specific lengths of induction periods are necessary to allow for a comprehensive comparison of costs across treatments. As such, throughout the induction period, patients transitioned through two-week tunnel states, a series of temporary states that can only be visited in a particular sequence, for between 2 and 12 weeks (and up to 12 additional weeks for delayed response assessment, also in two-week increments) to reach decision points. The 2-week cycle length was sufficiently short to facilitate accurate modelling of the lengths of induction periods for all interventions as per the respective labels (see Table 40).

At the end of the induction period, patients were classified as responders or non-responders. Response was defined as a decrease in total Mayo score of ≥3 points and ≥30% improvement from baseline, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1. This definition is in alignment with that used in the NMA (Section B.3.9) and encompasses patients in clinical remission.

As shown in the graphical representation of the model induction phase presented in Figure 29, patients who responded to treatment at the end of the induction period transitioned to the maintenance treatment state. In the base case, patients who did not respond transitioned to the no-treatment state. Note the decision-tree structure in Figure 29 is only included to illustrate the patient flow between decision nodes – the actual transitions are modelled using Markov tunnel states. Death is possible from all health states in each cycle.

Figure 29: Decision tree schematic for the induction phase



The induction period is implemented using a Markov model. The decision-tree like structure is only included to illustrate the patient flow between decision nodes. From the start of the model to the end of the induction period (maximum 26 weeks), patients transition through 2-week tunnel health states to decision nodes. The death health state is not shown, but can be reached from all health states in each cycle.
Abbreviations: UC: ulcerative colitis.

The inclusion of delayed response assessment (extended induction) in the model was explored in a scenario analysis and was implemented as an extended induction period. When modelling delayed response, all non-responders at the end of the induction period either entered the no-treatment state, or continued to be treated for an additional 8 weeks on ustekinumab (16 weeks total induction), an additional 4 weeks on vedolizumab (10 weeks total treatment) or an additional 12 weeks on mirikizumab (24 weeks total treatment) to assess delayed response. At the end of the delayed response assessment, patients were distributed according to their response status, i.e., responders transitioned to the maintenance state and non-responders transitioned to the no-treatment state.

B.4.2.1.2 Post-induction treatment (maintenance phase) Markov structure

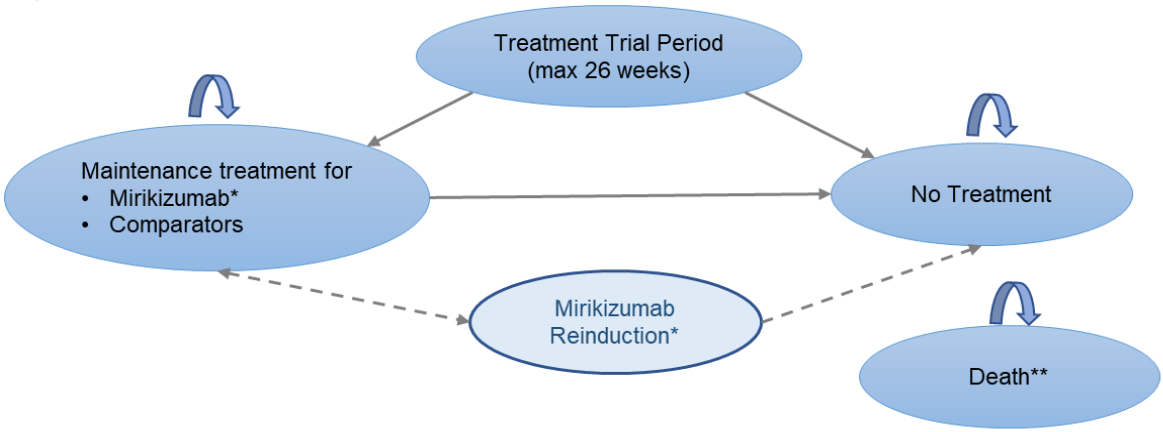
The post-induction phase Markov model structure is based on three distinct states, as illustrated in Figure 30: maintenance treatment, off-treatment, and death. Patients can transition from the maintenance treatment state to the off-treatment state, but not vice versa, and death was an absorbing state that patients could transition to from all other health states. In the maintenance phase, the model had 12-week cycles which reflects the expected disease course and frequency of treatment events in clinical practice.

In clinical practice, patients who lose response to treatment may be treated with increased doses or increased frequency of administration ("dose escalation", see "dose adjustments" in Table 40) instead of immediately discontinuing treatment. In the LUCENT-2 clinical trial, patients who lost response to mirikizumab during the maintenance phase were treated with re-induction. Re-induction is anticipated to be included in the marketing authorisation for mirikizumab and was therefore included in the base case of the cost comparison model.

To reflect clinical practice for treatment with advanced therapies, dose escalation was included for ustekinumab and vedolizumab. Consistent with previous NICE appraisals and as derived from published literature on the frequency of dose escalation in TNFis, 30% of patients were modelled to undergo dose escalation with these treatments during the maintenance phase of the model.[3, 54, 102] In line with its expected label, re-induction rather than dose escalation was modelled for mirikizumab with the re-induction dose of mirikizumab set to align with that in the mirikizumab SmPC: i.e., 300 mg IV mirikizumab at Week 12, 16 and 20. In the base case, [redacted] of patients receiving mirikizumab were modelled to undergo re-induction (equating to [redacted] per cycle),

reflecting the proportion of patients who were re-inducted in the LUCENT-2 trial of mirikizumab. A scenario analysis was explored in which 30% of patients receiving mirikizumab were modelled to undergo re-induction, in line with the assumption informing the dose escalation proportion for the comparators. Given the assumption of equal efficacy for all treatments, it was assumed that dose escalation and reinduction affected costs but not efficacy. In contrast to dose escalation, where the cost for the escalated dose is applied each cycle the patient remains on treatment, re-induction was assumed to occur during one cycle and was therefore modelled as a separate health state during maintenance treatment with mirikizumab and the cost for reinduction was applied only to the cycle during which the patient is re-inducted.

Figure 30: Markov structure for the maintenance phase



* For mirikizumab, dose escalation is not modelled. Patients who lost response during the maintenance phase were treated with reinduction.
** The death state is reachable from all other states.

B.4.2.1.3 Cycle length

As outlined above, the induction and maintenance phases of the model used cycle lengths of two weeks and 12 weeks, respectively. Given the different time reference of model inputs (e.g., annually, per three-month period etc.), calculations were performed in the model to rescale all variables to the cycle length. Two methods for rescaling were used, depending on whether the input type was a rate, probability, or absolute number.

For rates and probabilities, the geometric conversion was employed. The conversions were performed in two steps. Firstly, the annual probability was converted to an instantaneous rate. Secondly, this rate was converted back to a probability for the relevant duration (2 or 12 weeks). An example of conversion from an annual to a monthly probability is given below:[103]

$$r = -\ln(1 - P_{annual})$$

$$P_{monthly} = 1 - e^{-r/12}$$

(Equation 1)

$$Annual\ probability = P_{annual}$$
$$Instantaneous\ rate = r$$
$$Monthly\ probability = P_{monthly}$$

For the inputs related to absolute levels, such as annual costs, the linear conversion was applied by dividing the value to be adjusted by the number of time periods. For example, the conversion of yearly to biannual costs is given by:

$$\text{biannual cost} = \text{annual cost} / 2 \qquad \textit{(Equation 2)}$$

B.4.2.1.4 Efficacy in the induction period

As outlined in Section B.4.2.1.1, at the end of the induction period patients were classified by responder status. The distribution of response status at the end of induction (and, in the scenario analysis, delayed response assessment) was informed by the induction NMA.

Base case

Induction (LUCENT-1) and maintenance (LUCENT-2) efficacy data for mirikizumab were synthesised with data for all comparators of interest in the NMA (see Section B.3.9). The rates of response are assumed to be the same across all treatments but differ between biologic-naïve or biologic-failed patients, as shown in Table 37.

Table 37: Clinical response and response at the end of induction

Treatment	Response (including remission)	
	OR (95% CI) relative to placebo	Calculated absolute probability
Mirikizumab (for all treatments)		
Biologic-naive subgroup	[redacted]	[redacted]
Biologic-failed subgroup	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OR: odds ratio.

Scenario analysis

A scenario analysis was explored in which patients who did not respond could undergo a delayed response assessment. Delayed response assessment was selected as a sensitivity analysis rather than used in the base case analysis given that it is uncertain to what extent delayed response assessment is used in clinical practice, and that not all treatments have delayed response assessment in their SmPC.[63, 89, 104-110]

In this scenario analysis, patients transitioned through tunnel states from the start to the end of the delayed response assessment, at the end of which patients who responded to treatment transitioned to the maintenance state, and patients who had not responded transitioned to the no-treatment state. It was assumed the same proportion of patients receiving mirikizumab achieved response (including remission) at the end of the induction phase as ustekinumab, as presented in Table 38.[3] The use of data from the NMA to inform this analysis was explored, but the available data were considered to be insufficient given that delayed response assessment period was not placebo controlled in any trial, making indirect comparisons very limited as very few trials compare advanced treatments.

Table 38: Clinical response at the end of the delayed response assessment period

	Response (including remission)	Source

Treatment	Calculated absolute probability	
Biologic-naive subgroup	65.4%	Assumed same as ustekinumab overall response rate (data from ustekinumab TA633, Table 41)[3]
Biologic-failed subgroup	46.5%	

Abbreviations: CI: confidence interval; OR: odds ratio.

B.4.2.1.5 Efficacy in the maintenance state

Patients were assumed to remain on maintenance treatment until they discontinued treatment or died. Discontinuation of maintenance treatment was based on the notion that patients who lose response to treatment also discontinue treatment. The proportion of initial responders who lost response were assumed to do so at a continuous and constant rate during the maintenance period. The risk of treatment discontinuation was informed by the loss of response observed in maintenance RCTs. This approach for modelling treatment discontinuation is the same as for many cost-effectiveness models in UC.[3, 54, 55, 75]

In contrast to the cost-effectiveness models, the cost comparison model assumes that all treatments have the same risk of treatment discontinuation – the one estimate for mirikizumab in the NMA (Section B.3.9). The odds ratio for response at the end of the maintenance period (contingent on response at the end of the induction period) for mirikizumab relative to placebo was transformed to an absolute probability. The complement to the derived probability is the probability of loss of response during the maintenance period. Subsequently, the probability of loss of response during the duration of the maintenance trial was transformed to per cycle probabilities using the formulae presented in Section B.4.2.1.3, resulting in a risk of loss off response during the maintenance period of 6.7% and 12.3% per 12-week cycle for biologic-naïve patients and biologic-failed patients, respectively.

B.4.2.1.6 Efficacy in the off-treatment state

Patients in the off-treatment state were assumed to remain in the state until the end of the simulation unless they died (see Section B.4.2.1.8).

B.4.2.1.7 Patient characteristics

Patient baseline characteristics for age, sex and weight stratified by prior biologic failure that inform the cost comparison model are presented in Table 39.

Table 39: Patient baseline characteristics

	Biologic-naive	Biologic-failed
Age (years), mean (SD) [95% CI]	[redacted]	[redacted]
Male, %	[redacted]	[redacted]
Weight (kg), mean (SD) [95% CI]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; SD: standard deviation

B.4.2.1.8 Mortality

In alignment with the most recent NICE TAs, no increased mortality with UC was modelled.[3, 53, 54, 75] It was assumed that the mortality was the same across all health states and were based on UK national life tables, given the sex and age of the cohort in each cycle.[111]

B.4.2.2 Intervention and comparators' acquisition costs

Table 40 shows the key inputs, assumptions and acquisition costs included for mirikizumab, ustekinumab and vedolizumab.

Table 40: Acquisition costs of the intervention and comparator technologies

	Mirikizumab	Ustekinumab	Vedolizumab
Pharmaceutical formulation	Mirikizumab 300 mg (15 mL vial; 20 mg mirikizumab per mL) is available as a concentrate for solution for infusion A full maintenance dose consists of two 100 mg pre-filled pens	Ustekinumab 130 mg is available as a solution for infusion (26 mL, 5 mg per mL) Ustekinumab 90 mg is available as a pre-filled syringe (1 mL)	Vedolizumab 300 mg is available as a powder for concentrate for solution for infusion Vedolizumab 108 mg is available as a solution for injection in pre-filled syringe
(Anticipated) care setting	Secondary care		
Acquisition cost (excluding VAT) *	List price: [redacted] PAS price: [redacted]	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: £2050.00 108 mg/0.68 mL list price: £512.50
Method of administration	• **Induction**: IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC *or* IV
Doses	• **Induction**: 300 mg IV mirikizumab per administration • **Maintenance**: 200 mg SC mirikizumab per administration (two 100 mg injections)	IV dose at Week 0 is based on body weight (recommended dose: 6 mg/kg): • ≤55 kg: 260 mg • >56 to ≤85 kg: 390 • mg • >85 kg: 520 mg At Week 8, 90 mg SC ustekinumab, followed by 90 mg ustekinumab every 12 weeks	• **Induction**: 300 mg IV vedolizumab per administration • **Maintenance**: 300 mg IV vedolizumab or 108 mg SC vedolizumab
Dosing frequency	• **Induction**: Weeks 0, 4 and 8 • **Maintenance**: Every 4 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	Patients who do not respond after initial induction therapy, or those who lose response to maintenance therapy may receive re-induction (3 doses, one every 4 weeks, of 300 mg IV mirikizumab)	• Patients who have not shown adequate response at 8 weeks after the first SC dose (Week 16), may receive a second SC dose at this time to allow for delayed response • Patients who lose response on dosing	• 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 • There is no dose adjustment for

		every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks • Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment	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.		
Average cost of a course of treatment (acquisition costs only)[a]			
(Anticipated) average interval between courses of treatment			
(Anticipated) number of repeat courses of treatment			

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

Drug acquisition costs were estimated for the induction and maintenance phases. Where escalated dosage or re-induction was modelled (see Section B.4.2.1.2), drug acquisition costs during the maintenance phase accounted for the distribution of patients on standard and escalated doses.

Dosing regimens were used to calculate the total drug use and were based on the relevant SmPCs for ustekinumab and vedolizumab. All drug acquisition unit costs were sourced from MIMS and the British National Formulary (BNF).[112, 113] As ustekinumab is a weight-based drug, the weights presented in Table 39 were used. The drug acquisition costs are presented in Table 40. Total induction and total annual maintenance costs are presented in Table 41 and Table 42, respectively.

For ustekinumab, the treatment regimen is based on patients' body weight. 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. In the base case, vial-sharing was incorporated: any leftover drug was modelled to be used for another patient such that costs are accrued only for the actual amount of medication administered and there is no drug wastage. The vial size with the lowest cost per mg was selected. The incorporation of vial wastage, (i.e., any leftover drug not used by a specific patient is wasted) based on the selected vial size that provides the lowest acquisition cost for each dose, was explored in a scenario analysis.

Table 41: Drug acquisition costs for mirikizumab and the comparators during the induction phase

Treatment	Initial induction		Total treatment cost
	Duration (weeks)	Total doses (mg)	
Mirikizumab (IV, at PAS price)	12	1,200	[redacted]
Ustekinumab (IV/SC)	8	433	£7,145
Vedolizumab (IV)	6	900	£6,150
Vedolizumab (SC/IV)	6	900	£6,150

Abbreviations: IV: intravenous; SC: subcutaneous.

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

Treatment	% Re-induction	Re-induction cost (12 weeks)	% Escalated dose	Total doses per annum (mg)	Total treatment cost per annum
Mirikizumab (SC, at PAS price)	[redacted]	[redacted]	NA	2,609	[redacted]
Ustekinumab (IV/SC)	NA	NA	30%	450	£10,508
Vedolizumab (IV)	NA	NA	30%	2,544	£13,371
Vedolizumab (SC/IV)	NA	NA	0%	2,818	£11,702

Abbreviations: IV: intravenous; NA: not applicable; 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. Consistent with the most recent TAs for ustekinumab (TA633), tofacitinib (TA547) and filgotinib (TA792), the costs for IV administration were calculated as the mean of a consultant and a non-consultant led, non-admitted face-to-face follow-up appointment (code WF01A).[3, 54, 75] The unit costs were taken from the 2020/2021 NHS Reference Costs, and the cost per IV administration was estimated to be £172.50 (see Table 43).[21]

Consistent with the approach taken in the TA for ustekinumab (TA633), it was assumed that all patients self-inject subcutaneous treatment apart from the initial injection.[3] Therefore, the model has no administration cost for subcutaneous injections.

Table 43: Unit cost of treatment administration for IV therapies

Currency code and description	Number of attendances	National average unit cost
WF01A, Consultant led (CL), Non-Admitted Face-to-Face Attendance, Follow-up (Gastroenterology)	113,297	£122.58
WF01A, Non-consultant led (NCL), Non-Admitted Face-to-Face Attendance, Follow-up (Gastroenterology)	372,090	£187.70
Estimated cost of an IV administration (outpatient visit)		**£172.50**

Abbreviations: IV: intravenous.

Table 44 presents the number of administrations for mirikizumab and the comparators during the induction and maintenance phase.

Table 44: Drug administrations for mirikizumab and the comparators during the induction and maintenance phase

Treatment	Induction				Maintenance
	Initial induction		Delayed response assessment		
	Duration (weeks)	Total admins	Duration (weeks)	Total admins	Total admins per annum
Mirikizumab (IV/SC)	12	IV: 4	0	0	SC: 13
Ustekinumab (IV/SC)	8	IV: 1	8	SC: 1	5
Vedolizumab (IV)	6	3	4	0	8
Vedolizumab (SC/IV)	6	IV: 3	4	0	SC: 26

Abbreviations: IV: intravenous; SC: subcutaneous.

B.4.2.3.2 Disease management costs

Disease management costs in the model are health state specific and therefore driven by efficacy. Given that efficacy is assumed to be the same for all treatments, the health state distribution during maintenance treatment will 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.3.9.4.3) 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 cost-effectiveness analysis in UC, as identified by the economic SLR, and previous cost comparison models used in NICE appraisals for the treatment of autoimmune inflammatory disorders.[4-7] Assumptions underpinning the model were discussed with health economic experts in two workshops on cost-effectiveness model development in UC: one in March 2019 and one in August 2021.

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 45, with key assumptions of the cost-comparison model presented in Table 46.

Table 45: Settings and values used in the base case analysis

Item	Base-case setting	Reference
Perspective	UK NHS	Section B.4.2.1
Time horizon	10 years	Section B.4.2.1
Age in years, mean (SD)	Naïve: [redacted] Failed: [redacted]	Section B.4.2.1.7
Weight in kg, mean (SD)	Naïve: [redacted] Failed: [redacted]	Section B.4.2.1.7
Proportion male	Naïve: [redacted] Failed: [redacted]	Section B.4.2.1.7
Efficacy (%) induction period	Naïve: [redacted] from NMA Failed: [redacted] from NMA	Section B.4.2.1.4
Delayed response	No	Section B.4.2.1.4

Item	Base-case setting	Reference
Loss of response - probability per cycle (12 weeks) during maintenance (%)	Naïve: [redacted] from NMA Failed: [redacted] from NMA	Section B.4.2.1.5
Mirikizumab re-induction (%)	[redacted] per cycle	Section B.4.2.1.2
Dose escalation	30%	Section B.4.2.1.2
Cost discount rate	0	Section B.4.2.1

Abbreviations: NHS: National Health Service; NMA: network meta-analysis; SD: standard deviation.

Table 46: Key model assumptions

Assumption	Justification
Only responders continue treatment after the induction period	Consistent with clinical practice as per expert advice and consistent with previous submissions
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 ustekinumab and vedolizumab.
Responders continue maintenance therapy with the same treatment until loss of response	Expert advice suggests that clinicians and patients are unlikely to discontinue effective treatment.
Patients who do not respond at the end of the induction period or discontinue the maintenance period do not incur costs	Simplifying assumption. In reality, patients would incur costs. However, given the assumption on similar efficacy the costs would be the same across all treatment and therefore cancel out.
No disease management and monitoring costs	Disease management and monitoring costs largely reflect disease severity and should therefore be very similar across all modelled treatments.
Normal population mortality	Consistent with previous models. Does not introduce mortality benefits that have not been demonstrated in RCTs
No serious adverse events in the base case	Adverse events were not included in the model due to the NMA results demonstrating broadly similar safety outcomes for mirikizumab, ustekinumab and vedolizumab. s

Abbreviations: NMA: network meta-analysis; RCT: randomised controlled trial; UC: ulcerative colitis.

B.4.3 *Base-case results*

Base case results for a 10-year time horizon with mirikizumab (at list price and with-PAS price) are presented in Table 47 and Table 48 for patients in the biologic-naïve and biologic-failed populations, respectively. Confidential PAS discounts for comparators are not included in either analysis as these are not publicly known. These results indicate mirikizumab offers a cost-saving treatment option in the biologic-naïve and -failed populations as compared with ustekinumab and vedolizumab (IV and IV/SC) at their list prices.

Table 47: Base case results for a 10-year time horizon at mirikizumab list price (biologic-naïve population)

Treatment	Per patient costs				Incremental costs relative to mirikizumab (£)
	Induction costs (£)	Re-induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	
Mirikizumab at list price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab	£5,487	£0	£18,370	£23,857	[redacted]
Vedolizumab IV	£4,445	£0	£32,248	£36,693	[redacted]
Vedolizumab IV/SC	£4,445	£0.00	£22,881	£27,325	[redacted]
Mirikizumab at PAS price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab	£5,487	£0	£18,370	£23,857	[redacted]
Vedolizumab IV	£4,445	£0	£32,248	£36,692	[redacted]
Vedolizumab IV/SC	£4,445	£0	£22,881	£27,325	[redacted]

Abbreviations: PAS: patient access scheme.

Table 48: Base case results for a 10-year time horizon at mirikizumab list price (biologic-failed population)

Treatment	Per patient costs				Incremental costs relative to mirikizumab (£)
	Induction costs (£)	Re-induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	
Mirikizumab at list price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab	£5,695	£0	£7,870	£13,565	[redacted]
Vedolizumab IV	£4,445	£0	£13,815	£18,260	[redacted]
Vedolizumab IV/SC	£4,445	£0	£9,802	£14,247	[redacted]
Mirikizumab at PAS price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab	£5,695	£0	£7,870	£13,565	[redacted]
Vedolizumab IV	£4,445	£0	£13,815	£18,260	[redacted]
Vedolizumab IV/SC	£4,445	£0	£9,802	£14,247	[redacted]

Abbreviations: PAS: patient access scheme.

B.4.4 *Sensitivity and scenario analyses*

B.4.4.1 One-way sensitivity analysis

The one-way sensitivity analyses involved analysing the impact on the costs when changing a single parameter at a time to reflect the uncertainty/variability in the estimation of that parameter. The lower and upper bounds for the response and discontinuation rates were set based on the credible intervals estimated from the NMA, with confidence intervals being used for other parameters where available. However, when such information was not available, the upper and lower bounds were assumed to be within ± 20% of the base case value, as presented in Table 49.

Table 49: Summary of one-way sensitivity analyses

OWSA input - parameter	Base case	Lower bound	Upper bound	Source of bounds
Start age (years) – Naïve population	[redacted]	[redacted]	[redacted]	95% CI
Start age (years) – Failed population	[redacted]	[redacted]	[redacted]	95% CI
Proportion male patients – Naïve population	[redacted]	[redacted]	[redacted]	±20%
Proportion male patients –Failed population	[redacted]	[redacted]	[redacted]	±20%
Mean patient body weight (kg) – Naïve population	[redacted]	[redacted]	[redacted]	95% CI
Mean patient body weight (kg) – Failed population	[redacted]	[redacted]	[redacted]	95% CI
Proportion of patients with dose escalation	0.30	0.24	0.36	±20%
Mirikizumab response rate at induction phase for biologic naïve patients	[redacted]	[redacted]	[redacted]	95% CrI
Mirikizumab response rate at induction phase for biologic failed patients	[redacted]	[redacted]	[redacted]	95% CrI
Mirikizumab response rate after 12 weeks re-induction	[redacted]	[redacted]	[redacted]	±20%
Mirikizumab loss of response probability (per 12 weeks) for biologic naïve patients	[redacted]	[redacted]	[redacted]	95% CrI
Mirikizumab loss of response probability (per 12 weeks) for biologic failed patients	[redacted]	[redacted]	[redacted]	95% CrI
Proportion mirikizumab re-induction 12 weeks	[redacted]	[redacted]	[redacted]	±20%

Abbreviations: CI: confidence interval; CrI: credible interval; OWSA: one-way sensitivity analysis.

Tornado diagrams for mirikizumab versus ustekinumab, vedolizumab IV and vedolizumab IV/SC are presented in Figure 31, Figure 33 and Figure 35, respectively, in the biologic-naïve population, and in Figure 32, Figure 34 and Figure 36, respectively, in the biologic-failed population. For each comparison, the eight most influential parameters shown in descending order of cost difference sensitivity. These results demonstrate that the model is insensitive to all parameters.

Figure 31: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus ustekinumab in the biologic-naïve population

Abbreviations: PAS: patient access scheme.

Figure 32: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus ustekinumab in the biologic-failed population

Abbreviations: PAS: patient access scheme.

Figure 33: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV) in the biologic-naïve population

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

Figure 34: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV) in the biologic-failed population

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

Figure 35: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV/SC) in the biologic-naïve population

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

Figure 36: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV/SC) in the biologic-failed population

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

B.4.4.2 Scenario analyses

Seven scenario analyses, detailed in Table 50, were explored in the model.

Table 50: Scenario analyses

#	Scenario	Base case	Scenario values
1	Model horizon	10 years	5 years
2	Discount rates	0%	3.5%
3			5%

4	Dose escalation and re-induction	Increased dose or administration frequency for 30% of patients for relevant comparators and [redacted] of patients on treatment re-induction per cycle for mirikizumab, reflecting clinical data from the LUCENT trials	No dose escalation for relevant comparators and no re-induction for mirikizumab
5			Increased dose or administration frequency for 30% of patients for relevant comparators and 30% of patients on treatment re-induction per cycle for mirikizumab
6	Delayed response assessment	No extended induction period	Extended induction period as described in Section B.4.2.1.4
7	Drug wastage	Incorporation of vial sharing, so no drug wastage	Assumption of drug wastage

Results for these scenario analyses are presented in Table 51 and Table 52 for the biologic-naïve and biologic-failed populations, respectively. All scenario analyses resulted in minor changes in costs, except for scenarios on dose escalation and re-induction, which affects costs of treatments differently. This suggests that the model is reasonably robust to structural uncertainty.

Table 51: Scenario analysis for a 10-year time horizon in the biologic-naïve population

Scenario	Incremental costs relative to mirikizumab (list price)			Incremental costs relative to mirikizumab (PAS price)		
	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV: intravenous; PAS: Patient Access Scheme; SC: subcutaneous.

Table 52: Scenario analysis for a 10-year time horizon in the biologic-failed population

Scenario	Incremental costs relative to mirikizumab (list price)			Incremental costs relative to mirikizumab (PAS price)		
	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs relative to mirikizumab (list price)			Incremental costs relative to mirikizumab (PAS price)		
	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV: intravenous; PAS: Patient Access Scheme; SC: subcutaneous.

B.4.5 *Subgroup analysis*

Data for key subgroups of biologic-naïve and biologic-failed patients are presented in Sections B.4.3 and B.4.4. No other subgroups were considered.

B.4.6 *Interpretation and conclusions of economic evidence*

As outlined in Section B.1.1, vedolizumab and ustekinumab represent 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 ustekinumab and vedolizumab in relevant patient subgroups under the assumption that the treatments have the same efficacy.

Overall, mirikizumab at its with-PAS price was found to be cost-saving when compared to these comparators of relevance at their list prices. In the biologic-naïve and biologic-failed subgroups respectively, mirikizumab is associated with a cost-saving of [redacted] and [redacted] versus ustekinumab, [redacted] and [redacted] versus vedolizumab IV and [redacted] and [redacted] versus vedolizumab IV/SC. A series of sensitivity and scenario analyses all confirmed the base case analysis of mirikizumab as a cost-neutral option. If it were to be approved, the results of the analysis demonstrate that mirikizumab would offer patients with UC a valuable new treatment option, that is a well-tolerated and efficacious with a novel mode of action and a convenient maintenance dosing schedule, while at least offering budget neutrality to the NHS.

B.5 References

1. Eli Lilly (Data on File) Mirikizumab Draft SmPC (2022)
2. NICE. UK NICE health technology evaluations: the manual. Process and methods. Available at: www.nice.org.uk/process/pmg36. [Accessed 22 November 2022]. 2022.
3. National Institute for Health and Care Excellence (NICE). Ustekinumab for treating moderately to severely active ulcerative colitis [TA633]. Available at: https://www.nice.org.uk/guidance/ta633/evidence. [Accessed 06 September 2022].
4. National Institute for Health and Care Excellence (NICE). Guselkumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA521]. Available at: https://www.nice.org.uk/guidance/ta521 [Accessed: 11 October 2022].
5. National Institute for Health and Care Excellence (NICE). Risankizumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA596]. Available at: https://www.nice.org.uk/guidance/ta596 [Accessed: 11 October 2022].
6. National Institute for Health and Care Excellence (NICE). Bimekizumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA723]. Available at: https://www.nice.org.uk/guidance/ta723 [Accessed: 11 October 2022].
7. National Institute for Health and Care Excellence (NICE). Risankizumab for treating active psoriatic arthritis after inadequate response to DMARDs [TA803]. Available at: https://www.nice.org.uk/guidance/ta803. [Accessed 23 November 2022].
8. Tang C, Chen S, Qian H, et al. Interleukin-23: as a drug target for autoimmune inflammatory diseases. Immunology 2012;135:112-124.
9. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis. Gastroenterology 2020;158:537-549.e10.
10. Langrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. Journal of Experimental Medicine 2005;201:233-240.
11. Hue S, Ahern P, Buonocore S, et al. Interleukin-23 drives innate and T cell–mediated intestinal inflammation. Journal of Experimental Medicine 2006;203:2473-2483.
12. Teng MWL, Bowman EP, McElwee JJ, et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nature Medicine 2015;21:719-729.
13. Feuerstein JD, Cheifetz AS. Ulcerative Colitis: Epidemiology, Diagnosis, and Management. Mayo Clinic Proceedings 2014;89:1553-1563.
14. Hendrickson BA, Gokhale R, Cho JH. Clinical Aspects and Pathophysiology of Inflammatory Bowel Disease. Clinical Microbiology Reviews 2002;15:79-94.
15. Conrad K, Roggenbuck D, Laass MW. Diagnosis and classification of ulcerative colitis. Autoimmunity Reviews 2014;13:463-466.
16. Gajendran M, Loganathan P, Jimenez G, et al. A comprehensive review and update on ulcerative colitis. Disease-a-Month 2019;65:100851.
17. Harbord M, Annese V, Vavricka SR, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. Journal of Crohn's and Colitis 2015;10:239-254.
18. van Sommeren S, Janse M, Karjalainen J, et al. Extraintestinal Manifestations and Complications in Inflammatory Bowel Disease: From Shared Genetics to Shared Biological Pathways. Inflammatory Bowel Diseases 2014;20:987-994.
19. Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. Journal of Crohn's and Colitis 2017;11:649-670.
20. Roberts-Thomson IC, Bryant RV, Costello SP. Uncovering the cause of ulcerative colitis. JGH Open 2019;3:274-276.
21. National Health Service (NHS). Ulcerative colitis. Available at: https://www.nhs.uk/conditions/ulcerative-colitis/. [Accessed 03 August 2022].

22. Clarivate. Ulcerative Colitis Disease Landscape and Forecast. Available at: https://clarivate.com/products/research-reports/report/dlsfim0009-biopharma-ulcerative-colitis-landscape-forecast/. [Accessed 03 August 2022].
23. King D, Reulen RC, Thomas T, et al. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. Alimentary Pharmacology & Therapeutics 2020;51:922-934.
24. Pasvol TJ, Horsfall L, Bloom S, et al. Incidence and prevalence of inflammatory bowel disease in UK primary care: a population-based cohort study. BMJ Open 2020;10:e036584.
25. IBD Registry. IBD Biological Therapies Audit Annual Report 2021. Available at: https://ibdregistry.org.uk/wp-content/uploads/2021/07/2021-07-Annual-Biologics-Report-V01.pdf. [Accessed 15 November 2022].
26. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1-s106.
27. Sturm A, Maaser C, Calabrese E, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects. Journal of Crohn's and Colitis 2018;13:273-284.
28. Paine ER. Colonoscopic evaluation in ulcerative colitis. Gastroenterol Report 2014;2:161-168.
29. Naegeli AN, Hunter T, Dong Y, et al. Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients. Crohn's & Colitis 360 2021;3:otab007.
30. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an Integrated Clinical, Molecular and Serological Classification of Inflammatory Bowel Disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Canadian Journal of Gastroenterology 2005;19:269076.
31. Magro F, Rodrigues A, Vieira AI, et al. Review of the disease course among adult ulcerative colitis population-based longitudinal cohorts. Inflammatory Bowel Diseases 2012;18:573-583.
32. Fumery M, Singh S, Dulai PS, et al. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clinical Gastroenterology and Hepatology 2018;16:343-356.e3.
33. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. Journal of Crohn's and Colitis 2007;1:10-20.
34. Bhala N, Hart A, Watts D, et al. Disease activity, burden and suffering in patients with ulcerative colitis in the UK cohort recruited into the global ICONIC study. Frontline Gastroenterology 2022:doi:10.1136/flgastro-2022-102104.
35. Dubinsky MC, Watanabe K, Molander P, et al. Ulcerative Colitis Narrative Global Survey Findings: The Impact of Living With Ulcerative Colitis-Patients' and Physicians' View. Inflamm Bowel Dis 2021;27:1747-1755.
36. Schreiber S, Panés J, Louis E, et al. Perception gaps between patients with ulcerative colitis and healthcare professionals: an online survey. BMC Gastroenterology 2012;12:108.
37. Nocerino A, Nguyen A, Agrawal M, et al. Fatigue in Inflammatory Bowel Diseases: Etiologies and Management. Advances in Therapy 2020;37:97-112.
38. Srinath AI, Walter C, Newara MC, et al. Pain management in patients with inflammatory bowel disease: insights for the clinician. Therapeutic Advances in Gastroenterology 2012;5:339-357.
39. McMullan C, Pinkney TD, Jones LL, et al. Adapting to ulcerative colitis to try to live a 'normal' life: a qualitative study of patients' experiences in the Midlands region of England. BMJ Open 2017;7:e017544.
40. Vaizey CJ, Gibson PR, Black CM, et al. Disease status, patient quality of life and healthcare resource use for ulcerative colitis in the UK: an observational study. Frontline Gastroenterology 2014;5:183-189.

41. Irving P, Barrett K, Nijher M, et al. Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. Evidence Based Mental Health 2021;24:102-109.
42. Ghosh S, Sensky T, Casellas F, et al. A Global, Prospective, Observational Study Measuring Disease Burden and Suffering in Patients With Ulcerative Colitis, Using the Pictorial Representation of Illness and Self-measure Tool. Journal of Crohn's and Colitis 2020;15:228-237.
43. Adelphi. (Data on File). Adelphi Real World - Disease Specific Programme in Ulcerative Colitis, UK 2020-2021.
44. Ali T, Skup M, Yang M, et al. P477 Increased risk of comorbidities associated with ulcerative colitis. Journal of Crohn's and Colitis 2013;7:S200-S201.
45. Lin A, Roth H, Anyane-Yeboa A, et al. Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Inflammatory Bowel Diseases 2020;27:947-955.
46. Cohen RD, Yu AP, Wu EQ, et al. Systematic review: the costs of ulcerative colitis in Western countries. Alimentary Pharmacology & Therapeutics 2010;31:693-707.
47. Ruiz-Casas L, Evans J, Rose A, et al. The LUCID study: living with ulcerative colitis; identifying the socioeconomic burden in Europe. BMC Gastroenterology 2021;21:456.
48. National Institute for Health and Care Excellence (NICE). Ulcerative colitis: management (2019). Available at: https://www.nice.org.uk/guidance/ng130/chapter/recommendations#mild-moderate-and-severe-ulcerative-colitis. [Accessed 05 August 2022]. .
49. Damião A, de Azevedo MFC, Carlos AS, et al. Conventional therapy for moderate to severe inflammatory bowel disease: A systematic literature review. World J Gastroenterol 2019;25:1142-1157.
50. Kamath C, Brenner EJ. The safe use of inflammatory bowel disease therapies during the COVID-19 pandemic. Current Research in Pharmacology and Drug Discovery 2022;3:100101.
51. National Institute for Health and Care Excellence (NICE). Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [TA329]. Available at: https://www.nice.org.uk/guidance/ta329. [Accessed 08 August 2022].
52. Gemayel NC, Rizzello E, Atanasov P, et al. Dose escalation and switching of biologics in ulcerative colitis: a systematic literature review in real-world evidence. Current Medical Research and Opinion 2019;35:1911-1923.
53. National Institute for Health and Care Excellence (NICE). Vedolizumab for treating moderately to severely active ulcerative colitis [TA342]. Available at: https://www.nice.org.uk/guidance/ta342. [Accessed: 08 August 2022].
54. National Institute for Health and Care Excellence (NICE). Filgotinib for treating moderately to severely active ulcerative colitis [TA792]. Available at: https://www.nice.org.uk/guidance/ta792. [Accessed 22 July 2022].
55. National Institute for Health and Care Excellence (NICE). Ozanimod for treating moderately to severely active ulcerative colitis [TA828]. Available at: https://www.nice.org.uk/guidance/ta828. [Accessed 05 October 2022].
56. Singh H, Wilson L, Pandey A, et al. P540 Real-world evidence on treatment switching in patients with moderate-to-severe ulcerative colitis: a systematic review of literature. Journal of Crohn's and Colitis 2021;15:S511-S512.
57. Faubion WA, Jr., Loftus EV, Jr., Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001;121:255-60.
58. Su C, Lichtenstein GR. Treatment of inflammatory bowel disease with azathioprine and 6-mercaptopurine. Gastroenterology Clinics 2004;33:209-234.
59. Peyrin-Biroulet L, Sandborn WJ, Panaccione R, et al. Tumour necrosis factor inhibitors in inflammatory bowel disease: the story continues. Therapeutic Advances in Gastroenterology 2021;14:1-22.

60. Atreya R, Neurath MF and Siegmund B. Personalizing Treatment in IBD: Hype or Reality in 2020? Can We Predict Response to Anti-TNF? Frontiers in Medicine 2020;7:517.
61. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine 2013;369:699-710.
62. Gisbert JP, Chaparro M. Primary Failure to an Anti-TNF Agent in Inflammatory Bowel Disease: Switch (to a Second Anti-TNF Agent) or Swap (for Another Mechanism of Action)? Journal of Clinical Medicine 2021;10:5318.
63. European Medicines Agency. Summary of Product Characteristics - Ustekinumab. Available at https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. [Accessed 10 August 2022].
64. Rubin D, Panaccione R, Potts Bleakman A, et al. P028 Communicating Needs and Features of IBD Experiences (CONFIDE) Survey: Patient and Healthcare Professional Perspectives on Experience of Ulcerative Colitis Symptoms. Official journal of the American College of Gastroenterology | ACG 2021;116:S7.
65. Feuerstein JD, Moss AC, Farraye FA. Ulcerative Colitis. Mayo Clinic proceedings 2019;94:1357-1373.
66. Holmer A, Singh S. Overall and comparative safety of biologic and immunosuppressive therapy in inflammatory bowel diseases. Expert Review of Clinical Immunology 2019;15:969-979.
67. Armuzzi A, DiBonaventura MD, Tarallo M, et al. Treatment patterns among patients with moderate-to-severe ulcerative colitis in the United States and Europe. PLoS One 2020;15:e0227914.
68. Singh S, George J, Boland BS, et al. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. Journal of Crohn's and Colitis 2018;12:635-643.
69. Danese S, Allez M, van Bodegraven AA, et al. Unmet Medical Needs in Ulcerative Colitis: An Expert Group Consensus. Digestive Diseases 2019;37:266-283.
70. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. The American Journal of Gastroenterology 2019;114:384-413.
71. Dawwas GK, Jajeh H, Shan M, et al. Prevalence and Factors Associated With Fecal Urgency Among Patients With Ulcerative Colitis and Crohn's Disease in the Study of a Prospective Adult Research Cohort With Inflammatory Bowel Disease. Crohn's & Colitis 360 2021;3:otab046.
72. Cleveland N, Torres J, Rubin DT. What Does Disease Progression Look Like in Ulcerative Colitis, and How Might It Be Prevented? Gastroenterology 2022;162:1396-1408.
73. Hanauer SB, Present DH, Rubin DT. Emerging issues in ulcerative colitis and ulcerative proctitis: individualizing treatment to maximize outcomes. Gastroenterology & Hepatology 2009;5:4-16.
74. Ghosh S, Sanchez Gonzalez Y, Zhou W, et al. Upadacitinib Treatment Improves Symptoms of Bowel Urgency and Abdominal Pain, and Correlates With Quality of Life Improvements in Patients With Moderate to Severe Ulcerative Colitis. Journal of Crohn's and Colitis 2021;15:2022-2030.
75. National Institute for Health and Care Excellence (NICE). Tofacitinib for moderately to severely active ulcerative colitis. Technology appraisal guidance [TA547]. Available at: https://www.nice.org.uk/guidance/ta547. [Accessed 06 September 2022].
76. National Institute for Health and Care Excellence (NICE). Upadacitinib for treating moderately to severely active ulcerative colitis [GID-TA10866]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10866. [Accessed 05 October 2022].
77. Lindsay JO, Armuzzi A, Gisbert JP, et al. Indicators of suboptimal tumor necrosis factor antagonist therapy in inflammatory bowel disease. Digestive and Liver Disease 2017;49:1086-1091.

78. Tsai HH, Punekar YS, Morris J, et al. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Alimentary Pharmacology & Therapeutics 2008;28:1230-9.
79. Eli Lilly (Data on file): LUCENT-1 Clinical Study Report.
80. Eli Lilly (Data on file). LUCENT-2 Clinical Study Report.
81. Eli Lilly (Data on file). LUCENT-2 Clinical Study Report, Additional Analyses 1.
82. Center for Drug Evaluation and Research. Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry. Available at: https://www.fda.gov/files/drugs/published/Ulcerative-Colitis--Clinical-Trial-Endpoints-Guidance-for-Industry.pdf. [Accessed 15 November 2022].
83. Geboes K, Riddell R, Öst A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000;47:404-409.
84. Eli Lilly (Data on File). LUCENT-1 Statistical Analysis Plan (2021)
85. Eli Lilly (Data on File). LUCENT-2 Statistical Analysis Plan (2021)
86. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009;28:586-604.
87. Bretz F, Posch M, Glimm E, et al. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biometrical Journal 2011;53:894-913.
88. Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. Statistics in Medicine 2014;33:693-713.
89. European Medicines Agency. Summary of Product Characteristics - Upadacitinib. Available at https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf. [Accessed 10 August 2022].
90. Garud S, Brown A, Cheifetz A, et al. Meta-analysis of the placebo response in ulcerative colitis. Digestive Diseases and Sciences 2008;53:875-91.
91. Jairath V, Zou GY, Parker CE, et al. Placebo response and remission rates in randomised trials of induction and maintenance therapy for ulcerative colitis. Cochrane Database of Systematic Reviews 2017;9:Cd011572.
92. Sedano R, Hogan M, Nguyen TM, et al. Systematic Review and Meta-Analysis: Clinical, Endoscopic, Histological and Safety Placebo Rates in Induction and Maintenance Trials of Ulcerative Colitis. Journal of Crohn's and Colitis 2022;16:224-243.
93. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. Nature Reviews Gastroenterology & Hepatology 2015;12:472-85.
94. Sandborn WJ, Baert F, Danese S, et al. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology 2020;158:562-572.e12.
95. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine 2019;381:1201-1214.
96. Cameron C, Hutton B, Druchok C, et al. Importance of assessing and adjusting for cross-study heterogeneity in network meta-analysis: a case study of psoriasis. Journal of Comparative Effectiveness Research 2018;7:1037-1051.
97. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. Journal of Clinical Epidemiology 2009;62:857-64.
98. Loos AM, Liu S, Segel C, et al. Comparative effectiveness of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis. Journal of the American Academy of Dermatology 2018;79:135-144.e7.
99. Dias S, Sutton AJ, Welton NJ, et al. Evidence Synthesis for Decision Making 3: Heterogeneity—Subgroups, Meta-Regression, Bias, and Bias-Adjustment. Medical Decision Making 2013;33:618-640.
100. Macaluso FS, Maida M, Ventimiglia M, et al. Factors Affecting Clinical and Endoscopic Outcomes of Placebo Arm in Trials of Biologics and Small Molecule Drugs in Ulcerative Colitis: A Meta-Analysis. Inflammatory Bowel Diseases 2019;25:987-997.

101. Eli Lilly (Data on file). LUCENT-2 Clinical Study Report, Additional Analyses 2.
102. Einarson TR, Bereza BG, Ying Lee X, et al. Dose escalation of biologics in Crohn's disease: critical review of observational studies. Curr Med Res Opin 2017;33:1433-1449.
103. Briggs ASM, Claxton, K. Decision Modelling for Health Economic Evaluation. . International Journal of Epidemiology 2007;36:476-477.
104. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Infliximab. Available at: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf [Accessed 31 August 2022].
105. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Adalimumab. Available at: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf [Accessed 31 August 2022].
106. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Golimumab. Available at: https://www.ema.europa.eu/en/documents/product-information/simponi-epar-product-information_en.pdf [Accessed 31 August 2022].
107. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Vedolizumab. Available at https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf. [Accessed 31 August 2022].
108. European Medicines Agency. Summary of Product Characteristics - Tofacitinib. Available at https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. [Accessed 10 August 2022].
109. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Filgotinib. Available at https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf [Accessed 31 August 2022].
110. European Medicines Agency. Summary of Product Characteristics - Ozanimod. Available at https://www.ema.europa.eu/en/documents/product-information/zeposia-epar-product-information_en.pdf. Accessed 10 August 2022.
111. UK Office for National Statistics. National life tables: UK 2018-2020. Available at: https://www.ons.gov.uk/releases/nationallifetableslifeexpectancyintheuk2018to2020. [Accessed 23 November 2022].
112. Monthly Index of Medical Specialities (MIMS). Available at: https://www.mims.co.uk/. [Accessed 8 April 2022].
113. British National Formulary (BNF). Available at: https://bnf.nice.org.uk/. [Accessed 22 September 2022].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]

Summary of Information for Patients (SIP)

December 2022

File name	Version	Contains confidential information	Date
ID3973_Eli Lilly_Mirikizumab in Ulcerative Colitis_SIP	1.0	No	8th December 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: 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 ulcerative colitis (UC) for whom conventional treatment or biological treatment cannot be tolerated or is not working well enough. This means that patients may be eligible if they have never had a biologic therapy before (termed “biologic-naïve”) or if they have had a biologic therapy before and it didn’t work well enough for them (“biologic-failed”). This patient population is in line with the population expected to be included in the regulatory paperwork for mirikizumab in the United Kingdom (UK), known as its marketing authorisation (see response to 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 regulatory paperwork (marketing authorisation) for mirikizumab is currently pending. Please refer to Section B.1.2 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:

Lilly are currently working with Crohn's and Colitis UK and IBD Relief on developing sponsorship agreements to support disease awareness activities.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is ulcerative colitis (UC)?

UC is a long-term condition where the bowel becomes inflamed; it is a form of inflammatory bowel disease (IBD). The inflammation occurs because the body's immune system, which usually protects against sickness, becomes too highly activated and causes small ulcers to develop on the inside lining of the gut, which can bleed and produce pus.[1] In UC, this inflammation specifically affects the lower parts of the digestive system called the colon and rectum.[2]

How many people have UC, and what causes it?

UC is the most common inflammatory bowel disease in the UK.[3] It is estimated that around 1 in 420 people are living with the condition in England, equating to a total of around 146,000 people.[4] Worldwide, cases are also expected to increase over the next ten years from approximately 1.8 million in 2017 to around 1.9 million in 2027.[5] The exact cause of UC is unknown, but it has been found that people with a family history of inflammatory bowel disease or a history of smoking may be at a higher risk of developing UC.[6]

What are the main symptoms of UC?

People with UC report that the disease is changeable and unpredictable, with periods of feeling worse and having more symptoms (flare-ups) and other periods with fewer symptoms and feeling better (remission). Patients commonly report having bloody diarrhoea with or without mucus, bowel urgency (suddenly needing to go to the toilet) and varying degrees of abdominal pain which is relieved by going to the toilet.[7] These symptoms are usually experienced during a flare-up when the disease is more active. UC can be classified by how severe it is (mild, moderate or severe), and it is reported that over 50% of people living with UC in England have moderate to severe disease.[8]

Disease burden

People with UC have been reported to experience worse health-related quality of life (HRQoL) as compared with people without UC.[9] In a global survey conducted in 10 different countries, 84% of people with UC reported it to be mentally exhausting and 65% felt that it controlled their lives.[10] In addition, a large proportion of people (more than 8 in 10) with UC experience bowel urgency, a particularly bothersome symptom.[11] As such, it is not surprising that UC is

reported to have a negative impact on daily activities like attending school or work, or carrying out regular daily routines.[9]

As well as the symptoms directly related to UC, patients often report other medical conditions that occur at the same time. For example, a recent global study found that fatigue, anxiety/depression and sleep disorders were reported by more than 20% of surveyed people with UC.[12] People with UC also have a higher risk of developing issues associated with poor food absorption, diabetes and cardiovascular issues as compared with people without UC.[13]

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?

Although no 'gold standard' method exists to diagnose UC, the European Crohn's and Colitis Organisation recommends that a diagnosis should be made based on a combination of several approaches, including observation of the signs and symptoms of UC (clinical), the results of medical tests (laboratory), and visual inspection of the gastrointestinal tract (imaging, including an endoscopy which involves insertion of a small tube with a camera inside it into the body). Initial examination normally involves testing the patient's pulse and blood pressure, along with feeling and examining their abdomen.[14]

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.

Current treatments

In England and Wales, the management and treatment of UC is guided by advice from the National Institute for Health and Care Excellence (NICE), via the document NG130 which can be found here: https://www.nice.org.uk/guidance/ng130. In general, UC is treated in a stepwise manner, with medication changed when a patient does not respond to, or stops responding to, the current treatment. The primary aim of treatment is to manage patients' symptoms in order to achieve and maintain clinical remission (where no symptoms remain) or response (where symptoms are still present but improved). Clinical remission or response can be assessed by healthcare professionals using a rating scale called the Mayo scoring system. This involves various domains, such as stool frequency and rectal bleeding, being scored on a scale of 0–3 and summed to a maximum of 12, with a higher score corresponding to more severe disease. Clinical remission is typically defined as a Mayo score of 2 or less, with no

individual sub-score scoring above 1, whereas scores of 3–5, 6–10 and 11–12 broadly represent mild, moderate and severe disease, respectively.[15]

To begin with, moderate to severely active UC is treated with medicines which alter the functioning of the immune system as a whole, rather than specifically targeting the inflammation of UC. These treatments, known as immunomodulators and corticosteroids, are defined by the general term "conventional 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 effectively control their UC or its symptoms.[16, 17] If this happens, or if a patient is unsuitable to receive any conventional therapies at all, patients can be switched to receive stronger medicines which have specific targets within the immune system. These specific targets are stopped from working, thereby reducing the inflammation that occurs with UC.

Several targeted treatment options are available for patients with UC in the UK, as shown in Figure 1. People with UC may try more than one of these treatments in order to find one that works well for them, but they may find that if one drug within a class or sub-class does not work well, then others within the same class or sub-class might not work well either.[18] The end of the treatment pathway, for patients who continue to have poorly controlled disease or who elect to take it, is surgery to remove part of the gastrointestinal (GI) tract. However, this can be associated with serious complications, so it is typically reserved as a last resort.[19]

Limitations of current treatment options and unmet needs

In the UK, patients with UC and their clinicians currently have several treatment options to consider. However, these are associated with some limitations. Conventional therapies, typically used at first line, are associated with problems such as limited response, low rates of maintained remission and both short- and long-term side effects.[16, 17, 19]

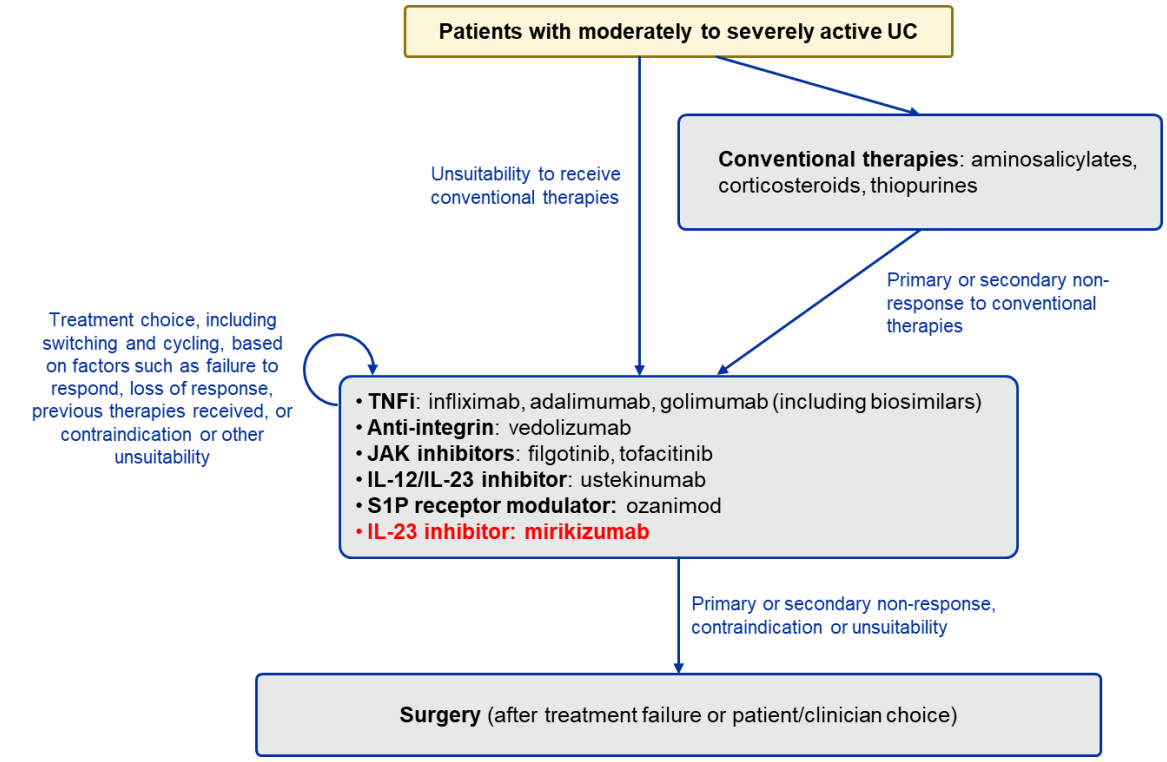
Biologic options considered after treatment failure with conventional therapies can be associated with issues such as taking a long time to begin working after treatment begins, which makes managing moving between different treatments more challenging, lower efficacy after patients have previously failed on one type of treatment called a TNF-alpha inhibitor (TNFi), and adverse effects risk.[20-22] In addition, while TNFis are often used as the first biologic option, a study showed that approximately one-third of patients showed no initial response to TNFi 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").[23, 24]

As such, despite several options being available, there remains an unmet need in the UK for a new treatment for patients with moderate to severe UC that works well, has a tolerable safety profile, and has a new mechanism of action.

Mirikizumab

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

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



Abbreviations: IL: interleukin; JAK: Janus kinase; S1P: sphingosine-1-phosphate; TNFi: tumour necrosis factor alpha inhibitors; UC: ulcerative colitis

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 above, the symptoms of UC 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 UC has a considerable negative impact on patients' lives which is reflected by reductions in their overall quality of life.

The impact of UC, as reported by patients

In 2021, a global survey of 2,100 patients with UC was carried out. For patients with moderate to severe disease, the key findings were that 84% felt UC was mentally exhausting and 65% felt that they spend more time in the bathroom than anywhere else, visiting the bathroom an average of 10 times a day on their worst days.[10] It was also found that the most important

aspects of UC management according to patients were the ability to perform daily activities (59%), avoidance of toileting accidents (55%) and the ability to control pain (53%).[10]

The quality of life of people with UC

Studies investigating the impact of a disease or condition on patients' quality of life typically make 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 2019 made use of two of these surveys, the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and the Brief Illness Perception Questionnaire (B-IPQ) to investigate the effect of UC in 143 people with the condition.[25] The study found that 53% of patients had low HRQoL, defined as a SIBDQ score of less than 50. Furthermore, 46% of patients reported anxiety and/or depression, 36% had poor sleep quality, 64% reported a negative impact on work and 73% had their social activities affected by UC over the disease course.[25]

Impact of current treatments on patients

In the UK, corticosteroids are commonly used for people with moderate to severe UC, but some people do not respond to them.[16] This was observed in a study of 185 patients with UC who were treated with corticosteroids, which reported that, although 54% entered complete remission, 16% did not respond at all.[16] Additionally, many patients 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 remained well, while nearly one-third (29%) had progressed to further disease.[16] HRQoL in these patients was reduced, and while disease progression was thought to be a factor in this, common side effects of corticosteroids such as weight gain and acne may have also contributed.[16] Biologic treatment options have been shown to have a positive impact on HRQoL, particularly when they are able to improve symptoms in the short-term.[26] 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 UC, and in particular, if loss of response occurs.[26]

Patient preferences for treatment objectives

A patient preference study carried out in 2017 found that people with UC 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 movement urgency (17.1%).[3]

Unmet need and the value of mirikizumab

The above studies show that there is a significant unmet need for an effective treatment option in UC that has manageable side effects, offers an alternative way of working to currently available options, and that can maintain corticosteroid-free remission and control of symptoms including bowel urgency.

How well mirikizumab works (its efficacy) and its side effects profile (its safety) were assessed in the Phase III, randomised LUCENT-1 and LUCENT-2 clinical trials, described further in response to Section 3d. These studies were 'placebo-controlled', meaning the efficacy and safety of mirikizumab was compared with placebo, an inert substance that has no effect on the body and is used as a control in clinical trials. Furthermore, the trials were 'double-blind': neither the patients nor the doctors in the studies knew whether each patient had been randomly assigned to receive mirikizumab or placebo. Regardless of whether patients were

assigned to receive mirikizumab or placebo, patients were permitted to continue stable doses of conventional therapy with immunomodulators or corticosteroids.

The results of the LUCENT trials showed that, as compared with placebo, mirikizumab was associated with statistically significant effects in key clinical outcomes, such as the achievement of clinical response and clinical remission, in which stool frequency, rectal bleeding and the visual assessment of the gastrointestinal tract are all improved. In addition, mirikizumab has also shown statistically significant effects, as compared with placebo, in reducing bowel movement urgency. In addition, treatment with mirikizumab was associated with a tolerable safety profile. See responses to Section 3e (efficacy) and 3g (safety) for additional details.[27]

Mirikizumab is a new treatment option in a disease that is chronic (long-term) in nature, and it works in the body in a way that is unique as compared with other currently available treatment options (see response to Question 3a for further details. Overall, it is anticipated that its novel way of working and good efficacy will reduce the need for patients to use corticosteroids, and may delay the need for surgery as a last-line option. Therefore, mirikizumab has the potential to fulfil the considerable unmet need that currently exists for people with moderate to severe UC.

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 digestive tract in UC. 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.[28] Therefore, by blocking the action of IL-23, mirikizumab reduces the inflammation in the colon and rectum that underlies the symptoms and disease activity of UC, and thus helps to reduce symptoms for patients. Clinical studies have demonstrated that genetic deletion or inhibition of IL-23 can prevent inflammation of the intestine, showing the importance of this as a target for UC.[28]

Innovation in patient care

As outlined in Section 2c, several biologic treatment options are available for patients with UC and switching between them in order to try to maintain control of the disease is common. However, once a person with UC has failed a biologic treatment with a certain way of working

("mechanism of action"), they may be less likely to respond to another treatment that acts in the same way.[21] For this reason, the availability of new options with new mechanisms of action would be valuable for patients and clinicians.

Currently, no treatment options approved for use in England and Wales work by inhibiting IL-23. As such, mirikizumab represents a new way of targeting the immune system for the treatment of UC. In the Phase III LUCENT trials, mirikizumab has shown high efficacy in these patient groups, reducing symptoms and the need for treatment with corticosteroids. Additionally, mirikizumab has been shown to reduces bowel urgency, which patients have identified as a particularly important unmet need (see response to section 2d for more information).[3, 27, 29] As such, the approval for use of mirikizumab would provide patients with UC, for whom other current treatment has not worked well enough, or who are unsuitable to receive currently available treatments due to medical reasons, with a new, effective and well-tolerated treatment option.

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?

Mirikizumab

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 it, and the maintenance dose which is given longer term to maintain disease control. Further details are outlined below:

- Induction dose: the first dose of 300 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 300 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, 200 mg mirikizumab will be given by an injection under the skin (subcutaneous [SC] injection) and then every four weeks from that point onwards. Treatment is given via a pre-filled pen, only containing 100 mg per pen, so two injections are required to receive the full 200 mg. 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 UC can do it themselves if they feel comfortable to do so.

The induction dosing takes place over 12 weeks. After this point, if a doctor concludes there has been a good enough clinical response to the induction treatment, patients will transition to receive the SC maintenance dosing. However, if patients do not show an adequate response after 12 weeks, induction dosing may be continued by IV infusion for another 12 weeks – this is called “extended induction”. The extended induction follows the same dosing schedule as the initial induction: patients receive one dose every 4 weeks for a total of three doses. If patients show an improvement in disease after the extended induction period, they can then switch to the maintenance dosing schedule. For patients who do not show any evidence of getting a clinical benefit to the induction therapy by this point, mirikizumab treatment should be stopped.

For patients who are receiving maintenance therapy but lose response to it, they may receive the induction dosing again: IV infusion of 300 mg mirikizumab by a healthcare professional for a total of three times, spaced four weeks apart – this is called “re-induction”. If patients begin to respond to mirikizumab again, they can resume the subcutaneous maintenance therapy they were previously receiving.

Other treatments

Other treatments for UC 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, patients receiving other treatment options cannot undergo a re-induction period if they lose response whilst receiving maintenance therapy. Instead, the regulatory paperwork for some treatment options, such as adalimumab, golimumab and vedolizumab, states that the maintenance dose should be increased (known as “dose escalation”), 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 ongoing and completed clinical trials for mirikizumab are outlined below:

- The completed Phase II trial, which evaluated the effectiveness of different doses of mirikizumab in the induction and maintenance phases compared with placebo, is summarised in Table 1.[30]
- The pivotal Phase III LUCENT-1 and LUCENT-2 trials are summarised in Table 2 and Table 3, respectively. These studies assessed how well the drug worked (the "efficacy") and how safe mirikizumab was compared with placebo.[31] LUCENT-1 was an induction study with IV mirikizumab treatment for up to 12 weeks, followed by a 40-week randomised-withdrawal maintenance study (LUCENT-2), representing up to 52 weeks of therapy.[30]
- The ongoing Phase III LUCENT-3 trial, designed to evaluate the long-term efficacy and safety of mirikizumab, is summarised in Table 4.

Table 1: Overview of the Phase II (NCT02589665) clinical trial

NCT02589665[32]	
Study design	Phase II, multicentre, randomised, double-blind, placebo-controlled study of mirikizumab[a]
Location	International
Population	Adult patients with moderate to severe ulcerative colitis
Total number of enrolled patients	249
Intervention	• Induction: mirikizumab IV 50 mg, 200 mg and 600 mg every 4 weeks • Maintenance: mirikizumab SC 200 mg every 12 weeks • Maintenance: mirikizumab SC 200 mg every 4 weeks • Open-label extension: mirikizumab IV 200 mg, 600 mg and 1,000 mg every 4 weeks
Comparator	• Induction: placebo IV every 4 weeks • Maintenance: placebo SC every 4 weeks

Key inclusion criteria	• Aged 18–75 years (inclusive) at initial screening
	• Have moderate to severe active UC as defined by a Mayo score of 6 to 12 with an endoscopic subscore ≥2 within 14 days before the first dose of study treatment
	• Either:
	  ○ Be naive to biologic therapy and have at least 1 of the following:
	  ▪ Inadequate response or failure to tolerate current treatment with oral or intravenous corticosteroids or immunomodulators, or
	  ▪ A history of corticosteroid dependence
	  Or
	  ○ Have received treatment with one or more biologic agents (e.g., TNF antagonists or vedolizumab) at doses approved for

	the treatment of UC with documented history of failure to respond to or tolerate such treatment
Key exclusion criteria	• Have been diagnosed with indeterminate colitis, proctitis or Crohn's Disease • Have had surgery for treatment of UC or are likely to require surgery for UC during the study • Have received any of the following for treatment of UC: cyclosporine or thalidomide within 30 days of screening, corticosteroid enemas, corticosteroid suppositories, or topical treatment with 5-aminosalicyclic acid within 30 days of screening
Completion date	7th May 2019

[a] A randomised study meant that mirikizumab was compared with placebo and patients were randomly allocated to either group. In a double-blind study, patients do not know whether they are receiving placebo or mirikizumab, and neither do the investigators.
Abbreviations: IV: intravenous; SC: subcutaneous; TNF: tumour necrosis factor; UC: ulcerative colitis.

Table 2: Overview of LUCENT-1 clinical trial

LUCENT-1 (NCT03518086)[31]	
Study design	Phase III, multicentre, randomised, double-blind, placebo-controlled induction study of mirikizumab[a]
Location	International
Population	Adult patients with moderately to severely active UC who have had an inadequate response to, loss of response, or intolerant to conventional or biologic therapy for UC
Total number of enrolled patients	1281
Intervention	300 mg mirikizumab IV every 4 weeks
Comparator	Placebo IV every 4 weeks
Key inclusion criteria	• Diagnosis of UC for at least 3 months prior to baseline • Confirmed diagnosis of moderately or severely active UC, as assessed by the modified Mayo score (MMS) • Demonstrated an inadequate response to, a loss of response to, or an intolerance to conventional or to biologic therapy for UC. • If female, must meet the contraception requirements
Key exclusion criteria	• Current diagnosis of Crohn's disease or unclassified inflammatory bowel disease • Participants with a previous colectomy • Participants with current evidence of toxic megacolon • Prior exposure to anti-IL12p40 antibodies (e.g. ustekinumab) or anti-IL-23p19 antibodies (e.g. risankizumab, brazikumab, guselkumab or tildrakizumab)
Completion date	21st January 2021

[a] A randomised study meant that mirikizumab was compared with placebo and patients were randomly allocated to either group. In a double-blind study, patients do not know whether they are receiving placebo or mirikizumab, and neither do the investigators.
Abbreviations: IV: intravenous; MMS: modified mayo score; SC: subcutaneous; UC: ulcerative colitis.

Table 3: Overview of LUCENT-2 clinical trial

LUCENT-2 (NCT03524092)[30]	
Study design	Phase III, multicentre, randomised, double-blind, placebo-controlled maintenance study of mirikizumab[a]

Location	International
Population	Adult patients with moderately to severely active UC who have had an inadequate response to, loss of response, or intolerant to conventional or biologic therapy for UC
Total number of enrolled patients	1178
Intervention	• 200 mg mirikizumab SC every 4 weeks • Open-label 300 mg mirikizumab IV every 4 weeks
Comparator	Placebo IV every 4 weeks
Key inclusion criteria	• Have completed Study LUCENT-1 (NCT03518086), with at least 1 study drug administration and without early termination of study drug • Are willing and able to complete the scheduled study assessments, including endoscopy and daily diary entry • If female, must meet the contraception requirements
Key exclusion criteria	• Participants diagnosed with Crohn's disease or unclassified inflammatory bowel disease during the LUCENT-1 induction study • Participants with a bowel resection or other surgery for the treatment of UC during LUCENT-1, or were likely to require surgery for the treatment of UC during LUCENT-1 • Participants with evidence of colonic dysplasia or have been diagnosed with cancer of the gastrointestinal tract during LUCENT-1 • Participants diagnosed with clinically important infection including, but not limited to, hepatitis B, hepatitis C, HIV/AIDS, and active tuberculosis during LUCENT-1 • Participants who initiate a new prohibited medication during LUCENT-1 • Participants with certain laboratory abnormalities prior to start of LUCENT-2 that would require permanent discontinuation from study drug
Completion date	3rd November 2021

[a] A randomised study meant that mirikizumab was compared with placebo and patients were randomly allocated to either group. In a double-blind study, patients do not know whether they are receiving placebo or mirikizumab, and neither do the investigators.
Abbreviations: AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus; IV: intravenous; SC: subcutaneous ; UC: ulcerative colitis.

Table 4. Overview of LUCENT-3 clinical trial

LUCENT-3 (NCT03519945)[33]	
Study design	Phase III, multicentre, open-label extension study[a]
Location	International
Population	Adult patients with moderately to severely active UC
Total number of enrolled patients	960 (estimated)
Intervention	Open-label 200 mg mirikizumab SC every 4 weeks
Comparator	N/A
Key inclusion criteria	• Participants from the Phase II study (NCT02589665) or LUCENT-2 (NCT03524092) who have had at least one study drug administration and have not had early termination of study drug • Female participants must agree to contraception requirements

Key exclusion criteria	• Participants must not have developed a new condition, including cancer in the originator study • Participants must not have any important infections including, but not limited to, hepatitis B, hepatitis C, HIV/AIDS, and active tuberculosis during either originator study • Participants may not have received surgery for UC in the originator study or are likely to require surgery for treatment of UC during the study. • Participants must not have developed adenomatous polyps during the originator study that have not been removed prior to the start of this study
Completion date	1st July 2025 (estimated)

[a] All patients receive the study medicine (mirikizumab) and this is known by the patients and investigators. The study evaluates the long-term effects of the drug.
Abbreviations: AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus; SC: subcutaneous; UC: ulcerative colitis.

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.

Direct evidence for mirikizumab in UC

The direct evidence for the efficacy of mirikizumab compared with placebo in adults with moderately to severely active ulcerative colitis comes from two Phase III randomised, double-blind, placebo-controlled, multicentre studies (LUCENT-1 and LUCENT-2) (see response to 3d for detailed information).[27]

The key primary outcome of the LUCENT-1 induction trial was the proportion of patients who achieved clinical remission after 12 weeks of treatment with mirikizumab or placebo. Clinical remission was assessed based on the extent of rectal bleeding, stool frequency and endoscopic improvement a patient showed by this timepoint, and a modified version of the well-established Mayo scoring system was used to define and quantify whether a patient had improved enough to be defined as being in remission.[15, 34]

The results found that just less than double the proportion of patients receiving mirikizumab achieved clinical remission at Week 12 than those receiving placebo. Improvements were also seen in the proportion of patients who achieved clinical response and who saw improvement in bowel urgency in patients receiving mirikizumab compared to the placebo. Statistical tests found that these results are very unlikely to have happened due to chance and instead indicates mirikizumab to be more effective than placebo at allowing patients to achieve clinical remission, clinical response and improvements in bowel urgency. These results were broadly consistent regardless of whether patients had previously received biologic therapy before enrolment to the LUCENT trials or not.

In LUCENT-2, the primary endpoint was the achievement of clinical remission at Week 40 in patients who responded to mirikizumab induction dosing at Week 12 of the LUCENT-1 trial.

Therefore, at this timepoint, these patients had received a total of 52 weeks of mirikizumab treatment, including the 12 weeks in LUCENT-1. Similar to the results of the LUCENT-1 trial, the results showed that approximately double the proportion of receiving mirikizumab achieved clinical remission at Week 40 than those receiving placebo. In addition, more patients receiving mirikizumab in LUCENT-2 maintained the remission they showed at the end of the LUCENT-1 trial, as compared with those receiving placebo in LUCENT-2. As in LUCENT-1, similar results were seen for patients who had previously received biologic therapy before enrolment to the LUCENT trials as compared with those who had not.

In summary, the LUCENT-1 and -2 trials showed mirikizumab to be more effective at controlling the symptoms of UC than placebo.

Indirect evidence for mirikizumab in UC

As discussed in Section 2c, people with moderate to severe UC 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. However, the clinical trials discussed above provide data for the efficacy and safety of mirikizumab compared with placebo only, which is typical across previous clinical trials in UC, including in studies of comparators to mirikizumab. As such, a statistical method called a network meta-analysis (NMA) was used to obtain the necessary safety and efficacy information for mirikizumab compared with these other treatments.

Results from the NMAs which compared the LUCENT-1 trial with other induction trials and the LUCENT-2 trial with other maintenance trials 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 anticipated 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.

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 LUCENT-1 and LUCENT-2 trials measured how patient quality of life changed after taking mirikizumab or placebo. Quality of life was measured using a questionnaire that was completed by patients who received mirikizumab and those who received placebo. Patients

completed these questionnaires at Week 12 of the LUCENT-1 trial and at Week 40 of the LUCENT-2 trial. The questionnaires used were the Inflammatory Bowel Disease Questionnaire (IBDQ), the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the European Quality of Life 5-Dimension 5 Level (EQ-5D-5L). The questionnaires ask patients about different aspects of their daily life and ask them to quantify on various scales the extent to which UC impairs these aspects of daily living.[35, 36]

At Week 12 of the LUCENT-1 study, it was found that patients receiving mirikizumab showed greater improvements on the IBDQ, EQ-5D and SF-36 scales compared with those receiving placebo. Additionally, at Week 40 of the LUCENT-2 study, more than 7 in 10 patients achieved maintenance of remission on the IBDQ scale, whereas only around 4 in 10 patients receiving placebo achieved this.[27, 29] Therefore, these clinical trial results indicate that patients receiving mirikizumab have greater improvements in quality of life than those who received placebo.

Additionally, in both the LUCENT-1 and LUCENT-2 studies it was found that mirikizumab showed statistically significant improvements in bowel urgency as compared with the placebo. This is particularly important because patients have placed high value on improving bowel urgency as a symptom (see response to Question 2d).[3, 27, 29]

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.

As with all medications, mirikizumab can cause side effects, although not everyone will experience them.

Serious side effects

Stop using mirikizumab and tell your doctor or seek medical help immediately if you get any of the following side effects:

- Possible infection. The signs may include fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat or pain during urination
- Serious allergic reaction. The signs may include rash, fainting, dizziness, low blood pressure, swelling of the face, lips, mouth, tongue or throat, trouble breathing or sensation of throat tightening, or chest tightness

Other side effects

Most of the side effects presented in Table 5 are mild to moderate.

Table 5: Commonly reported side effects of mirikizumab

Frequency	Side effect

Common (may affect up to 1 in 10 people)	• Injection site reactions, with symptoms such as red skin and pain • Upper respiratory tract infections with symptoms, such as a sore throat and stuffy nose • Headache • Rash
Uncommon (may affect up to 1 in 100 people)	• Infusion-related allergic reaction, with symptoms such as itch or hives) • Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor

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

Currently, many patients with UC experience treatments that do not work well enough and therefore continue to experience poor control of inflammation and clinical symptoms, including diarrhoea, bleeding and bowel urgency. For example, it has been estimated that clinical remission rates in patients receiving current biologic therapies may be as low as 20 to 30%.[37] The need for an effective treatment is heightened in patients who can't receive current treatment options for medical reasons, and for whom current treatment is not effective enough.

In the LUCENT-1 and LUCENT-2 clinical trials, mirikizumab was shown to have high efficacy as compared with placebo. In particular, patients in the LUCENT-2 trial who were treated with mirikizumab were more likely to maintain clinical remission without the use of corticosteroids than patients treated with placebo. In addition, indirect comparisons to other available treatments using an NMA predicted mirikizumab to have similar or greater efficacy than currently available treatments. This is clinically important because although corticosteroids have previously been effective in treating UC, patients can experience corticosteroid dependence, where the symptoms of UC flare up if they do not take enough corticosteroids, or unresponsiveness to corticosteroids, where their disease stops responding to these medications altogether. In addition, when used long-term, corticosteroids can also be associated with predictable and potentially serious side effects, such as diabetes, weight gain, high blood pressure and osteoporosis (thinning of the bones).[38] Therefore, mirikizumab offers a highly effective treatment option, including in the achievement of remission without needing to use corticosteroids, thus significantly reducing the burden of corticosteroid treatment.

Furthermore, in the LUCENT-1 and LUCENT-2 clinical trials, mirikizumab was found to be well-tolerated. Indeed, a higher proportion of patients receiving placebo than mirikizumab experienced at least one side effect when receiving treatment, a serious side effect, a side effect that caused them to stop treatment, or death. There were no deaths that were assessed to be directly related to treatment in the trials.

In contrast, currently available treatment options for patients who did not respond well enough to first-line conventional therapies may be associated with poor initial response, a loss of response over time, limited efficacy and safety concerns. As compared with these treatment

options, mirikizumab also represents a new mechanism of action to patients in the UK which is anticipated to be highly valuable to patients and clinicians, as outlined in Section 3a.

In summary, mirikizumab offers patients who have previously experienced an inadequate response to biologic therapy or conventional therapy a treatment option with high efficacy, a tolerable safety profile, offers a corticosteroid-free treatment option and has been shown to improve symptoms valued of high importance by patients, such as bowel urgency.

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 LUCENT trials, mirikizumab was associated with some side effects. However, as outlined in Section 3h, more patients allocated to receive placebo in the LUCENT-2 trial experienced a side effect during treatment (a "treatment emergent adverse event", TEAE) than in the mirikizumab treatment arm, with the most common TEAE reported being ulcerative colitis. However, these side effects were generally mild or moderate in severity, with only a small proportion of the TEAEs seen in the mirikizumab arm of the LUCENT-2 trial reported as being serious; the proportion of serious TEAEs was higher in the placebo arm.

3i) Value and economic considerations

Introduction for patients:

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

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

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

How the model reflects UC

A cost comparison tool was created for mirikizumab 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. It was designed to reflect the usual way that UC is treated

within the NHS and compares patients receiving either mirikizumab, vedolizumab or ustekinumab.

Vedolizumab and ustekinumab were considered relevant comparators for the model as they are recommended for use in the same patient population for which mirikizumab is being positioned. In addition, ustekinumab has a similar mechanism of action to mirikizumab, and both treatments are administered in the same way (intravenously during the induction period and then subcutaneously during maintenance therapy) as mirikizumab.[39, 40] For these reasons, it is anticipated that mirikizumab would be considered by doctors as an alternative treatment to vedolizumab and ustekinumab in the proposed treatment population. Consequently, they were selected as the most relevant comparators to consider in the analysis.

Based on the results from the network meta-analysis (see response to section 3e), the efficacy of mirikizumab, as well as its effect on patient quality of life, was assumed to be comparable to vedolizumab and ustekinumab. The costs associated with treatment using vedolizumab and ustekinumab were compared with those of using mirikizumab to determine whether mirikizumab would be a cost-effective treatment.

How mirikizumab improves primary outcomes

Primary outcomes in the model include bowel urgency remission and endoscopic remission, where disease is at a very low level of activity meaning that bowel urgency and inflammation in the colon and rectum are decreased. The efficacy data included in the model came from the NMA results for mirikizumab; the results were applied identically to all treatments in the model to assess only the difference in costs.

How the costs of treatment differ with mirikizumab

In the model, these were the costs included:

- Cost of the medicine (including re-induction for mirikizumab)
- Cost of giving the treatment to patients (administration costs)

It is anticipated that mirikizumab will be provided to the NHS at a confidential discounted price which has been considered in the results because it is known to Eli Lilly. It should be noted that confidential discounts may apply to 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, vedolizumab and ustekinumab, the cost-comparison tool predicted mirikizumab (at its discounted price) to cost less than vedolizumab and ustekinumab (at their full price). This means that the introduction of mirikizumab to clinical practice is not likely to cost NHS England a lot of money, and may even represent a cost-saving.

Uncertainty

Some key assumptions were made in the model which cause uncertainty including the following: it was assumed that only patients who responded to treatment continued treatment after the induction period and that also that patients who responded to treatment continued the same treatment until they lose response to it, have emergency surgery, or die. There was also

uncertainty surrounding the long-term outcomes of mirikizumab because the clinical trials are still ongoing. Additionally, it was assumed that patients stop taking (discontinue) mirikizumab at a constant rate in the maintenance period because there is a lack of data suggesting otherwise.

Although some assumptions were made in the model, in order to determine the impact of the assumptions on the overall results, they were varied in the model and it was found that varying them didn't change the overall conclusion.

Conclusion

Overall, the results of the economic analysis showed mirikizumab to be a good use of NHS resources as an additional treatment option for patients with UC who have failed, or are not eligible for prior therapies. This was shown when considering that the efficacy of mirikizumab, vedolizumab and ustekinumab is comparable, with only the difference in costs associated with each treatment differing.

3j) Innovation

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

Mirikizumab is a first-in-class antibody that binds to the IL-23 protein, representing a completely new mechanism of action in the treatment of patients with moderate to severely active UC. Due to current treatment options being associated with considerable limitations, with many patients showing a lack of response or an inability to tolerate these treatments, the introduction of a treatment option with a different mechanism of action to the medicines currently available is expected to reduce this unmet need.

In addition, the switching of treatments to one with a different mechanism of action is a potential way to overcome resistance to certain biologic therapies in inflammatory bowel disease, highlighting the potential that introducing mirikizumab to UK practice would bring significant positive impact.[24]

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.[3, 27, 29]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
N/A

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/ • 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
Biologic-failed	Patients who have previously received one or more biologic treatment but it did not work well enough for them
Biologic-naïve	Patients who have previously received conventional therapy but it did not work well enough for them
Bowel urgency	The urgent need to have a bowel movement/defecate
Clinical remission	A period of relative disease improvement, specifically defined using the Mayo scoring system as: • Stool frequency subscore = 0 or 1, with ≥1-point decrease from baseline • Rectal bleeding subscore = 0 • Endoscopic subscore = 0 or 1 (excluding friability)
Clinical response	Where a patient shows a response to a drug, specifically defined

	as: • ≥2-point and ≥30% decrease in the modified Mayo score from baseline • Rectal bleeding subscore = 0 or 1, or ≥1-point decrease from baseline
Double-blind	Where neither the patient or investigator know which drug is given to which patient
Gastrointestinal (GI) tract	Also known as the digestive tract, is the passageway from the mouth to the anus
Induction dose	The amount of drug needed to give a response at the start of treatment
Inflammation	The result of the immune response to injury of tissues including redness, swelling and loss of function
Flare-up	Period where the disease is very bad
Maintenance dose	The amount of drug given throughout treatment to maintain effective drug concentration in the blood
Primary non-response	When patients do not have an adequate response to a treatment
Placebo-controlled	When the study drug is compared to a drug that has no therapeutic effect, using this drug as a control
Randomised trial	A trial where a drug is compared to one or more comparators, which can include a placebo, and patients are randomly allocated to one treatment group
Remission	Period of relative disease inactivity
Secondary non-response	When patients experience a response when first given the treatment, but then lose this response over time

Abbreviations

Acronym	Abbreviation
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
EQ-5D-5L	European Quality of Life 5-Dimension 5 Level
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IL	Interleukin
IV	Intravenous
JAK	Janus Kinase
MMS	Modified Mayo Score
NHS	National Health Service

NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
PCIG	Patient and Citizens Involvement Group
Q12W	Once every 12 weeks
Q4W	Once every 4 weeks
SC	Subcutaneous
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SIP	Summary of information for patients
S1P	Sphingosine-1-phosphate
TEAE	Treatment-emergent adverse event
TNFi	Tumour necrosis factor alpha inhibitors
UC	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:

1. NHS. Ulcerative colitis. Available at: https://www.nhs.uk/conditions/ulcerative-colitis/. (accessed 03 August 2022).
2. National Health Service. National cost collection for the NHS. NHS reference costs 2019/20. Available at: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ [Last accessed: 12/07/22]. 2022.
3. Casellas F, Herrera-de Guise C, Robles V, et al. Patient preferences for inflammatory bowel disease treatment objectives. Digestive and Liver Disease 2017;49:152-156.
4. Crohn's & Colitis UK. Ulcerative Colitis Your Guide. Available at: http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/ulcerative-colitis.pdf (accessed 03 August 2022).
5. Clarivate. Ulcerative Colitis Disease Landscape and Forecast. Available at: https://clarivate.com/products/research-reports/report/dlsfim0009-biopharma-ulcerative-colitis-landscape-forecast/. (accessed 03 August 2022).
6. Sicilia B, Arribas F, Nerín J, et al. Risk factors for ulcerative colitis: A population-based, case-control study in Spain. J Crohns Colitis 2008;2:158-61.
7. Gajendran M, Loganathan P, Jimenez G, et al. A comprehensive review and update on ulcerative colitis. Disease-a-Month 2019;65:100851.
8. National Institute for Health and Care Excellence. Tofacitinib for moderately to severely active ulcerative colitis. Technology appraisal guidance [TA547]. Available at:https://www.nice.org.uk/guidance/ta547. (Accessed 06 September 2022).
9. Irvine EJ. Quality of life of patients with ulcerative colitis: past, present, and future. Inflamm Bowel Dis 2008;14:554-65.
10. Dubinsky MC, Watanabe K, Molander P, et al. Ulcerative Colitis Narrative Global Survey Findings: The Impact of Living With Ulcerative Colitis-Patients' and Physicians' View. Inflamm Bowel Dis 2021;27:1747-1755.
11. Petryszyn PW, Paradowski L. Stool patterns and symptoms of disordered anorectal function in patients with inflammatory bowel diseases. Adv Clin Exp Med 2018;27:813-818.
12. Ghosh S, Sensky T, Casellas F, et al. A Global, Prospective, Observational Study Measuring Disease Burden and Suffering in Patients With Ulcerative Colitis, Using the

Pictorial Representation of Illness and Self-measure Tool. Journal of Crohn's and Colitis 2020;15:228-237.
13. Ali T, Skup M, Yang M, et al. P477 Increased risk of comorbidities associated with ulcerative colitis. Journal of Crohn's and Colitis 2013;7:S200-S201.
14. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Official journal of the American College of Gastroenterology | ACG 2019;114:384-413.
15. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1-s106.
16. Faubion WA, Jr., Loftus EV, Jr., Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001;121:255-60.
17. Su C, Lichtenstein GR. Treatment of inflammatory bowel disease with azathioprine and 6-mercaptopurine. Gastroenterology Clinics 2004;33:209-234.
18. Singh H, Wilson L, Pandey A, et al. P540 Real-world evidence on treatment switching in patients with moderate-to-severe ulcerative colitis: a systematic review of literature. Journal of Crohn's and Colitis 2021;15:S511-S512.
19. Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. Journal of Crohn's and Colitis 2017;11:649-670.
20. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine 2013;369:699-710.
21. Gisbert JP, Chaparro M. Primary Failure to an Anti-TNF Agent in Inflammatory Bowel Disease: Switch (to a Second Anti-TNF Agent) or Swap (for Another Mechanism of Action)? Journal of Clinical Medicine 2021;10:5318.
22. European Medicines Agency. Summary of Product Characteristics - Ustekinumab. Available at https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. Accessed 10 August 2022.
23. Peyrin-Biroulet L, Sandborn WJ, Panaccione R, et al. Tumour necrosis factor inhibitors in inflammatory bowel disease: the story continues. Therapeutic Advances in Gastroenterology 2021;14:17562848211059954.
24. Atreya R, Neurath MF and Siegmund B. Personalizing Treatment in IBD: Hype or Reality in 2020? Can We Predict Response to Anti-TNF? Frontiers in Medicine 2020;7:517.
25. Larussa T, Flauti D, Abenavoli L, et al. The Reality of Patient-Reported Outcomes of Health-Related Quality of Life in an Italian Cohort of Patients with Inflammatory Bowel Disease: Results from a Cross-Sectional Study. J Clin Med 2020;9.
26. Armuzzi A, Liguori G. Quality of life in patients with moderate to severe ulcerative colitis and the impact of treatment: A narrative review. Digestive and Liver Disease 2021;53:803-808.
27. D'Haens G, Kobayashi T, Morris N, et al. OP26 Efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active Ulcerative Colitis: Results from the Phase 3 LUCENT-1 study. Journal of Crohn's and Colitis 2022;16:i028-i029.
28. Hanžel J, D'Haens GR. Anti-interleukin-23 agents for the treatment of ulcerative colitis. Expert Opinion on Biological Therapy 2020;20:399-406.
29. ClinicalTrials.gov. A Maintenance Study of Mirikizumab in Participants With Moderately to Severely Active Ulcerative Colitis (LUCENT 2). Available at: https://clinicaltrials.gov/ct2/show/NCT03524092 (accessed 08 August 2022).
30. A Study of Mirikizumab (LY3074828) in Participants With Moderate to Severe Ulcerative Colitis. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02589665. (Accessed 21/09/2022).
31. An Induction Study of Mirikizumab in Participants With Moderately to Severely Active Ulcerative Colitis (LUCENT 1). Available at: https://clinicaltrials.gov/ct2/show/NCT03518086. (Accessed 21/09/2022).

32. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis. Gastroenterology 2020;158:537-549.e10.
33. A Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Participants With Moderately to Severely Active Ulcerative Colitis (LUCENT 3). Available at: https://clinicaltrials.gov/ct2/show/NCT03519945. (Accessed: 21/09/2022).
34. Sturm A, Maaser C, Calabrese E, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects. Journal of Crohn's and Colitis 2018;13:273-284.
35. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol 1996;91:1571-8.
36. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-36.
37. Achra M, Karpe K, Franklin B. PGI6 TREATMENT FAILURE AND REMISSION IN MODERATE TO SEVERE ULCERATIVE COLITIS (UC) AND CROHN'S DISEASE (CD) IN EUROPE. Value in Health 2019;22:S617.
38. Xu CT, Meng SY, Pan BR. Drug therapy for ulcerative colitis. World J Gastroenterol 2004;10:2311-7.
39. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active ulcerative colitis [TA342]. Available at: https://www.nice.org.uk/guidance/ta342. Date accessed: 08 August 2022.
40. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active ulcerative colitis [TA633]. Available at: https://www.nice.org.uk/guidance/ta633/evidence. (Accessed 06 September 2022).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]

Addendum to Company Submission

February 2023

File name	Version	Contains confidential information	Date
ID3973_Eli Lilly_Mirikizumab in Ulcerative Colitis_Addendum to Company Submission_Fully Redacted.docx	1.0	Yes	10th February 2023

Contents

List of tables

List of figures

Section 1 Summary of changes from original Company Submission

In line with correspondence between the National Institute for Health and Care Excellence (NICE) and Eli Lilly and Company (henceforth referred to as "the Company"), this document is positioned as an addendum to the main Company Submission submitted on 8th December 2022. This addendum amends input errors identified in the network meta-analysis (NMA) presented in the original Company submission for mirikizumab in patients with moderately to severely active ulcerative colitis (UC).

In order to facilitate the review by NICE and the External Assessment Group (EAG), a summary table listing the sections of relevance addressed in this addendum are presented in Table 1 below. Please note sections that have not changed since the original company submission have not been re-presented in this addendum.

Table 1: Summary table of amendments addressed in this addendum

Section title	Sub-section	Location in original company submission	Location in addendum to company submission
NMA results	Efficacy outcomes (biologic-naïve population)	Section B.3.9.4.1	Section 2.1.1 (induction) and Section 2.1.2 (maintenance)
	Efficacy outcomes (biologic-failed population)	Section B.3.9.4.2	Section 2.2.1 (induction) and Section 2.2.2 (maintenance)
	Safety outcomes (overall mixed population)	Section B.3.9.4.3	Section 2.3
	Conclusions	Section B.3.9.6	Section 2.4
Cost-comparison analysis	Efficacy in the induction period	Section B.4.2.1.4	Section 3.1.1.1
	Efficacy in the maintenance state	Section B.4.2.1.5	Section 3.1.1.2
	Uncertainties in the inputs and assumptions	Section B.4.2.7	Section 3.1.2
	Base case results	Section B.4.3	Section 3.2
	One-way sensitivity analysis	Section B.4.4.1	Section 3.3.1
	Scenario analyses	Section B.4.4.2	Section 3.3.2
	Interpretations and conclusions of economic evidence	Section B.4.6	0
	Summary of trials used for indirect comparison	Appendix D.1.5	Section 5.1

Identification and selection of relevant studies	Explorative analysis for baseline risk adjustment	Appendix D.1.6.2	Section 5.2
NMA results: additional base case results	Efficacy outcomes (biologic-naïve population)	Appendix D.1.10.1	Section 5.3.1.1 and Section 5.3.1.2 (induction); Section 5.3.1.3 and Section 5.3.1.4 (maintenance):
	Efficacy outcomes (biologic-failed population)	Appendix D.1.10.2	Section 5.3.2.1 and Section 5.3.2.2 (induction); Section 5.3.2.3 and Section 5.3.2.4 (maintenance)
	Safety outcomes (overall mixed population)	Appendix D.1.10.3	Section 5.3.3

Abbreviations: NMA: network meta-analysis.

Section 2 Updated NMA results

The results of the NMAs are presented in the subsections which follow, further broken down 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 (fixed effects and random effects) are presented in Section 5.3.1 (efficacy outcomes, biologic-naïve population), Section 5.3.2 (efficacy outcomes, biologic-failed population) and Section 5.3.3 (safety outcomes, overall population). Results from all sensitivity and exploratory analyses are presented in Sections 3.1 to Section 3.3 of the NMA report appendices in the reference pack.

As previously presented in Appendix D.1.10 of the original Company Submission Appendices, abbreviated treatment labelling was used in all figures presented in the NMA. For clarity, the summary of figure labelling, and the associate dosing regimen at induction and maintenance, has been reproduced in Table 13 in Section 5. No edits have been made as compared with the same table in the original submission (Table 33 in Appendix D.1.10).

Section 2.1 Efficacy outcomes (biologic-naïve population): amended from Section B.3.9.4.1

Section 2.1.1 Induction

Clinical response and remission

The network diagram, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the induction period of the biologic-naïve population are presented in Section 5.3.1.1. Model fit statistics can be found in Section 2.1.1.1 of the NMA report appendices, as provided in the reference pack. As described further in Section Section 5.3.1.1, primary results for clinical response and remission during the induction period for the biologic-naïve population described in this section were derived from the random effects model (**without** baseline risk adjustment); the complementary results with baseline risk adjustment are presented in Section 3.1.1 of the NMA report appendices, as provided in the reference pack.

[redacted] (see Figure 1 and Figure 2).

Figure 1: All pairwise odds ratios with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: clinical response, induction, biologic-naïve 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 2: All pairwise odds ratios with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: clinical remission, induction, biologic-naïve 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and ORs for all active treatments, including mirikizumab, versus placebo for mucosal healing during the induction period of the biologic-naïve population are presented in Section 5.3.1.2. Model fit statistics can be found in Section 2.1.1.2 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.1.2, primary results for mucosal healing during the induction period for the biologic-naïve population described in this section were derived from the random effects model (**with** baseline risk adjustment).

[redacted]

(Figure 3).

Figure 3: All pairwise odds ratios with random treatment effects with baseline risk meta-regression and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: mucosal healing, induction, biologic-naïve 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 2.1.2 Maintenance

Clinical response and remission

The network diagram, input data and ORs for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the maintenance period of the biologic-naïve population are presented in Section 5.3.1.3. Model fit statistics can be found in Section 2.1.2.1 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.1.3, primary results for clinical response and remission during the maintenance period for the biologic-naïve population described in this section were derived from the fixed effect model (**with** baseline risk adjustment); the complementary results without baseline risk adjustment are presented in Section 3.2.1 of the NMA report appendices, as provided in the reference pack.

[redacted] (Figure 4 and Figure 5).

Complete results for the sensitivity analysis of clinical response and remission including only re-randomised studies of the biologic-naïve population at maintenance are also provided in Section 2.1.2.2 of the NMA report appendices, provided in the reference pack.

Figure 4: All pairwise odds ratios with fixed treatment effects with baseline risk meta-regression: clinical response, maintenance, biologic-naïve 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 5: All pairwise odds ratios with fixed treatment effects with baseline risk meta-regression: clinical remission, maintenance, biologic-naïve 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for mucosal healing during the maintenance period of the biologic-naïve population are presented in Section 5.3.1.4. Model fit statistics can be found in Section 2.1.2.3 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.1.4, primary results for mucosal healing during the maintenance period for the biologic-naïve population described in this section were derived from the fixed effects model (**with** baseline risk adjustment).

As shown in Figure 6, in terms of mucosal healing, [redacted].

Figure 6: All pairwise odds ratios with fixed treatment effects with baseline risk meta-regression: mucosal healing, maintenance, biologic naïve 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 2.2 Efficacy outcomes (biologic-failed population): amended from Section B.3.9.4.2

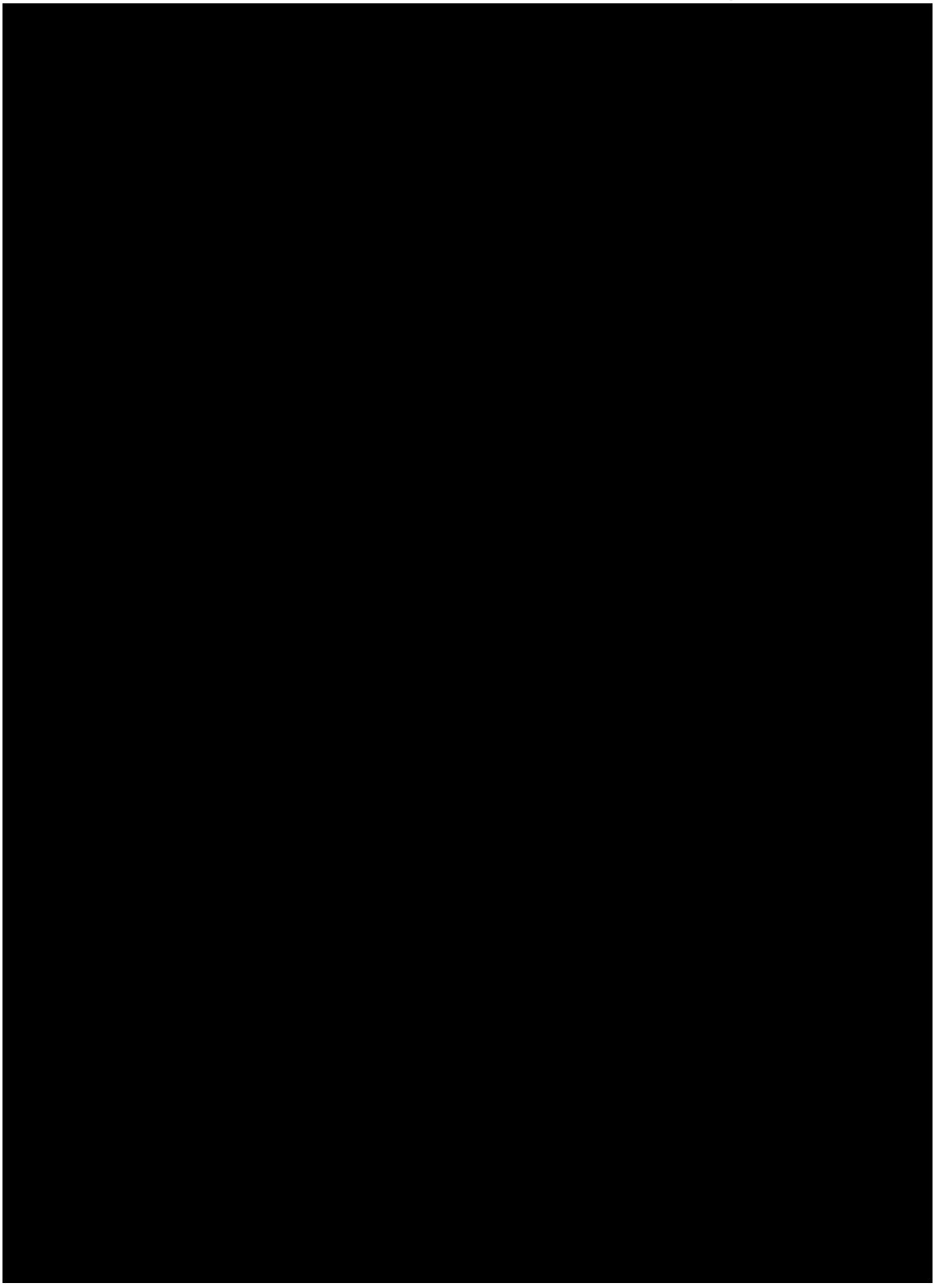
Section 2.2.1 Induction

Clinical response and remission

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the induction period of the biologic-failed population are presented in Section 5.3.2.1. Model fit statistics can be found in Section 2.2.1.1 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.2.1, primary results for clinical response and remission during the induction period for the biologic-failed population described in this section were derived from the fixed effect model (**without** baseline risk adjustment); the complementary results with baseline risk adjustment are presented in Section 3.1.2 of the NMA report appendices, as provided in the reference pack.

[redacted] (Figure 7).

Figure 7: All pairwise odds ratios with fixed treatment effects (response and response with remission): clinical response and remission, induction, biologic-failed 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for mucosal healing during the induction period of the biologic-failed population are presented in Section 5.3.2.2. Model fit statistics can be found in Section 2.2.1.2 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.2.2, primary results for mucosal healing during the induction period for the biologic-failed population described in this section were derived from the fixed effects model (**with** baseline risk adjustment).

[redacted] (Figure 8).

Figure 8: All pairwise odds ratios with fixed treatment effects with baseline risk meta-regression: mucosal healing, induction, biologic-failed 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.

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 2.2.2 Maintenance

Clinical response and remission

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for clinical response and remission during the maintenance period of the biologic-failed population are presented in Section 5.3.2.3. Model fit statistics can be found in Section 2.2.2.1 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.2.3, primary results for clinical response and remission during the maintenance period for the biologic-failed population described in this section were derived from the fixed effects model (**without** baseline risk adjustment); the complementary results with baseline risk adjustment are presented in Section 3.3.1 of the NMA report appendices, as provided in the reference pack. Complete results for the sensitivity analysis of clinical response and remission including only re-randomised studies of the biologic-failed population at maintenance are provided in Section 2.2.2.2 of the NMA report appendices, as provided in the reference pack.

[redacted] (Figure 9 and Figure 10).

Figure 9: All pairwise odds ratios with fixed treatment effects: clinical response, maintenance, biologic-failed 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 10: All pairwise odds ratios with fixed treatment effects: clinical remission, maintenance, biologic-failed 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Mucosal healing

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for mucosal healing during the maintenance period of the biologic-failed population are presented in Section 5.3.2.4. Model fit statistics can be found in Section 2.2.2.3 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.2.4, primary results for mucosal healing during the maintenance period for the biologic-failed population described in this section were derived from the fixed effects model (**without** baseline risk adjustment).

[redacted] (Figure 11).

Figure 11: All pairwise odds ratios with fixed treatment effects: mucosal healing, maintenance, biologic-failed 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 2.3 Safety outcomes (overall mixed population): amended from Section B.3.9.4.3

Section 2.3.1 Induction

All cause discontinuation

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for all cause discontinuation in the overall population are presented in Section 5.3.3.1. Model fit statistics can be found in Section 2.3.1.1 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.3.1, the fixed effect model was selected for inference based on parsimony and the uncertain estimates provided by the random effects model. Results under the random effects models have been provided as supplementary results figures and tables.

[redacted] (Figure 12).

Figure 12: All pairwise odds ratios with fixed treatment effects: 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, meaning fewer discontinuations.
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Serious adverse events

The network diagram, input data and odds ratios for all active treatments, including mirikizumab, versus placebo for SAEs in the overall population are presented in Section 5.3.3.2. Model fit statistics can be found in Section 2.3.1.2 of the NMA report appendices, as provided in the reference pack. As described further in Section 5.3.3.2, the random effects model seems most appropriate for inference as this better captures the uncertainty in the estimates.

The results of the random effects NMA are presented with Figure 13 depicting the pairwise ORs.

Figure 13: All pairwise odds ratios with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: serious adverse events, 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.
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OR: odds ratio; OZD: ozanimod; PBO: Placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 2.4 Conclusions: amended from Section B.3.9.6

Overall, these NMAs demonstrated that at induction, mirikizumab offered similar efficacy to most treatments, with only upadacitinib 45 mg demonstrating statistically significant increased rates of clinical response and remission versus mirikizumab, regardless of prior therapy, and increased rates of mucosal healing in patients who were biologic-failed. Furthermore, mirikizumab demonstrated statistically significant increased rates of clinical response and remission versus adalimumab in the biologic-failed population at induction. At maintenance, after adjusting for differences in study design, baseline risk adjusted models for patients who were biologic-naïve indicated mirikizumab demonstrated statistically significant benefits in terms of clinical response and remission, and similar mucosal healing compared to several other comparators. In unadjusted models for biologic-failed patients in the maintenance setting, mirikizumab demonstrated similar efficacy to most treatments, with only upadacitinib 30 mg demonstrating statistically significant improvements versus mirikizumab, in rates of clinical response and remission and mucosal healing. In addition, mirikizumab demonstrated statistically significant improvements in rates of mucosal healing compared to ustekinumab 90 mg Q12W.

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. Of particular importance, these updated results support the assumption presented in the original Company Submission that mirikizumab offers a comparable clinical benefit to currently available comparators, including ustekinumab and vedolizumab, in both the induction and maintenance phases.

Section 3 Updated cost-comparison analysis

Section 3.1 Cost-comparison inputs and assumptions: amended from Section B.4.2

Section 3.1.1 Features of the cost-comparison analysis

Section 3.1.1.1 Efficacy in the induction period: amended from Section B.4.2.1.4

At the end of the induction period patients were classified by responder status. The distribution of response status at the end of induction (and, in the scenario analysis, delayed response assessment) was informed by the induction NMA.

Base case

Induction (LUCENT-1) and maintenance (LUCENT-2) efficacy data for mirikizumab were synthesised with data for all comparators of interest in the NMA (see Section 3.9 of the original Company Submission for full NMA details, and Section 2 above for updated results). The rates of response are assumed to be the same across all treatments but differ between biologic-naïve or biologic-failed patients, as shown in Table 2.

Table 2: Clinical response and response at the end of induction

Treatment	Response (including remission)	
	OR (95% CI) relative to placebo	Calculated absolute probability
Mirikizumab (for all treatments)		
Biologic-naive subgroup	[redacted]	[redacted]
Biologic-failed subgroup	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OR: odds ratio.

Scenario analysis

A scenario analysis was explored in which patients who did not respond could undergo a delayed response assessment. Delayed response assessment was selected as a sensitivity analysis rather than used in the base case analysis given that it is uncertain to what extent delayed response assessment is used in clinical practice, and that not all treatments have delayed response assessment in their Summary of Product Characteristics (SmPC).[1-9]

In this scenario analysis, patients transitioned through tunnel states from the start to the end of the delayed response assessment, at the end of which patients who responded to treatment transitioned to the maintenance state, and patients who had not responded transitioned to the no-treatment state. It was assumed the same proportion of patients receiving mirikizumab achieved response (including remission) at the end of the induction phase as ustekinumab, as presented in Table 3.[10] The use of data from the NMA to inform this analysis was explored, but the available data were considered to be insufficient given that delayed response assessment

period was not placebo controlled in any trial, making indirect comparisons very limited as very few trials compare advanced treatments.

Table 3: Clinical response at the end of the delayed response assessment period

Treatment	Response (including remission)	Source
	Calculated absolute probability	
Biologic-naive subgroup	[redacted]	Assumed same as ustekinumab overall response rate (data from ustekinumab TA633, Table 41)[10]
Biologic-failed subgroup	[redacted]	

Abbreviations: CI: confidence interval; OR: odds ratio.

Section 3.1.1.2 Efficacy in the maintenance state: amended from B.4.2.1.5

Patients were assumed to remain on maintenance treatment until they discontinued treatment or died. Discontinuation of maintenance treatment was based on the notion that patients who lose response to treatment also discontinue treatment. The proportion of initial responders who lost response were assumed to do so at a continuous and constant rate during the maintenance period. The risk of treatment discontinuation was informed by the loss of response observed in maintenance randomised controlled trials (RCT). This approach for modelling treatment discontinuation is the same as for many cost-effectiveness models in UC.[10-13]

In contrast to the cost-effectiveness models, the cost comparison model assumes that all treatments have the same risk of treatment discontinuation – the one estimate for mirikizumab in the NMA (Section B.3.9 of the original Company Submission). The odds ratio for response at the end of the maintenance period (contingent on response at the end of the induction period) for mirikizumab relative to placebo was transformed to an absolute probability. The complement to the derived probability is the probability of loss of response during the maintenance period. Subsequently, the probability of loss of response during the duration of the maintenance trial was transformed to per cycle probabilities using the formulae presented in Section B.4.2.1.3 of the original Company Submission, resulting in a risk of loss off response during the maintenance period of [redacted] and [redacted] per 12-week cycle for biologic-naïve patients and biologic-failed patients, respectively.

Section 3.1.2 Uncertainties in the inputs and assumptions: amended from Section B.4.2.7

Settings and values used in the base case analysis are presented in Table 4, with key assumptions of the cost-comparison model presented in Table 5.

Table 4: Settings and values used in the base case analysis

Item	Base-case setting	Reference
Perspective	UK NHS	Section B.4.2.1 (original Company Submission)
Time horizon	10 years	Section B.4.2.1 (original Company Submission)

Item	Base-case setting	Reference
Age in years, mean (SD)	Naïve: [redacted] Failed: [redacted]	Section B.4.2.1.7 (original Company Submission)
Weight in kg, mean (SD)	Naïve: [redacted] Failed: [redacted]	Section B.4.2.1.7 (original Company Submission)
Proportion male	Naïve: [redacted] Failed: [redacted]	Section B.4.2.1.7 (original Company Submission)
Efficacy (%) induction period	Naïve: [redacted] from NMA Failed: [redacted] from NMA	Section 3.1.1.1
Delayed response	No	Section B.4.2.1.7 (original Company Submission)
Loss of response - probability per cycle (12 weeks) during maintenance (%)	Naïve: [redacted] from NMA Failed: [redacted] from NMA	Section 3.1.1.2
Mirikizumab re-induction (%)	[redacted] per cycle	Section B.4.2.1.2 (original Company Submission)
Dose escalation	30%	Section B.4.2.1.2 (original Company Submission)
Cost discount rate	0	Section B.4.2.1 (original Company Submission)

Abbreviations: NHS: National Health Service; NMA: network meta-analysis; SD: standard deviation.

Table 5: Key model assumptions

Assumption	Justification
Only responders continue treatment after the induction period	Consistent with clinical practice as per expert advice and consistent with previous submissions
All modelled treatments have the same efficacy	Given the results of the NMA (Section B.3.9 of the original Company Submission and Section 2 above), mirikizumab is associated with a similar relative efficacy as ustekinumab and vedolizumab.
Responders continue maintenance therapy with the same treatment until loss of response	Expert advice suggests that clinicians and patients are unlikely to discontinue effective treatment.
Patients who do not respond at the end of the induction period or discontinue the maintenance period do not incur costs	Simplifying assumption. In reality, patients would incur costs. However, given the assumption on similar efficacy the costs would be the same across all treatment and therefore cancel out.
No disease management and monitoring costs	Disease management and monitoring costs largely reflect disease severity and should therefore be very similar across all modelled treatments.
Normal population mortality	Consistent with previous models. Does not introduce mortality benefits that have not been demonstrated in RCTs
No serious adverse events in the base case	Adverse events were not included in the model due to the NMA results demonstrating broadly similar safety outcomes for mirikizumab, ustekinumab and vedolizumab.

Abbreviations: NMA: network meta-analysis; RCT: randomised controlled trial; UC: ulcerative colitis.

Section 3.2 Base case results: amended from Section B.4.3

Base case results for a 10-year time horizon with mirikizumab (at list price and with-PAS price) are presented in Table 6 and Table 7 for patients in the biologic-naïve and biologic-failed populations, respectively. Confidential PAS discounts for comparators are not included in either analysis as these are not publicly known. These results indicate mirikizumab offers a cost-saving treatment option in the biologic-naïve and -failed populations as compared with ustekinumab and vedolizumab (IV and IV/SC) at their list prices.

Table 6: Base case results for a 10-year time horizon at mirikizumab list price (biologic-naïve population)

Treatment	Per patient costs				Incremental costs relative to mirikizumab (£)
	Induction costs (£)	Re-induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	
Mirikizumab at list price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab	£5,487	£0	£17,823	£23,310	[redacted]
Vedolizumab IV	£4,445	£0	£31,288	£35,732	[redacted]
Vedolizumab IV/SC	£4,445	£0	£22,199	£26,644	[redacted]
Mirikizumab at PAS price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab	£5,487	£0	£17,823	£23,310	[redacted]
Vedolizumab IV	£4,445	£0	£31,288	£35,732	[redacted]
Vedolizumab IV/SC	£4,445	£0	£22,199	£26,644	[redacted]

Abbreviations: PAS: patient access scheme.

Table 7: Base case results for a 10-year time horizon at mirikizumab list price (biologic-failed population)

Treatment	Per patient costs				Incremental costs relative to mirikizumab (£)
	Induction costs (£)	Re-induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	
Mirikizumab at list price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab	£5,695	£0	£4,847	£10,542	[redacted]
Vedolizumab IV	£4,445	£0	£8,508	£12,952	[redacted]
Vedolizumab IV/SC	£4,445	£0	£6,037	£10,481	[redacted]
Mirikizumab at PAS price					
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-

Treatment	Per patient costs				Incremental costs relative to mirikizumab (£)
	Induction costs (£)	Re-induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	
Ustekinumab	£5,695	£0	£4,847	£10,542	[redacted]
Vedolizumab IV	£4,445	£0	£8,508	£12,952	[redacted]
Vedolizumab IV/SC	£4,445	£0	£6,037	£10,481	[redacted]

Abbreviations: PAS: patient access scheme.

Section 3.3 Sensitivity and scenario analyses: amended from B.4.4

Section 3.3.1 One-way sensitivity analysis: amended from Section B.4.4.1

The one-way sensitivity analyses involved analysing the impact on the costs when changing a single parameter at a time to reflect the uncertainty/variability in the estimation of that parameter. The lower and upper bounds for the response and discontinuation rates were set based on the credible intervals estimated from the NMA, with confidence intervals being used for other parameters where available. However, when such information was not available, the upper and lower bounds were assumed to be within ± 20% of the base case value, as presented in Table 8.

Table 8: Summary of one-way sensitivity analyses

OWSA input - parameter	Base case	Lower bound	Upper bound	Source of bounds
Start age (years) – Naïve population	[redacted]	[redacted]	[redacted]	95% CI
Start age (years) – Failed population	[redacted]	[redacted]	[redacted]	95% CI
Proportion male patients – Naïve population	[redacted]	[redacted]	[redacted]	±20%
Proportion male patients –Failed population	[redacted]	[redacted]	[redacted]	±20%
Mean patient body weight (kg) – Naïve population	[redacted]	[redacted]	[redacted]	95% CI
Mean patient body weight (kg) – Failed population	[redacted]	[redacted]	[redacted]	95% CI
Proportion of patients with dose escalation	0.30	0.24	0.36	±20%
Mirikizumab response rate at induction phase for biologic naïve patients	[redacted]	[redacted]	[redacted]	95% CrI
Mirikizumab response rate at induction phase for biologic failed patients	[redacted]	[redacted]	[redacted]	95% CrI
Mirikizumab response rate after 12 weeks re-induction	[redacted]	[redacted]	[redacted]	±20%
Mirikizumab loss of response probability (per 12 weeks) for biologic naïve patients	[redacted]	[redacted]	[redacted]	95% CrI
Mirikizumab loss of response probability (per 12 weeks) for biologic failed patients	[redacted]	[redacted]	[redacted]	95% CrI
Proportion mirikizumab re-induction 12 weeks	[redacted]	[redacted]	[redacted]	±20%

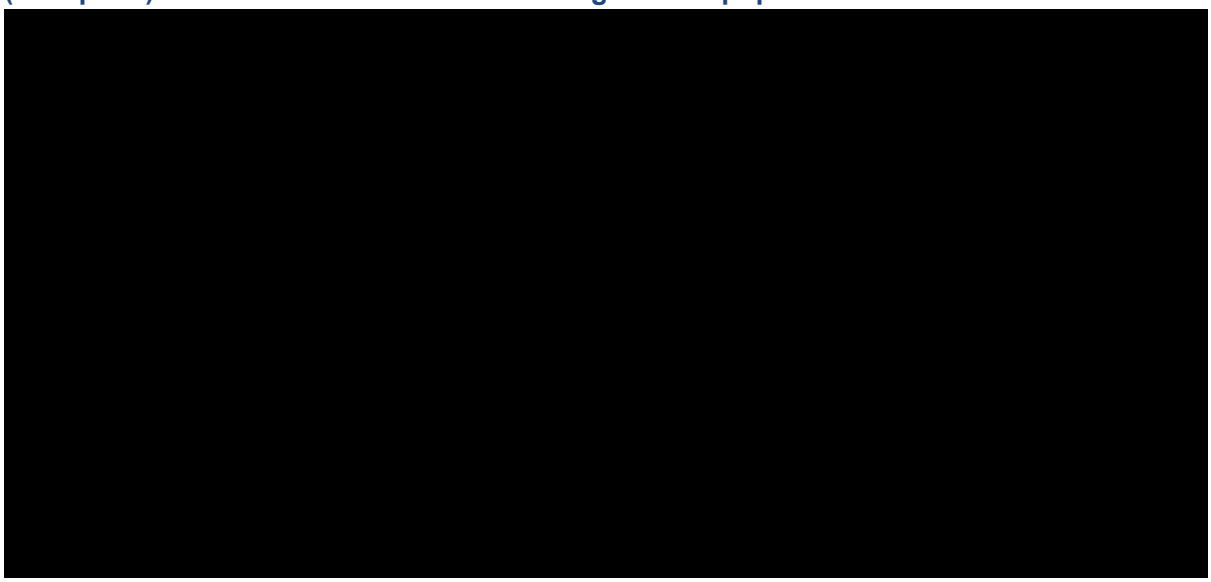
Abbreviations: CI: confidence interval; CrI: credible interval; OWSA: one-way sensitivity analysis.

Tornado diagrams for mirikizumab versus ustekinumab, vedolizumab IV and vedolizumab IV/SC are presented in Figure 14, Figure 16 and Figure 18, respectively, in the biologic-naïve population, and in Figure 15, Figure 17 and Figure 19, respectively, in the biologic-failed population. For each comparison, the eight most influential parameters shown in descending order of cost difference sensitivity. These results demonstrate that the model is insensitive to all parameters.

Figure 14: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus ustekinumab in the biologic-naïve population

Abbreviations: PAS: patient access scheme.

Figure 15: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus ustekinumab in the biologic-failed population



Abbreviations: PAS: patient access scheme.

Figure 16: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV) in the biologic-naïve population

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

Figure 17: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV) in the biologic-failed population

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

Figure 18: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV/SC) in the biologic-naïve population

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

Figure 19: Tornado plot with results from the one-way sensitivity analysis – mirikizumab (PAS price) versus vedolizumab (IV/SC) in the biologic-failed population

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

Section 3.3.2 Scenario analyses: amended from Section B.4.4.2

Seven scenario analyses, detailed in Table 9, were explored in the model.

Table 9: Scenario analyses

#	Scenario	Base case	Scenario values
1	Model horizon	10 years	5 years
2	Discount rates	0%	3.5%
3			5%

4	Dose escalation and re-induction	Increased dose or administration frequency for 30% of patients for relevant comparators and [redacted] of patients on treatment re-induction per cycle for mirikizumab, reflecting clinical data from the LUCENT trials	No dose escalation for relevant comparators and no re-induction for mirikizumab
5			Increased dose or administration frequency for 30% of patients for relevant comparators and 30% of patients on treatment re-induction per cycle for mirikizumab
6	Delayed response assessment	No extended induction period	Extended induction period as described in Section B.4.2.1.4 (original Company Submission)
7	Drug wastage	Incorporation of vial sharing, so no drug wastage	Assumption of drug wastage

Results for these scenario analyses are presented in Table 10 and Table 11 for the biologic-naïve and biologic-failed populations, respectively. All scenario analyses resulted in minor changes in costs, except for scenarios on dose escalation and re-induction, which affects costs of treatments differently. This suggests that the model is reasonably robust to structural uncertainty.

Table 10: Scenario analysis for a 10-year time horizon in the biologic-naïve population

Scenario	Incremental costs relative to mirikizumab (list price)			Incremental costs relative to mirikizumab (PAS price)		
	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV: intravenous; PAS: Patient Access Scheme; SC: subcutaneous.

Table 11: Scenario analysis for a 10-year time horizon in the biologic-failed population

Scenario	Incremental costs relative to mirikizumab (list price)			Incremental costs relative to mirikizumab (PAS price)		
	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs relative to mirikizumab (list price)			Incremental costs relative to mirikizumab (PAS price)		
	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV: intravenous; PAS: Patient Access Scheme; SC: subcutaneous.

Section 3.4 Updated interpretations and conclusions of economic evidence: amended from Section B.4.6

As outlined in Section B.1.1 of the original Company Submission, vedolizumab and ustekinumab represent 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 ustekinumab and vedolizumab in relevant patient subgroups under the assumption that the treatments have the same efficacy.

Overall, mirikizumab at its with-PAS price was found to be cost-saving when compared to these comparators of relevance at their list prices. In the biologic-naïve and biologic-failed subgroups respectively, mirikizumab is associated with a cost-saving of [redacted] and [redacted] versus ustekinumab, [redacted] and [redacted] versus vedolizumab IV and [redacted] and [redacted] versus vedolizumab IV/SC. A series of sensitivity and scenario analyses all confirmed the base case analysis of mirikizumab as a cost-neutral option. If it were to be approved, the results of the analysis demonstrate that mirikizumab would offer patients with UC a valuable new treatment option, that is ~~a~~ well-tolerated and efficacious with a novel mode of action and a convenient maintenance dosing schedule, while at least offering budget neutrality to the NHS.

Section 4 References

1. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Infliximab. Available at: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf [Accessed 31 August 2022].
2. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Adalimumab. Available at: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf [Accessed 31 August 2022].
3. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Golimumab. Available at: https://www.ema.europa.eu/en/documents/product-information/simponi-epar-product-information_en.pdf [Accessed 31 August 2022].
4. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Vedolizumab. Available at https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf. [Accessed 31 August 2022].
5. European Medicines Agency. Summary of Product Characteristics - Tofacitinib. Available at https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. [Accessed 10 August 2022].
6. European Medicines Agency. Summary of Product Characteristics - Ustekinumab. Available at https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. [Accessed 10 August 2022].
7. European Medicines Agency. European Medicines Agency. Summary of Product Characteristics - Filgotinib. Available at https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf [Accessed 31 August 2022].
8. European Medicines Agency. Summary of Product Characteristics - Ozanimod. Available at https://www.ema.europa.eu/en/documents/product-information/zeposia-epar-product-information_en.pdf. Accessed 10 August 2022.
9. European Medicines Agency. Summary of Product Characteristics - Upadacitinib. Available at https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf. [Accessed 10 August 2022].
10. National Institute for Health and Care Excellence (NICE). Ustekinumab for treating moderately to severely active ulcerative colitis [TA633]. Available at: https://www.nice.org.uk/guidance/ta633/evidence. [Accessed 06 September 2022].
11. National Institute for Health and Care Excellence (NICE). Tofacitinib for moderately to severely active ulcerative colitis. Technology appraisal guidance [TA547]. Available at: https://www.nice.org.uk/guidance/ta547. [Accessed 06 September 2022].
12. National Institute for Health and Care Excellence (NICE). Filgotinib for treating moderately to severely active ulcerative colitis [TA792]. Available at: https://www.nice.org.uk/guidance/ta792. [Accessed 22 July 2022].
13. National Institute for Health and Care Excellence (NICE). Ozanimod for treating moderately to severely active ulcerative colitis [TA828]. Available at: https://www.nice.org.uk/guidance/ta828. [Accessed 05 October 2022].
14. Cameron C, Hutton B, Druchok C, et al. Importance of assessing and adjusting for cross-study heterogeneity in network meta-analysis: a case study of psoriasis. Journal of Comparative Effectiveness Research 2018;7:1037-1051.
15. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. Journal of Clinical Epidemiology 2009;62:857-64.
16. Loos AM, Liu S, Segel C, et al. Comparative effectiveness of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis. Journal of the American Academy of Dermatology 2018;79:135-144.e7.
17. Dias S, Sutton AJ, Welton NJ, et al. Evidence Synthesis for Decision Making 3: Heterogeneity—Subgroups, Meta-Regression, Bias, and Bias-Adjustment. Medical Decision Making 2013;33:618-640.
18. Garud S, Brown A, Cheifetz A, et al. Meta-analysis of the placebo response in ulcerative colitis. Digestive Diseases and Sciences 2008;53:875-91.

19. Jairath V, Zou GY, Parker CE, et al. Placebo response and remission rates in randomised trials of induction and maintenance therapy for ulcerative colitis. Cochrane Database of Systematic Reviews 2017;9:Cd011572.
20. Sedano R, Hogan M, Nguyen TM, et al. Systematic Review and Meta-Analysis: Clinical, Endoscopic, Histological and Safety Placebo Rates in Induction and Maintenance Trials of Ulcerative Colitis. Journal of Crohn's and Colitis 2022;16:224-243.
21. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. Nature Reviews Gastroenterology & Hepatology 2015;12:472-85.
22. Macaluso FS, Maida M, Ventimiglia M, et al. Factors Affecting Clinical and Endoscopic Outcomes of Placebo Arm in Trials of Biologics and Small Molecule Drugs in Ulcerative Colitis: A Meta-Analysis. Inflammatory Bowel Diseases 2019;25:987-997.

Section 5 Identification and selection of relevant studies: amended from Appendix D.1

Section 5.1 Summary of trials used for indirect comparison (amended from Appendix D.1.5)

All information presented in the originally submitted Appendix D.1.5, including Table 21, Table 22, and Table 24–26, remain accurate and thus have not been reproduced here. The exception is the table of studies included by population and outcome of interest in the induction NMAs (previously Table 23 in Appendix D.1.5), which has been reproduced and amended below (Table 12).

Table 12: Overview of studies included by population and outcome of interest, induction NMAs

Study	Intervention	Timepoint (weeks)	Biologic-naïve			Biologic-failed			Overall (mixed[a]) population	
			Population definition	Clinical response and remission	Mucosal healing	Population definition	Clinical response and remission	Mucosal healing	All cause discontinuation	SAEs
ACT 1	IFX	8	TNF naïve	✓	✓					
ACT 2	IFX	8	TNF naïve	✓	✓					
GEMINI 1	VED	6	TNF naïve	✓	✓	TNF failure	✓	✓	✓	✓
HIBISCUS 1	ADA	10	***TNF naïve***	✓					✓	✓
HIBISCUS 2	ADA	10	***TNF naïve***	✓					✓	✓
Jiang 2015	IFX	8	TNF naïve	✓	✓					
Kobayashi 2016	IFX	8	TNF naïve	✓	✓				✓	✓
LUCENT	MIRI	12	Biologic naïve	✓	✓	Biologic failed	✓	✓	✓	✓

Motoya 2019	VED	10	TNF naïve	✓	✓	TNF experienced	✓	✓	✓	✓
OCTAVE 1	TOF	8	TNF naïve	✓	✓	TNF failure	✓	✓	✓	✓
OCTAVE 2	TOF	8	TNF naïve	✓	✓	TNF failure	✓	✓	✓	✓
Probert 2003	IFX	6								✓
PURSUIT-SC 2	GOL	6	TNF naïve	✓	✓				✓	✓[b]
PURSUIT-SC 3	GOL	6	TNF naïve	✓	✓				✓	
Sandborn 2012	TOF	8[c]	TNF naïve	✓		TNF experienced	✓		✓	✓
SELECTION A	FIL	10	Biologic naïve	✓	✓				✓	✓[d]
SELECTION B	FIL	10				Biologic experienced	✓	✓	✓	
Suzuki 2014	ADA	8	TNF naïve	✓	✓				✓	✓
TRUE NORTH	OZD	10	TNF naïve	✓		TNF experienced	✓		✓	✓
U-ACCOMPLISH	UPA	8	No biologic failure	✓	✓	Biologic failure	✓	✓	✓	✓
U-ACHIEVE	UPA	8	No biologic failure	✓	✓	Biologic failure	✓	✓	✓	✓
U-ACHIEVE Ph2b	UPA	8	***No biologic failure***	✓	✓	***Biologic failure***	✓	✓	✓	✓
ULTRA 1	ADA	8	TNF naïve	✓	✓				✓	✓

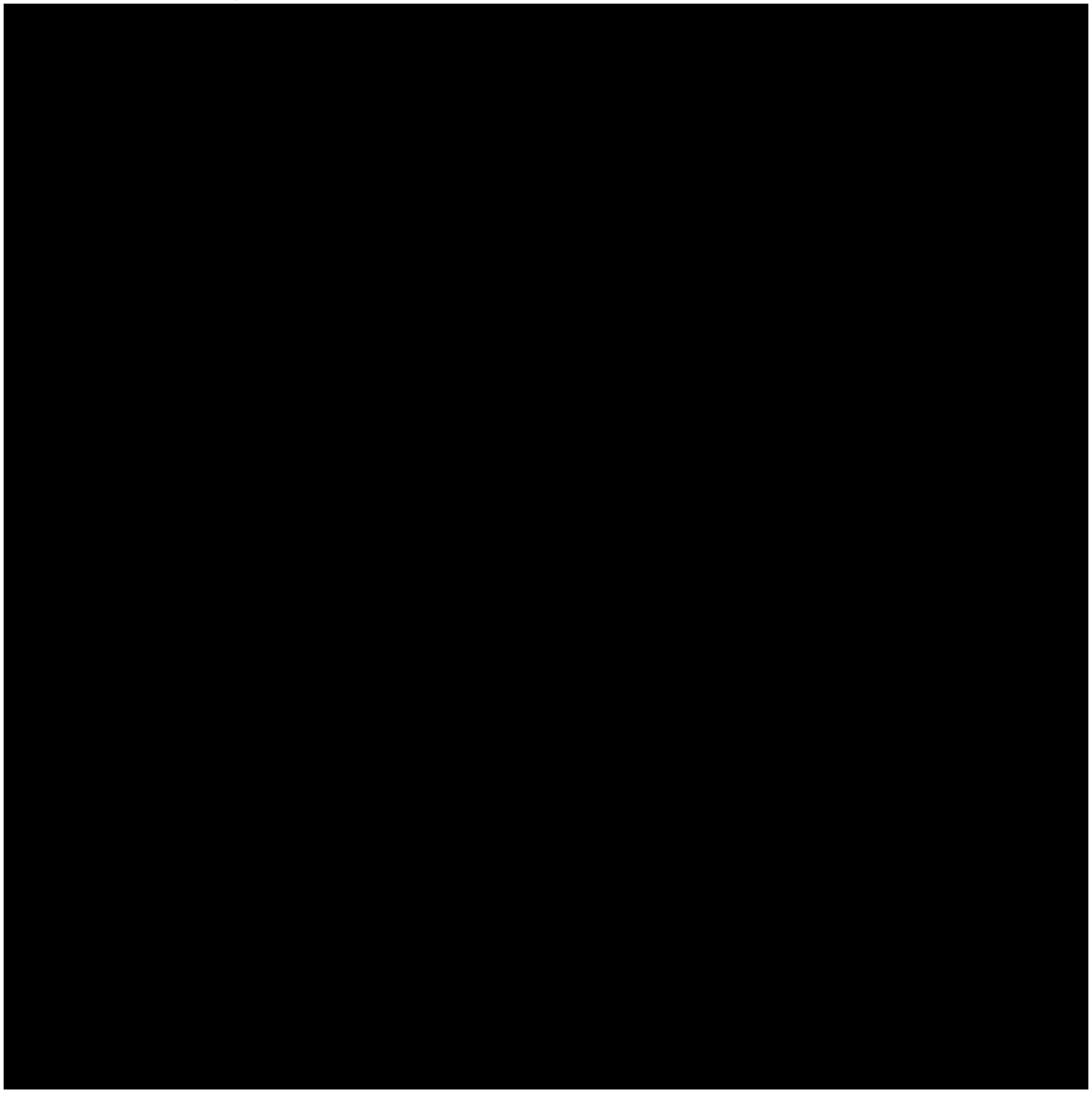
ULTRA 2	ADA	8	TNF naïve	✓	✓	TNF experienced	✓	✓		✓
UNIFI	UST	8	Biologic naïve	✓	✓	Biologic failure	✓	✓	✓	✓
VARSITY	VED ADA	14	TNF naïve	✓		TNF experienced	✓			

Bold and italicised values have been amended from original Company Submission Appendices. [a] Mixed population with regards to prior medication; [b] PURSUIT-SC Total study results (i.e., phase 2 and phase 3) were used in the NMA of SAEs; [c] Safety outcomes for Sandborn et al., 2012 were assessed at week 12; [d] Pooled results for SELECTION A and B were used in the NMA of SAEs.
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; SAE: serious adverse events; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 5.2 Explorative analysis for baseline risk adjustment (amended from Appendix D.1.6.2)

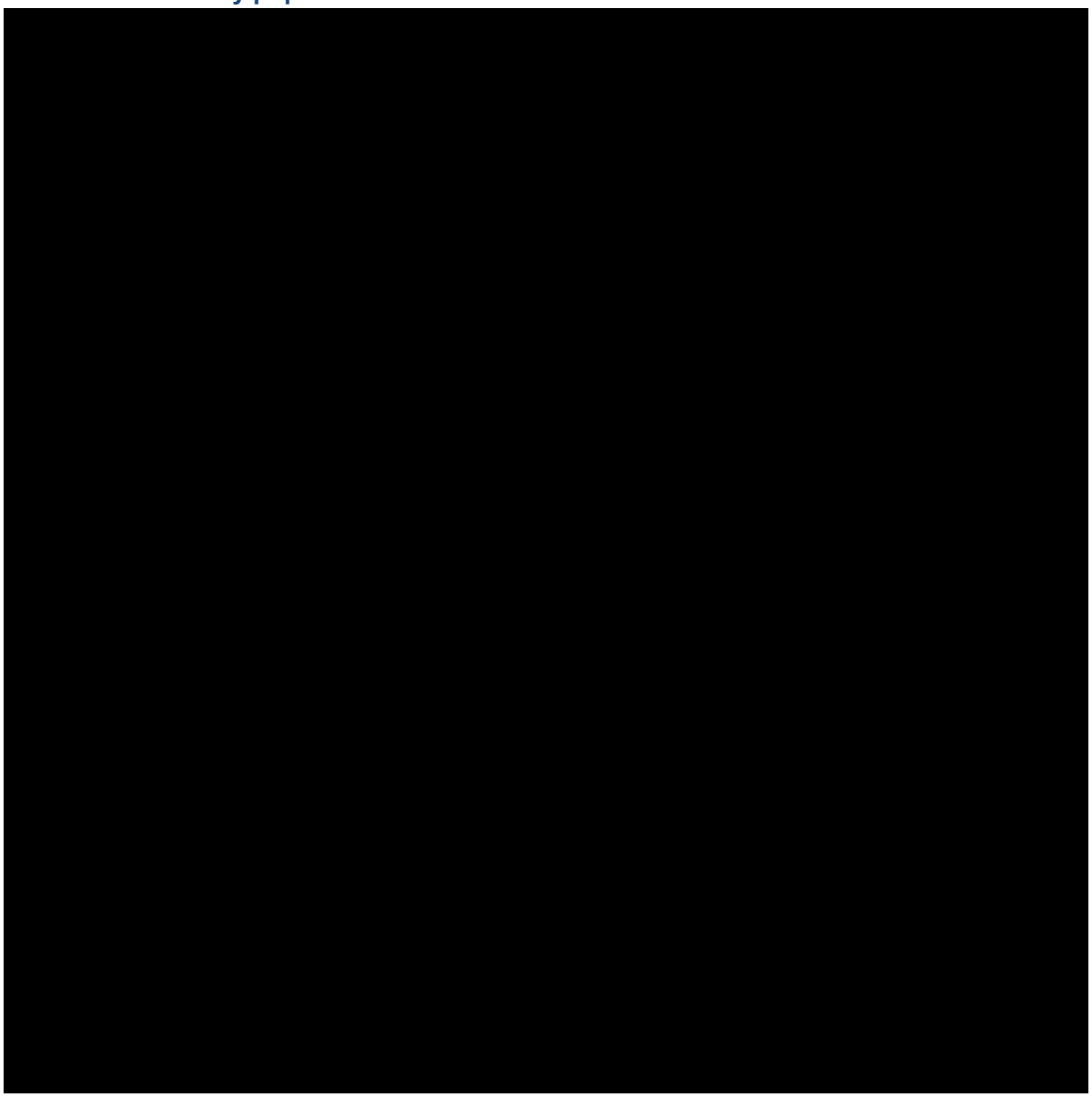
Several studies have presented the importance of investigating, and when appropriate, analytically accounting for between-study heterogeneity.[14-17] Differences in placebo response rates (or baseline risk) across UC trials have been reported previously.[18-22] Most recently, the NICE ERG reviewing the company submission for ozanimod for treating moderately to severely active ulcerative colitis (TA828)[13] performed a random-effects meta-analyses of the response (no remission) and remission proportions in the placebo arms of the studies included in the company's NMA. Substantial heterogeneity was observed, most notably in the maintenance setting for response (no remission) (I^2 = 65%). This result mirrored those observed in a prior study of placebo arm outcomes from UC trials.[22] Variations in placebo response rates may affect NMA results as placebo response rates are a component of the denominator in the relative treatment effect calculation of odds ratio (OR), i.e., dividing by a higher placebo response rates may dilute the relative treatment effect estimates and dividing by a smaller number can inflate relative effects. [redacted].

Figure 20: Forest plot of placebo response rates across included studies for induction and maintenance by population - clinical response



Vertical line represents the weighted average placebo response rate (i.e., number of responders divided by total sample size).
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; Q4W: once every 4 weeks; Q8W: once every 8 weeks; Q12W: once every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 21: Forest plot of placebo response rates across included studies for induction and maintenance by population - clinical remission



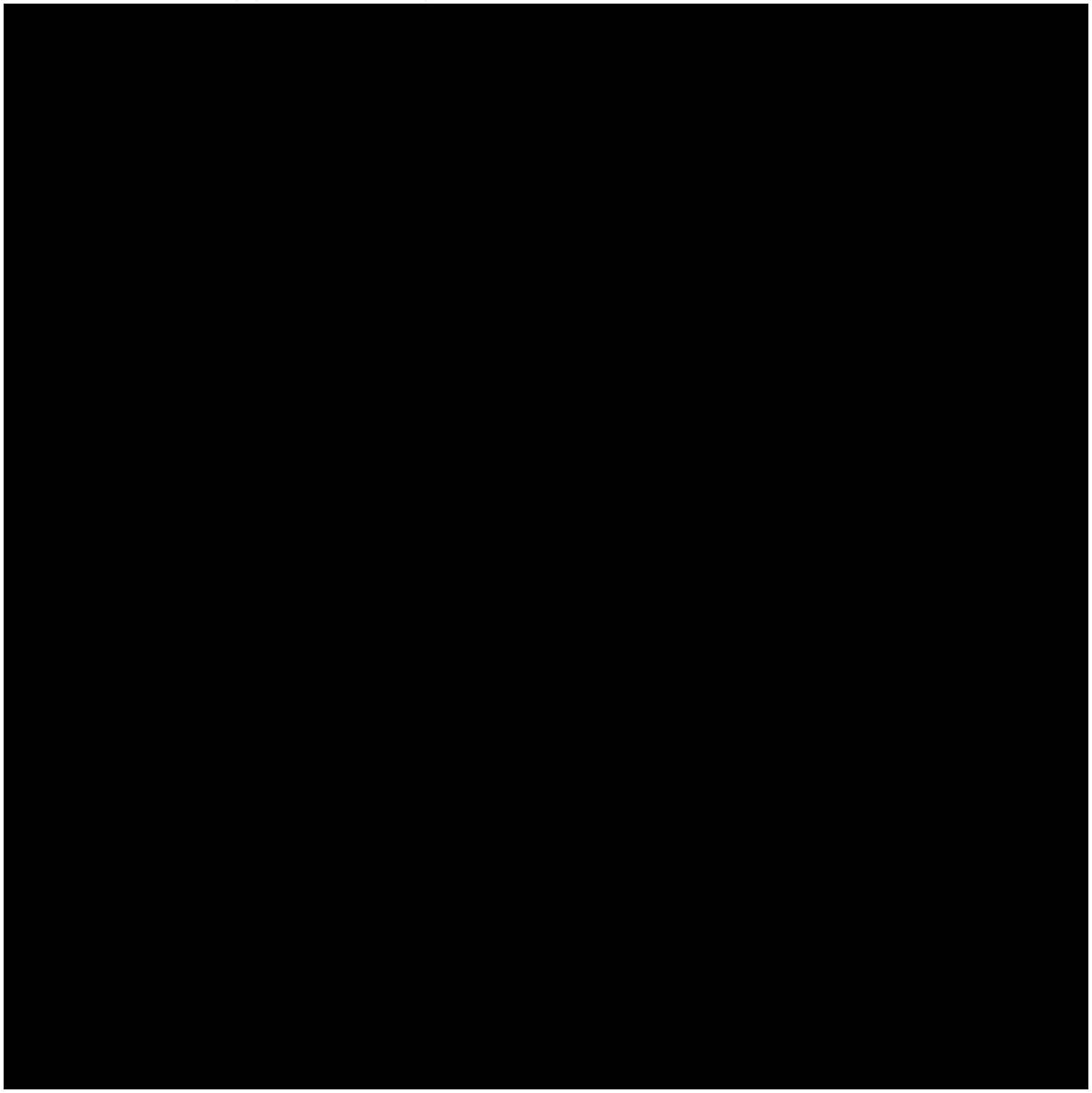
Vertical line represents the weighted average placebo response rate (i.e., number of responders divided by total sample size).
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; Q4W: once every 4 weeks; Q8W: once every 8 weeks; Q12W: once every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

A number of population characteristics have previously been shown to impact placebo response rates within trials of patients with UC,[18-22] including:

- Study location (European [increased placebo response] versus non-European [decreased placebo response])
- Trial duration and timepoint of assessment (increased placebo response)
- Disease status (more active disease, decreased placebo rates)
- Disease duration (< 5 years, decreased placebo rates)
- Prior exposure to biologic therapy at enrolment (decreased placebo rates)

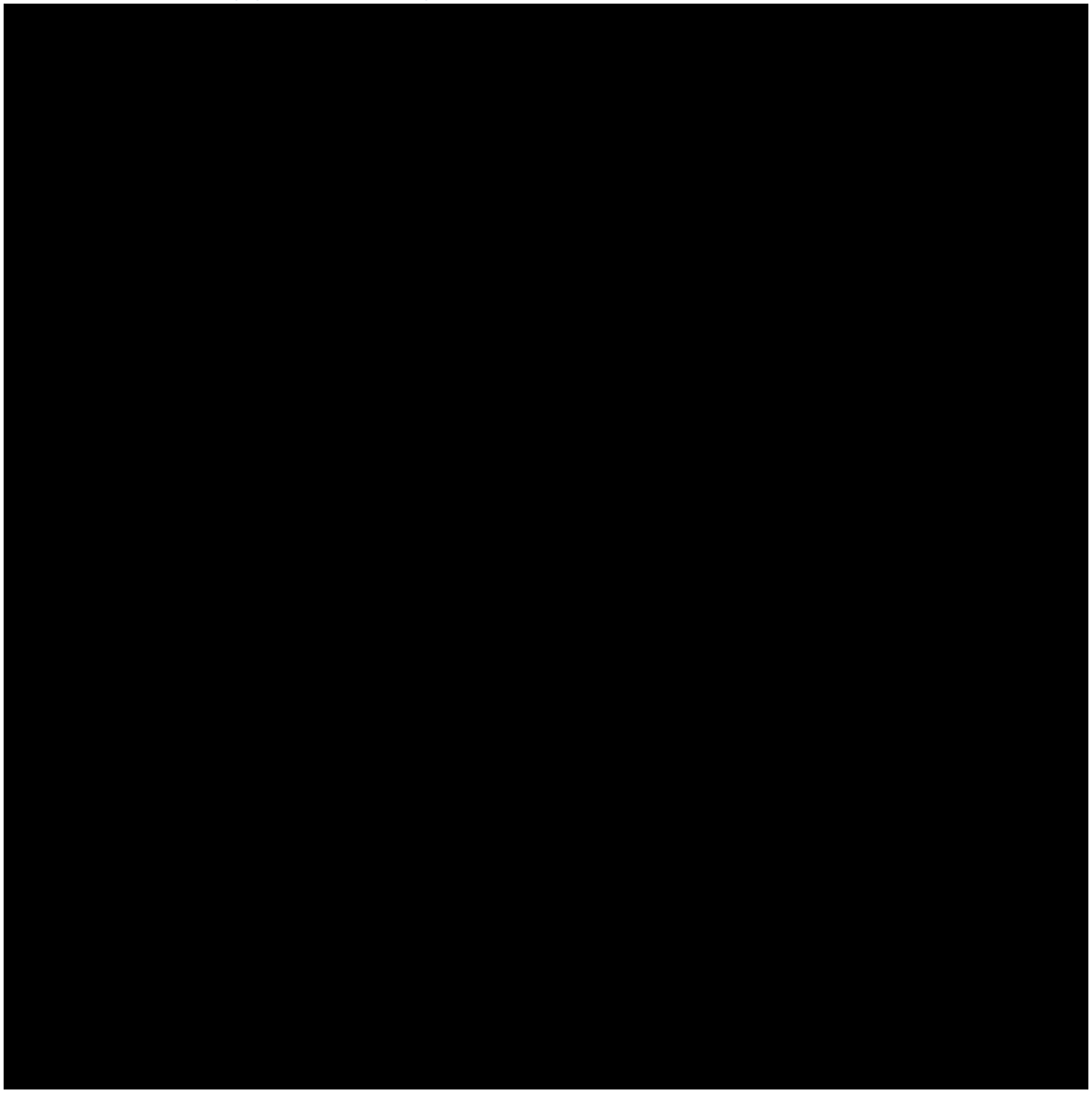
Further, it is acknowledged that the treatment landscape in UC has developed considerably over time which can lead to heterogeneity in the prior treatments received by placebo patients. Measures have been taken in the NMA to reduce the heterogeneity by limiting the time point of assessment at maintenance, analysing the biologic-naïve and -failed populations independently. However, a previous report identified consistent increases in placebo response and remission rates from 1987 to 2007 (from 13% to 33% and 5% to 14%, respectively), with constant rates observed from 2008 to 2015 (32%-34% and 12%-14%, respectively).[19] Thus, visual assessment of the placebo data was performed to assess if there is any continued systematic placebo creep for the up-to-date evidence base or whether it is a sampling effect. The year of study for each trial was plotted against the placebo response and remission results to investigate this relationship (Figure 22 and Figure 23, respectively), with some evidence of higher response rates for the more recently published studies, particularly in the maintenance phase. Placebo event rates plotted by year of publication for additional outcomes of interest by timepoint (induction and maintenance) and population (biologic-naïve and biologic-failed) are presented in Section 1.2 of the NMA report appendices provided in the reference pack.

Figure 22: Scatter plot of placebo response rates across included studies for induction and maintenance by year of primary publication and population - clinical response



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

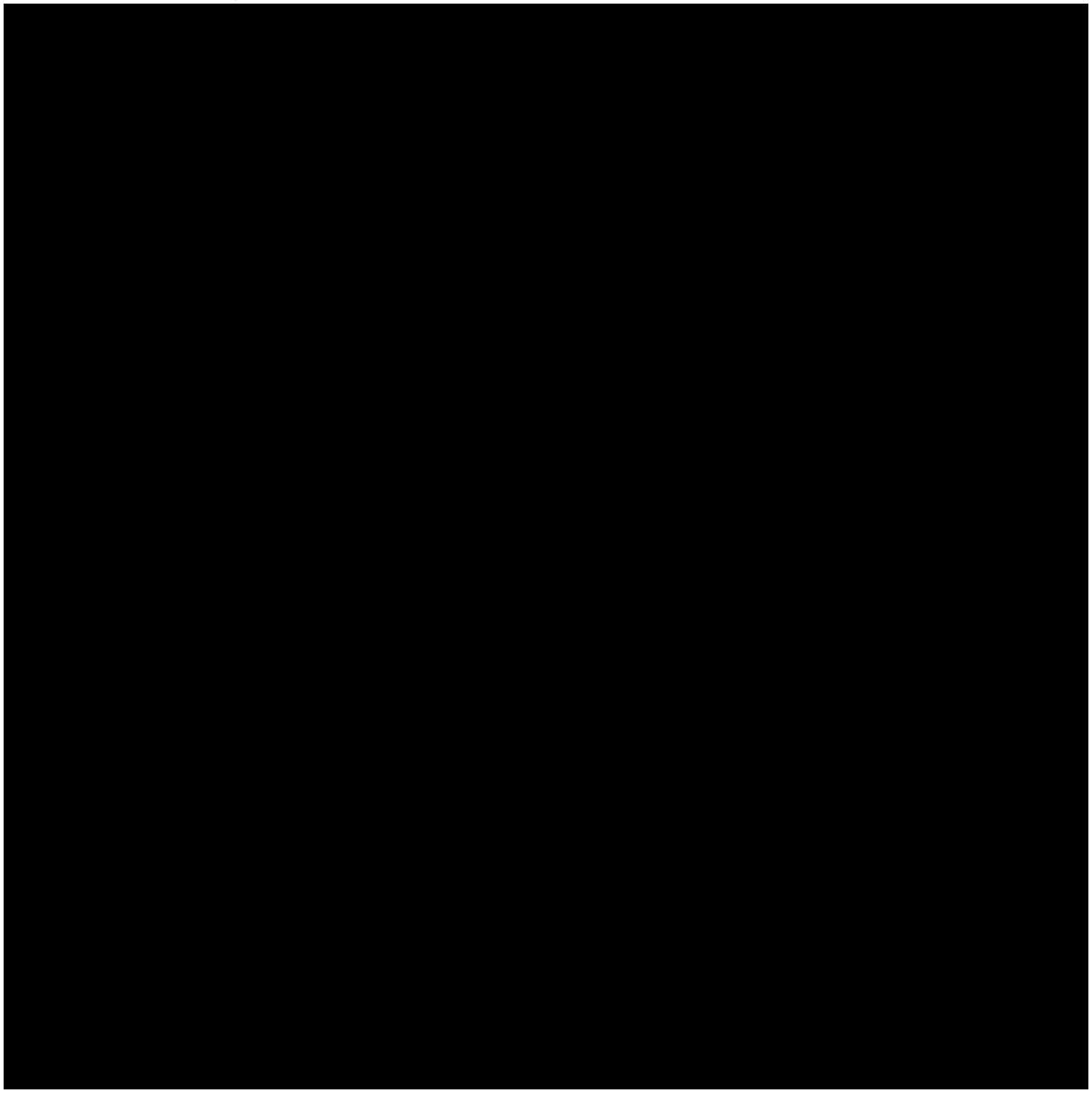
Figure 23: Scatter plot of placebo response rates across included studies for induction and maintenance by year of primary publication and population - clinical remission



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

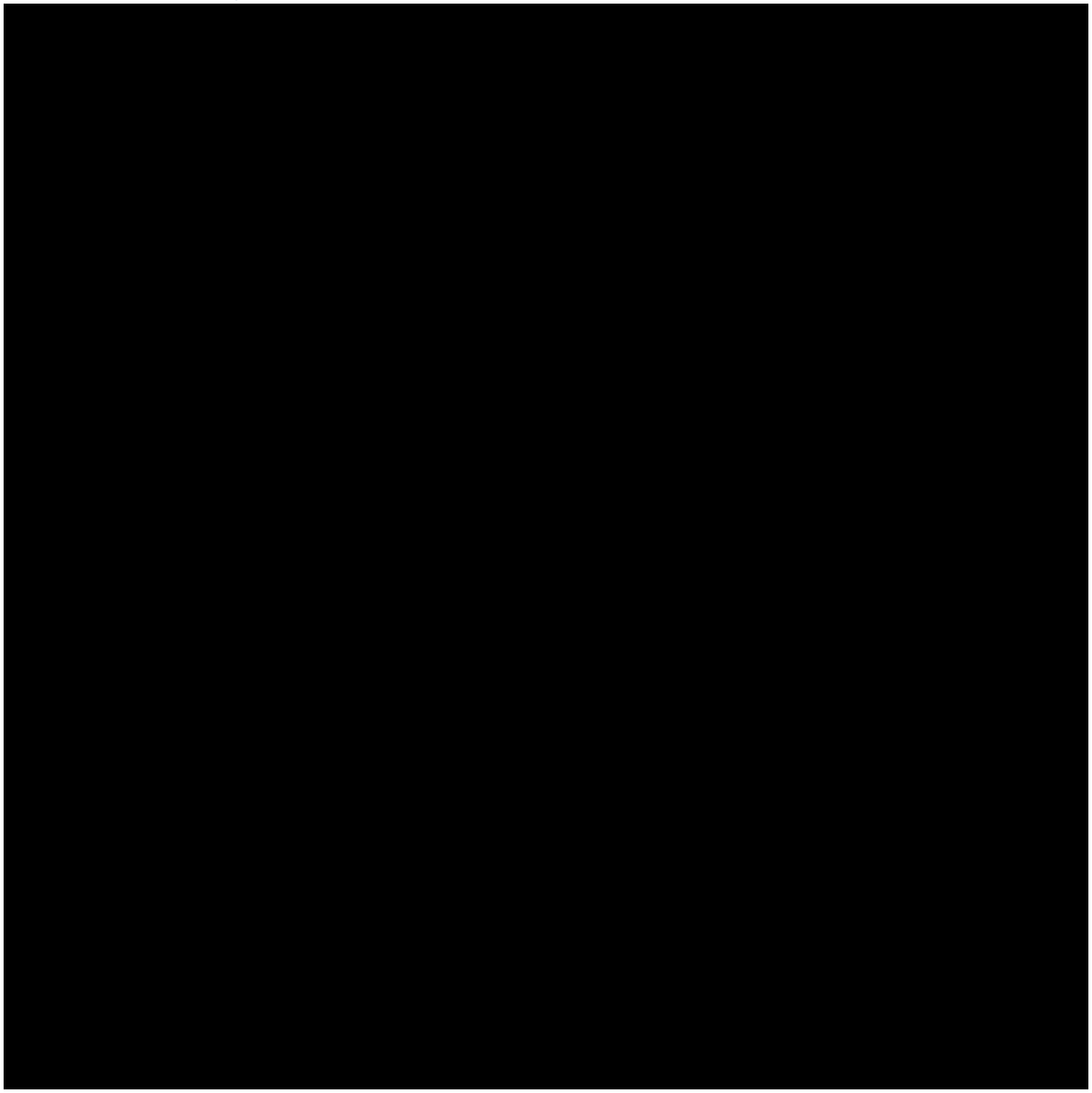
Reviewing placebo response and remission rates by time point of assessment (Figure 24 and Figure 25) aligned with previous reports that later timepoints of assessment at induction may be associated with increased placebo response rates, whereas shorter timepoints of assessment at maintenance may be associated with higher placebo response rates. Placebo event rates plotted by time point of assessment for additional outcomes of interest by timepoint (induction and maintenance) and population (biologic-naïve and biologic-failed) are presented in Section 1.2 of the NMA report appendices provided in the reference pack.

Figure 24: Scatter plot of placebo response rates across included studies for induction and maintenance by timepoint and population - clinical response



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 25: Scatter plot of placebo response rates across included studies for induction and maintenance by timepoint and population - clinical remission



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Baseline risk adjustment (i.e., placebo response adjustment) via a meta-regression model with baseline risk as a covariate may be explored when heterogeneity in placebo response across studies are expected to influence treatment effectiveness. The figures presented above illustrate areas of heterogeneity which cannot be further adjusted for by restricting NMA inclusion criteria without reducing the evidence base and/or removing comparators of interest. Further, a baseline risk adjusted meta-regression approach can be beneficial in its statistical efficiency to adjust for multiple known and unknown between-study differences versus consideration of multiple covariates simultaneously (which may be underpowered given the number of studies available and structure of the evidence base). In addition, for some studies, where outcome data were reported for subgroups by prior therapy, limited data were available on measured covariates by subgroup (see Appendix D.1.6.1 of the original Company Submission Appendices) and the summary of key baseline characteristics of studies included in Section 1.3 of the NMA report

appendices provided in the reference pack). Thus, an exploratory analysis using a meta-regression model adjusting for baseline risk was performed. The methodology for implementing this exploratory analysis will follow that outlined in the NICE DSU Technical Supplement Document 3[17] and is described further in Appendix D.1.7.4 of the original Company Submission Appendices. The baseline risk adjustment NMA results were then compared to the unadjusted NMA, and a decision was made on the most appropriate analyses based on goodness of fit and significance of the covariate coefficient.

Section 5.3 Updated NMA results: additional base-case results (amended from Appendix D.1.10)

In line with the treatments and comparators of interest presented in Table 27 in Appendix D.1.6.1 of the original Company Submission, abbreviated treatment labelling was used in all figures presented in the NMA. Table 13 presents a summary of the figure labelling and associated dosing regimen at induction and maintenance.

Table 13: Summary of abbreviated NMA figure labels

Intervention/ Comparator	Abbreviated NMA label	Dosing regimen	
		Induction	Maintenance
Adalimumab	ADA	160 mg at week 0, 80 mg at week 2	40 mg Q2W
Filgotinib	FIL	200 mg QD	200 mg QD
Golimumab	GOL	200 mg at week 0, 100 mg at week 2	-
	GOL 50mg	-	50 mg Q4W
	GOL 100mg	-	100 mg Q4W
Infliximab	IFX	5 mg/kg week 0, 2 and 6	5 mg/kg Q8W
Mirikizumab	MIRI	300 mg Q4W	***200 mg Q4W***
Ozanimod	OZD	1 mg QD	1 mg QD
Tofacitinib	TOF	10 mg BID	-
	TOF 5mg	-	5 mg BID
	TOF 10mg	-	10 mg BID
Upadacitinib	UPA	45 mg QD	-
	UPA 15mg	-	15 mg QD
	UPA 30mg	-	30 mg QD
Ustekinumab	UST	6 mg/kg	-
	UST 90mg Q8W	-	90 mg Q8W
	UST 90mg Q12W	-	90 mg Q12W
Vedolizumab	VED	300 mg week 0, 2 and 6	-
	VED 300mg Q4W	-	300 mg Q8W
	VED 300mg Q8W	-	300 mg Q4W
	VED 108mg Q2W	-	108 mg Q2W

Bold and italicised labels have been amended from original Company Submission Appendices.
Abbreviations: BID: twice daily; NMA: network meta-analysis; QD: once daily; Q2W: once every 2 weeks; Q4W: once every 4 weeks; Q8W: once every 8 weeks; Q12W: once every 12 weeks.

Section 5.3.1 Efficacy outcomes: biologic-naïve population: amended from Appendices Section D.1.10.1

Section 5.3.1.1 Induction: Clinical response and remission

Figure 26 presents the network for clinical response and remission during the induction period for the biologic-naïve population. In total, 24 studies were included in the analysis evaluating ten

interventions (adalimumab, filgotinib, golimumab, infliximab, mirikizumab, ozanimod, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Most interventions were assessed in one or two placebo-controlled studies, with one head-to-head study comparing adalimumab and vedolizumab (VARSITY). Table 14 presents the clinical response and remission input data.

Figure 26: Network plot for clinical response and remission in the induction period and biologic-naïve population

Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 14: Summary of NMA input data: clinical response and remission, induction, biologic-naïve population

Study	Treatment arm	N	No Response	Response without Remission	Response with Remission
ACT 1	Placebo	121	76 (62.8%)	27 (22.3%)	18 (14.9%)
	IFX 5mg/kg	121	37 (30.6%)	37 (30.6%)	47 (38.8%)
ACT 2	Placebo	123	87 (70.7%)	29 (23.6%)	7 (5.7%)
	IFX 5mg/kg	121	43 (35.5%)	37 (30.6%)	41 (33.9%)

Study	Treatment arm	N	No Response	Response without Remission	Response with Remission
GEMINI 1	Placebo	76	56 (73.7%)	15 (19.7%)	5 (6.6%)
	VED 300 mg	130	61 (46.9%)	39 ***(30.0%)***	30 (23.1%)
HIBISCUS 1	***Placebo***	***72***	***NR***	***NR***	***6 (8.3%)***
	ADA 160/80 mg	***142***	***NR***	***NR***	***34 (23.9%)***
HIBISCUS 2	***Placebo***	***72***	***NR***	***NR***	***8 (11.1%)***
	ADA 160/80 mg	***143***	***NR***	***NR***	***37 (25.9%)***
Jiang 2015	Placebo	41	26 (63.4%)	6 (14.6%)	9 ***(22.0%)***
	IFX 5mg/kg	41	9 ***(22.0%)***	10 (24.4%)	22 (53.7%)
Kobayashi 2016	Placebo	104	67 (64.4%)	26 (25%)	11 (10.6%)
	IFX 5mg/kg	104	47 (45.2%)	36 (34.6%)	21 (20.2%)
LUCENT	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	MIRI 300 mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Motoya 2019	Placebo	41	26 (63.4%)	9 ***(22.0%)***	6 (14.6%)
	VED 300 mg	79	37 (46.8%)	20 (25.3%)	22 (27.8%)
OCTAVE 1[a]	Placebo	57	35 (61.4%)	13 (22.8%)	9 (15.8%)
	TOF 10 mg	222	79 (35.6%)	87 (39.2%)	56 (25.2%)
OCTAVE 2[a]	Placebo	47	29 (61.7%)	14 (29.8%)	4 (8.5%)
	TOF 10 mg	195	69 (35.4%)	83 (42.6%)	43 (22.1%)
PURSUIT-SC 2	Placebo	41	28 (68.3%)	9 ***(22.0%)***	4 (9.8%)
	GOL 200/100 mg	41	23 (56.1%)	11 (26.8%)	7 (17.1%)
PURSUIT-SC 3	Placebo	251	175 (69.7%)	60 (23.9%)	16 (6.4%)
	GOL 200/100 mg	253	124 (49%)	84 (33.2%)	45 (17.8%)
Sandborn 2012[b]	Placebo	33	18 (54.5%)	10 (30.3%)	5 (15.2%)
	TOF 10 mg	23	9 (39.1%)	3 ***(13.0%)***	11 (47.8%)
SELECTION A	Placebo	137	73 (53.3%)	47 (34.3%)	17 (12.4%)
	FIL 200 mg QD	245	82 (33.5%)	103 (42%)	60 (24.5%)
Suzuki 2014	Placebo	96	62 (64.6%)	23 (24%)	11 (11.5%)
	ADA 160/80 mg	90	45 ***(50.0%)***	36 ***(40.0%)***	9 ***(10.0%)***
TRUE NORTH[c]	Placebo	152	108 (71.1%)	34 (22.4%)	10 (6.6%)
	OZD 1 mg QD	299	142 (47.5%)	91 (30.4%)	66 (22.1%)
U-ACCOMPLISH	Placebo	85	58 (68.2%)	22 (25.9%)	5 (5.9%)

Study	Treatment arm	N	No Response	Response without Remission	Response with Remission
	UPA 45 mg QD	168	34 (20.2%)	71 (42.3%)	63 (37.5%)
U-ACHIEVE	Placebo	76	44 (57.9%)	25 (32.9%)	7 (9.2%)
	UPA 45 mg QD	151	27 (17.9%)	71 (47%)	53 (35.1%)
U-ACHIEVE Ph2b	***Placebo***	***12***	***8 (66.7%)***	***4 (33.3%)***	***0 (0.0%)***
	UPA 45 mg QD	***14***	***3 (21.4%)***	***5 (35.7%)***	***6 (42.9%)***
ULTRA 1	Placebo	130	72 (55.4%)	46 (35.4%)	12 (9.2%)
	ADA 160/80 mg	130	59 (45.4%)	47 (36.2%)	24 (18.5%)
ULTRA 2	Placebo	145	89 (61.4%)	40 (27.6%)	16 ***(11.0%)***
	ADA 160/40 mg	150	61 (40.7%)	57 ***(38.0%)***	32 (21.3%)
UNIFI	Placebo	151	97 (64.2%)	39 (25.8%)	15 (9.9%)
	UST 6 mg/kg	147	49 (33.3%)	71 (48.3%)	27 (18.4%)
VARSITY	ADA 160/80 mg	305	154 (50.5%)	79 (25.9%)	72 (23.6%)
	VED 300 mg	304	91 (29.9%)	129 (42.4%)	84 (27.6%)

Bold and italicised values have been amended from original Company Submission Appendices.
[a] Response data by prior therapy subgroup is not available in the published literature identified in the SLR for the OCTAVE 1 and 2 trials independently (only as a pooled analysis). However, this data was reported in the committee papers for TA792 Filgotinib for treating moderately to severely active ulcerative colitis and has been extracted for use in the NMA.
[b] Remission data by prior therapy subgroup is not available in the published literature identified in the SLR for this study. However, this data was reported in the appendix documents (Table 89 and Table 90) supporting the company submission for TA547 Tofacitinib for previously treated active ulcerative colitis and has been extracted for use in the NMA.
[c] Response without remission and response with remission rates calculated using the n/N (%) responders reported for the overall TRUE NORTH population and the % responders reported for the TNF-experienced population. For the subgroup TNF naïve only remission rates were reported in the identified publications.
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; NR: not reported; OZD: ozanimod; QD: once daily; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.1.1.1 of the NMA report appendix, provided in the reference pack), convergence diagnostics, and visual assessment of model performance (as described in Appendix D.1.7.6 of the original Company Submission Appendices) suggested that the random effects model using a half-Normal prior for the between-trial standard deviation (without baseline risk adjustment) was associated with an improved fit relative to other models. In all models fitted using meta-regression, adjusting for baseline risk the 95% CrI for the interaction term β included the possibility of no interaction (i.e., includes zero).

Reviewing the unadjusted models, the residual deviance for the random effects model using a half-Normal prior was lower than the fixed effect model ([redacted] versus [redacted]) and the 95% CrI for the posterior estimate of the between study standard deviation (tau) was reasonable ([redacted]). Whilst the DIC was marginally larger in the random effects model ([redacted] versus [redacted] for the fixed effect model), clinical heterogeneity, discussed in Section B.3.9.2 of the original Company Submission, favours the random effects model. A review of inconsistency (as described in Appendix D.1.7.8 of the original Company Submission Appendices) determined

there to be little evidence of inconsistency between direct and indirect estimates for either model. Therefore, primary results for clinical response and remission during the induction period for the biologic-naïve population described in this section were derived from the random effects model (without baseline risk adjustment). Complementary results with baseline risk adjustment and results under the fixed effect model and random effects model with a flat prior have been provided in the reference pack (Section 3.1.1 of the NMA report appendix). As presented in Figure 1 and Figure 2 in Section 2.1.1, [redacted](Figure 27 and Figure 28, respectively).

Figure 27: Odds ratios versus placebo with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: clinical response, induction, biologic-naïve population

[redacted]

Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 28: Odds ratios versus placebo with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: clinical remission, induction, biologic-naïve population

Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

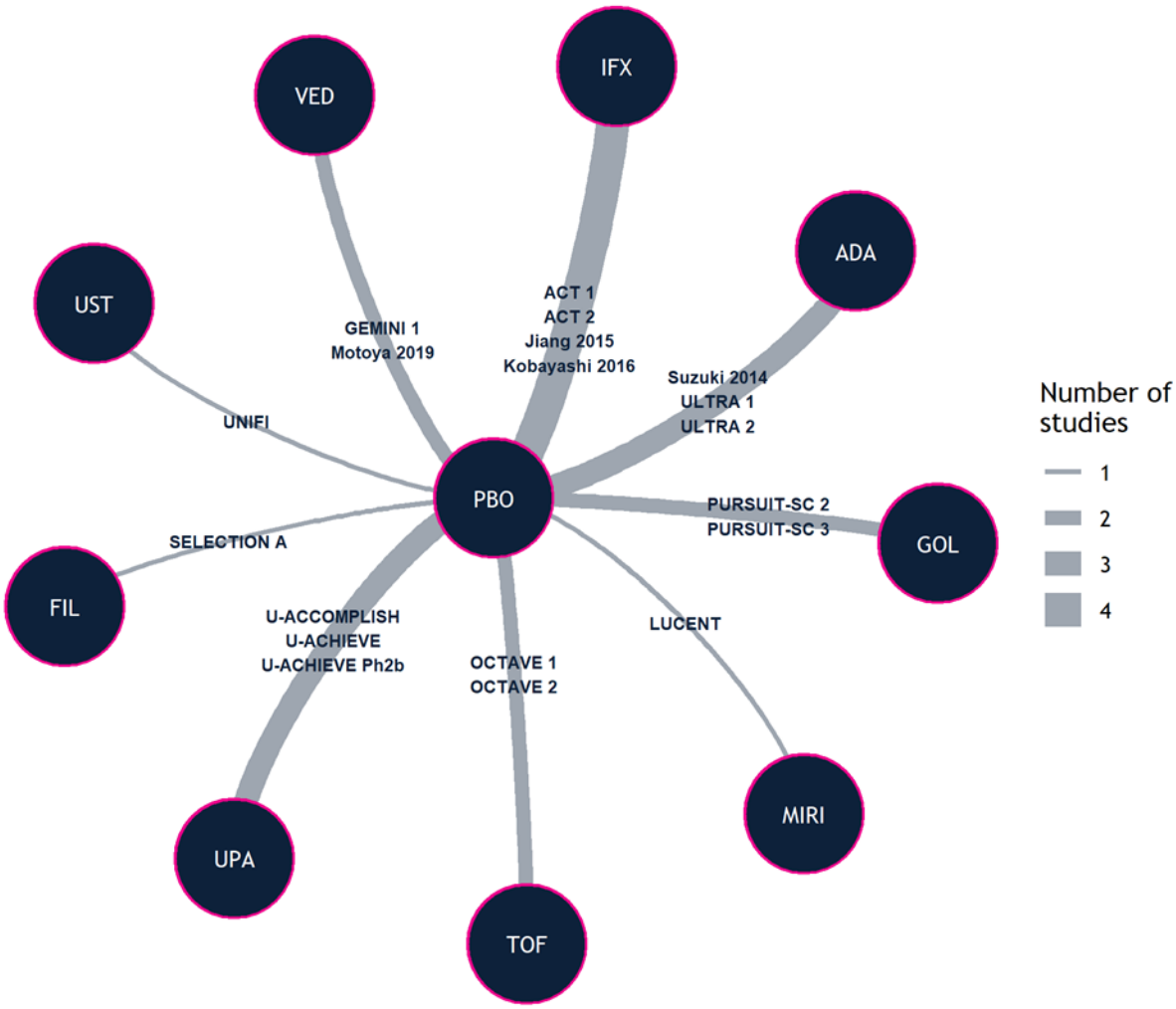
Absolute predictions and all pairwise comparisons of risk ratios, risk differences, and number needed to treat, as well as the cumulative rank probabilities and SUCRA values are presented in Section 2.1.1.1 of the NMA report appendix, provided in the reference pack.

Section 5.3.1.2 Induction: Mucosal healing

Figure 29 presents the network for mucosal healing during the induction period for the biologic-naïve population. In total, 19 studies were included in the analysis evaluating ten interventions (adalimumab, filgotinib, golimumab, infliximab, mirikizumab, ozanimod, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Table 15 presents the input data.

As described in Section B.3.9.2.4 of Document B of the original Company Submission, terminology around mucosal healing and endoscopic improvement are often used interchangeably across studies of UC. For the purpose of this NMA, data were included in analyses of mucosal healing where outcomes were defined as “Endoscopic subscore of 0 or 1”, in line with the LUCENT trial.

Figure 29: Network plot for mucosal healing in the induction period and biologic-naïve population



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 15: Input data for mucosal healing in the Induction period and biologic-naïve population

Study	Year	Treatment	Timepoint	Number analysed	Number of patients with mucosal healing
ACT 1	2005	PBO	8	121	41
ACT 1	2005	IFX	8	121	75
ACT 2	2005	PBO	8	123	38
ACT 2	2005	IFX	8	121	73
GEMINI 1	2013	PBO	6	76	19
GEMINI 1	2013	VED	6	130	64
Jiang 2015	2015	PBO	8	41	10
Jiang 2015	2015	IFX	8	41	24
Kobayashi 2016	2016	PBO	8	104	29
Kobayashi 2016	2016	IFX	8	104	48
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Motoya 2019	2019	PBO	10	79	38
Motoya 2019	2019	VED	10	41	13
OCTAVE 1	2017	PBO	8	57	***15***
OCTAVE 1	2017	TOF	8	222	***18***
OCTAVE 2	2017	PBO	8	47	9
OCTAVE 2	2017	TOF	8	195	71
PURSUIT-SC 2	2014	PBO	6	41	10

Study	Year	Treatment	Timepoint	Number analysed	Number of patients with mucosal healing
PURSUIT-SC 2	2014	GOL	6	41	14
PURSUIT-SC 3	2014	PBO	6	251	72
PURSUIT-SC 3	2014	GOL	6	253	107
SELECTION A	2021	PBO	10	137	28
SELECTION A	2021	FIL	10	245	83
Suzuki 2014	2014	PBO	8	96	29
Suzuki 2014	2014	ADA	8	90	40
U-ACCOMPLISH	2022	PBO	8	85	10
U-ACCOMPLISH	2022	UPA	8	168	86
U-ACHIEVE	2020	PBO	8	76	10
U-ACHIEVE	2020	UPA	8	151	71
U-ACHIEVE Ph2b	***2020***	***PBO***	***8***	***12***	***1***
U-ACHIEVE Ph2b	***2020***	***UPA***	***8***	***14***	***9***
ULTRA 1	2011	PBO	8	130	54
ULTRA 1	2011	ADA	8	130	61
ULTRA 2	2012	PBO	8	145	51
ULTRA 2	2012	ADA	8	150	74
UNIFI	2019	PBO	8	151	32
UNIFI	2019	UST	8	147	49

Bold and italicised values have been amended from original Company Submission Appendices. **Abbreviations:** ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab

Inspection of model fit statistics (presented in Section 2.1.1.2 of the NMA report appendices in the reference pack), convergence diagnostics, and visual assessment of model performance (as described in Appendix D.1.7.6 of the original Company Submission) suggested that the random effects model using a half-Normal prior for the between-trial standard deviation with baseline risk adjustment was associated with an improved fit relative to other models. In both random effects models fitted using meta-regression adjusting for baseline risk the 95% CrI for the interaction term β did not include the possibility of no interaction (i.e., zero). The adjusted fixed effect model fitted the data very poorly, reflected by the high residual deviance and resulting high DIC. The 95% CrI for the posterior estimate of the between study standard deviation (tau) was low ([redacted] [redacted] to [redacted]). Therefore, primary results for mucosal healing during the induction period for the biologic-naïve population described in this section were derived from the random effects model (with baseline risk adjustment). As presented in Figure 3 in Section 2.2.1, [redacted] The odds ratios versus placebo for all active comparators are presented in Figure 30. Absolute predictions, all pairwise comparisons of risk ratios, risk differences, and number needed to treat are presented, along with the cumulative rank probabilities and SUCRA values, in Section 2.1.1.2 of the NMA report appendices included in the reference pack. In terms of SUCRA ranking, [redacted].

Figure 30: Odds ratios against placebo with random treatment effects with baseline risk meta-regression and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: mucosal healing, induction, biologic-naïve population

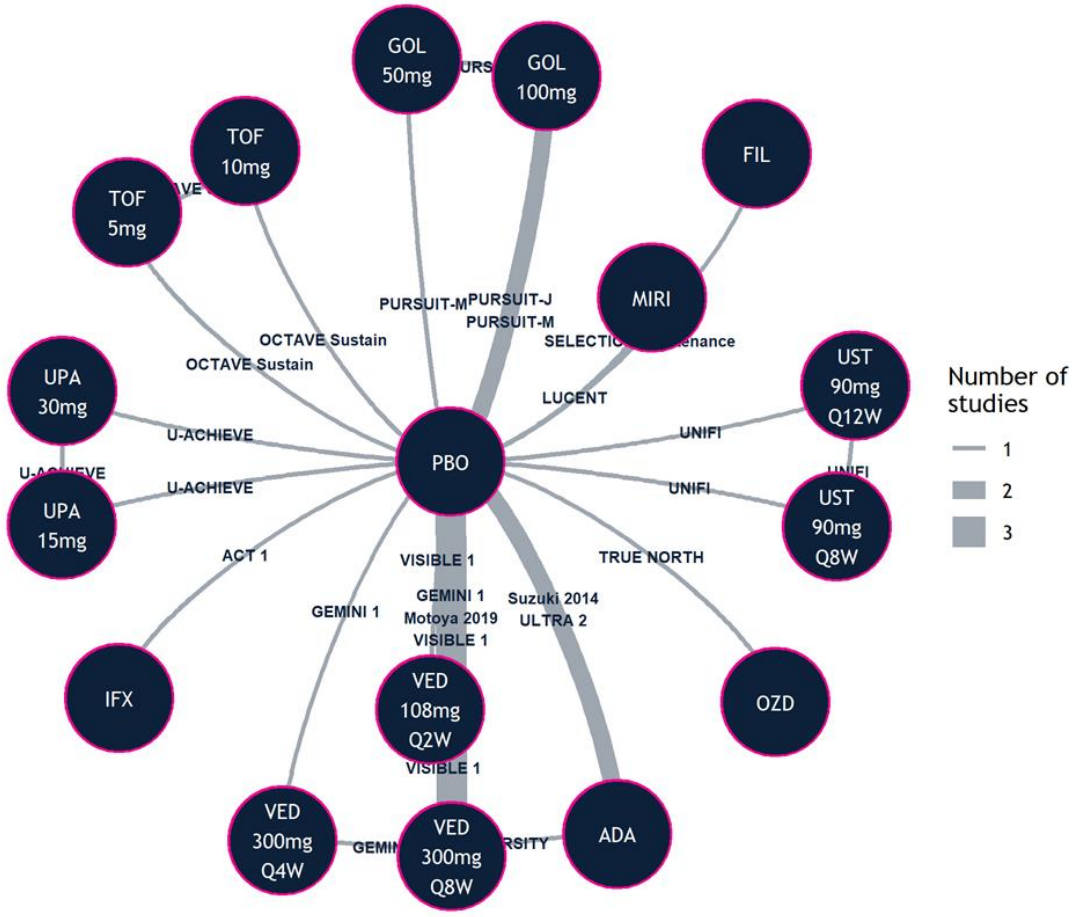
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 5.3.1.3 Maintenance: Clinical response and remission

Base case analysis

Figure 31 presents the network for clinical response and remission during the maintenance period for the biologic-naïve population. In total, 15 studies were included in the analysis evaluating 10 interventions (adalimumab, filgotinib, golimumab, infliximab, mirikizumab, ozanimod, tofacitinib, upadacitinib, ustekinumab, and vedolizumab), across 16 dosing regimens, and placebo. Most interventions were assessed in one placebo-controlled study, with one head-to-head study comparing adalimumab and vedolizumab (VARSITY). Table 16 presents the clinical response and remission input data. Table 17 presents a summary of the recalculation of treat-through studies to obtain inputs for the NMA, as described in Appendix D.1.7.7 of the original Company Submission.

Figure 31: Network plot for clinical response and remission in the maintenance period and biologic-naïve population.



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UST: ustekinumab; UPA: upadacitinib; VED: vedolizumab.

Table 16: Summary of NMA input data: clinical response and remission, maintenance, biologic-naïve population

Study	Treatment arm	N	No Response	Response without Remission	Response with Remission
Treat-through trials					
ACT 1	Placebo	45	28 (62.2%)	4 (8.9%)	13 (28.9%)
	IFX 5mg/kg Q8W	84	37 (44%)	5 (6%)	42 (50%)
Suzuki 2014	Placebo	34	22 (64.7%)	5 (14.7%)	7 (20.6%)
	ADA 40 mg Q2W	82	37 (45.1%)	4 (4.9%)	41 (50%)
ULTRA 2	Placebo	56	32 (57.1%)	6 (10.7%)	18 (32.1%)
	ADA 40 mg Q2W	89	45 (50.6%)	16 (18%)	28 (31.5%)
VARSITY	ADA 40 mg Q2W	151	NR	NR	74 (49%)
	VED 300 mg Q8W	213	NR	NR	104 (48.8%)
Re-randomised trials					
GEMINI 1	Placebo	79	58 (73.4%)	6 (7.6%)	15 (19%)
	VED 300 mg Q8W	72	25 (34.7%)	14 (19.4%)	33 (45.8%)
	VED 300 mg Q4W	73	32 (43.8%)	6 (8.2%)	35 (47.9%)
LUCENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Motoya 2019	VED 300 mg Q8W	24	8 (33.3%)	3 (12.5%)	13 (54.2%)
	Placebo	28	18 (64.3%)	0 (0%)	10 (35.7%)
OCTAVE Sustain	Placebo	109	82 (75.2%)	15 (13.8%)	12 (11%)
	TOF 5 mg BID	115	50 (43.5%)	17 (14.8%)	48 (41.7%)
	TOF 10 mg BID	104	37 (35.6%)	21 (20.2%)	46 (44.2%)
PURSUIT-J[a]	GOL 100 mg	32	14 (43.8%)	2 (6.3%)	16 (50%)

Study	Treatment arm	N	No Response	Response without Remission	Response with Remission
	Placebo	31	25 (80.6%)	4 (12.9%)	2 (6.5%)
PURSUIT-M	Placebo	154	106 (68.8%)	14 (9.1%)	34 (22.1%)
	GOL 100 mg	151	76 (50.3%)	24 (15.9%)	51 (33.8%)
	GOL 50 mg	151	77 (51%)	24 (15.9%)	50 (33.1%)
SELECTION Maintenance	Placebo	54	32 (59.3%)	13 (24.1%)	9 (16.7%)
	FIL 200 mg QD	107	27 (25.2%)	28 (26.2%)	52 (48.6%)
TRUE NORTH[b]	Placebo	158	***82 (51.9%)***	***41 (25.9%)***	35 (22.2%)
	OZD 1 mg QD	154	***58 (37.7%)***	***33 (21.4%)***	63 (40.9%)
U-ACHIEVE	Placebo	63	49 (77.8%)	3 (4.8%)	11 (17.5%)
	UPA 15mg	71	25 (35.2%)	15 (21.1%)	31 (43.7%)
	UPA 30mg	78	13 (16.7%)	23 (29.5%)	42 (53.8%)
UNIFI	Placebo	84	40 (47.6%)	17 (20.2%)	27 (32.1%)
	UST 90 mg Q8W	79	18 (22.8%)	21 (26.6%)	40 (50.6%)
	UST 90 mg Q12W	95	22 (23.2%)	28 (29.5%)	45 (47.4%)
VISIBLE 1	Placebo	37	NR	NR	7 (18.9%)
	VED 108 mg Q2W	67	NR	NR	36 (53.7%)
	VED 300 mg Q8W	32	NR	NR	17 (53.1%)

Bold and italicised values have been amended from original Company Submission Appendices. **Bold and underlined** values correspond to re-calculated input data for treat-through studies that was used in the NMA, corresponding calculations are provided in Table 17. [a] Remission data was not reported for only week 52, in line with previous UC NMAs, sustained clinical remission data (remission at week 30 and 52) was included in the NMA for this study. [b] Sample size was derived from the number and proportion of patients achieving clinical remission in the naïve subgroup. Number of patients achieving clinical response in the naïve subgroup was not reported in the identified publications and was derived using results for the overall study population minus those reported for the experienced subgroup.

Abbreviations: ADA: adalimumab; BID: twice daily; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; NR: not reported; OZD: ozanimod; QD: once daily; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UST: ustekinumab; UPA: upadacitinib; VED: vedolizumab.

Table 17: Summary of trial design adjustments for treat-through study designs: clinical response and remission, maintenance, biologic-naïve population

Study	Tx arm	Raw Data				Calculated Data			Description
		MAIN N	IND response, n (%)	Durable/ sustained response at MAIN, n (%)	Remission at MAIN, n (%)	Assumed patients re-randomised	Assumed patients response MAIN[b]	Assumed patients remission MAIN[c]	
ACT 1	Placebo	121	45 (37.2%)	17 (14%)	24 (19.8%)	**45**	**17**	***13***	Response is number of sustained responders (i.e., response at week 8, 30, and 54). Remission calculated using the number of clinical remitters at the end of maintenance produced an illogical value (n=20, i.e., number of remitters greater than number of responders (n=17). Thus, a weighted average of placebo data for the percentage of responders who were remitters from the combined placebo data from the re-randomised trials (***78.7%***) was applied to the number of responders, producing an estimate of ***13*** remitters.
	IFX 5mg/kg Q8W	121	84 (69.4%)	47 (38.8%)	55 (45.5%)	**84**	**47**	**42**	Response is number of sustained responders (i.e., response at week 8, 30, and 54). Remission is the number of clinical remitters at the end of maintenance.

Study	Tx arm	Raw Data				Calculated Data			Description
		MAIN N	IND response, n (%)	Durable/ sustained response at MAIN, n (%)	Remission at MAIN, n (%)	Assumed patients re-randomised	Assumed patients response MAIN[b]	Assumed patients remission MAIN[c]	
Suzuki 2014	Placebo	96	34 (35.4%)	NR	17 (18%)	**34**	**12**	**7**	Weighted average ratio for response. Remission is the number of clinical remitters at the end of maintenance.
	ADA 40 mg Q2W	177	82 (37.3%)	NR	55 (31%)	**82**	**45**	**41**	Weighted average ratio for response. Remission is the number of clinical remitters at the end of maintenance.
ULTRA 2	Placebo	145	56 (38.6%)	24 (16.6%)	35 (24.1%)	**56**	**24**	**18**	Response is number of durable responders. Remission is the number of clinical remitters at the end of maintenance.
	ADA 40 mg Q2W	150	89 (59.3%)	44 (29.3%)	55 (36.7%)	**89**	**44**	**28**	Response is number of durable responders. Remission in induction phase responders was reported directly in a secondary publication for this trial (Sandborn et al., 2013).
VARSITY	ADA 40 mg Q2W	305	151 (49.5%)	NR	NR	**151**	**NR**	**74**	Remission is the number of clinical remitters at the end of maintenance.

Study	Tx arm	Raw Data				Calculated Data			Description
		MAIN N	IND response, n (%)	Durable/ sustained response at MAIN, n (%)	Remission at MAIN, n (%)	Assumed patients re-randomised	Assumed patients response MAIN[b]	Assumed patients remission MAIN[c]	
	VED 300 mg Q8W	304	213 (70.1%)	NR	NR	**213**	**NR**	**104**	Remission is the number of clinical remitters at the end of maintenance.

Bold and italicised values have been amended from original Company Submission Appendices. [a] The total numbers of responders in the treat-through trials during the induction phase provides a proxy for the number of patients who enter maintenance.[b] Clinical response for maintenance from the treat-through trials was based on the proportion achieving sustained clinical response during the maintenance phase (this mitigates the risk of counting maintenance phase responders who were induction phase non-responders). [c] Clinical remission for maintenance from the treat-through trials is based on the reported number of remitters at end of maintenance (from TT) based on the assumption that maintenance phase remitters achieved response at induction and therefore were used as a proxy when estimating the re-randomised maintenance remission proportions.

Abbreviations: ADA: adalimumab; IND: induction; IFX: infliximab; MAIN: maintenance; NR: not reported; Tx: treatment; VED: vedolizumab; Q2W: every 2 weeks; Q8W: every 8 weeks.

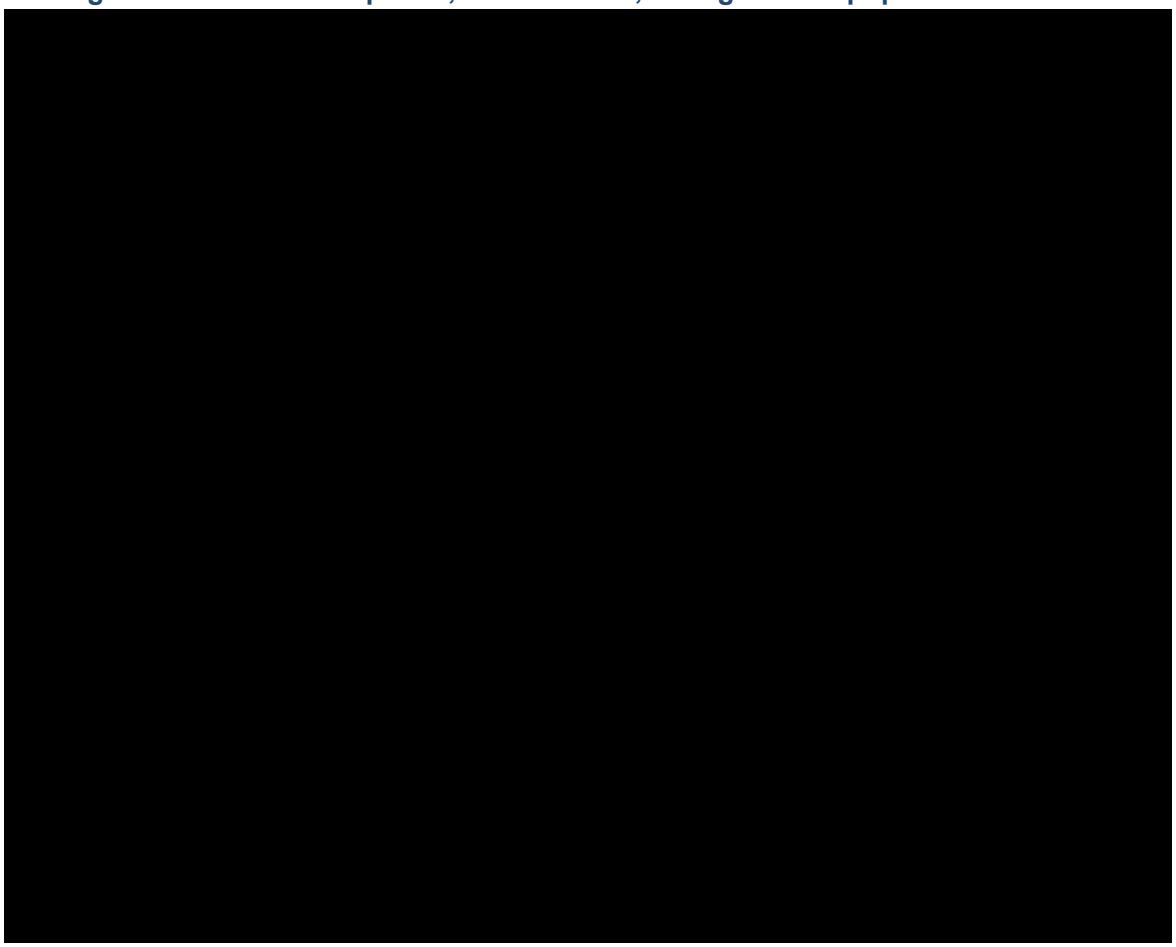
Inspection of model fit statistics (presented in Section 2.1.2.1 of the NMA report appendices in the reference pack), convergence diagnostics, and visual assessment of model performance (as described in Appendix D.1.7.6 of the original Company Submission) suggested that the fixed effect model with baseline risk adjustment was associated with an improved fit relative to other models. In the fixed effect model fitted using meta-regression adjusting for baseline risk the 95% CrI for the interaction term β excluded the possibility of no interaction (i.e., excludes zero), suggesting an association between baseline risk and treatment effects which should be adjusted for. The fixed effect model had reasonable fit in terms of DIC and residual deviance. Although clinical heterogeneity, discussed in Section B.3.9.2 of the original Company Submission, favours the random effects model, [redacted] Further, the baseline risk adjustment accounts for some of the observed and unobserved heterogeneity previously described.

A review of inconsistency (as described in Appendix D.1.7.8 of the original Company Submission) determined there to be little evidence of inconsistency between direct and indirect estimates for either model. Therefore, primary results for clinical response and remission during the maintenance period for the biologic-naïve population described in this section were derived from the fixed effect model with baseline risk adjustment. Complementary results without baseline risk adjustment and results under random effects models have been provided in the reference pack (Section 3.2.1 of the NMA report appendices).

As outlined in Section 2.1.2, [redacted] (Figure 32 and Figure 33).

Absolute predications, all pairwise comparisons of risk ratios, risk differences, and number needed to treat, along with the cumulative rank probabilities and SUCRA values are presented in Section 2.1.2.1 of the NMA report appendices, provided in the reference pack. [redacted]

Figure 32: Odds ratios against placebo with fixed treatment effects with baseline risk meta-regression: clinical response, maintenance, biologic-naïve population



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 33: Odds ratios against placebo with fixed treatment effects with baseline risk meta-regression: clinical remission, maintenance, biologic-naïve population

Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Sensitivity analysis

Complete results for the sensitivity analysis of clinical response and remission including only re-randomised studies of the biologic-naïve population at maintenance are presented in Section 2.1.2.2 of the NMA report appendices provided in the reference pack. The reduced network of evidence included 11 studies, notably this network excluded infliximab and adalimumab as those interventions are evaluated only in treat-through trials. Unlike the network pooling both treat-through and re-randomised studies, the best fitting model for the NMA with only re-randomised studies was the fixed effect model without meta-regression adjusting for baseline risk. Whilst some differences in placebo response are still observed across re-randomised studies (see Appendix D.1.6.2 of the original Company Submission), the 95% CrI for the interaction term β from the fixed effect model fitted using meta-regression adjusting for baseline risk included the possibility of no interaction (i.e. includes zero) (95% CrI:).

In line with results from the network pooling both study types, all interventions offered statistically significant improvements in the rate of clinical response and remission over placebo. However, in the reduced network without baseline risk adjustment,

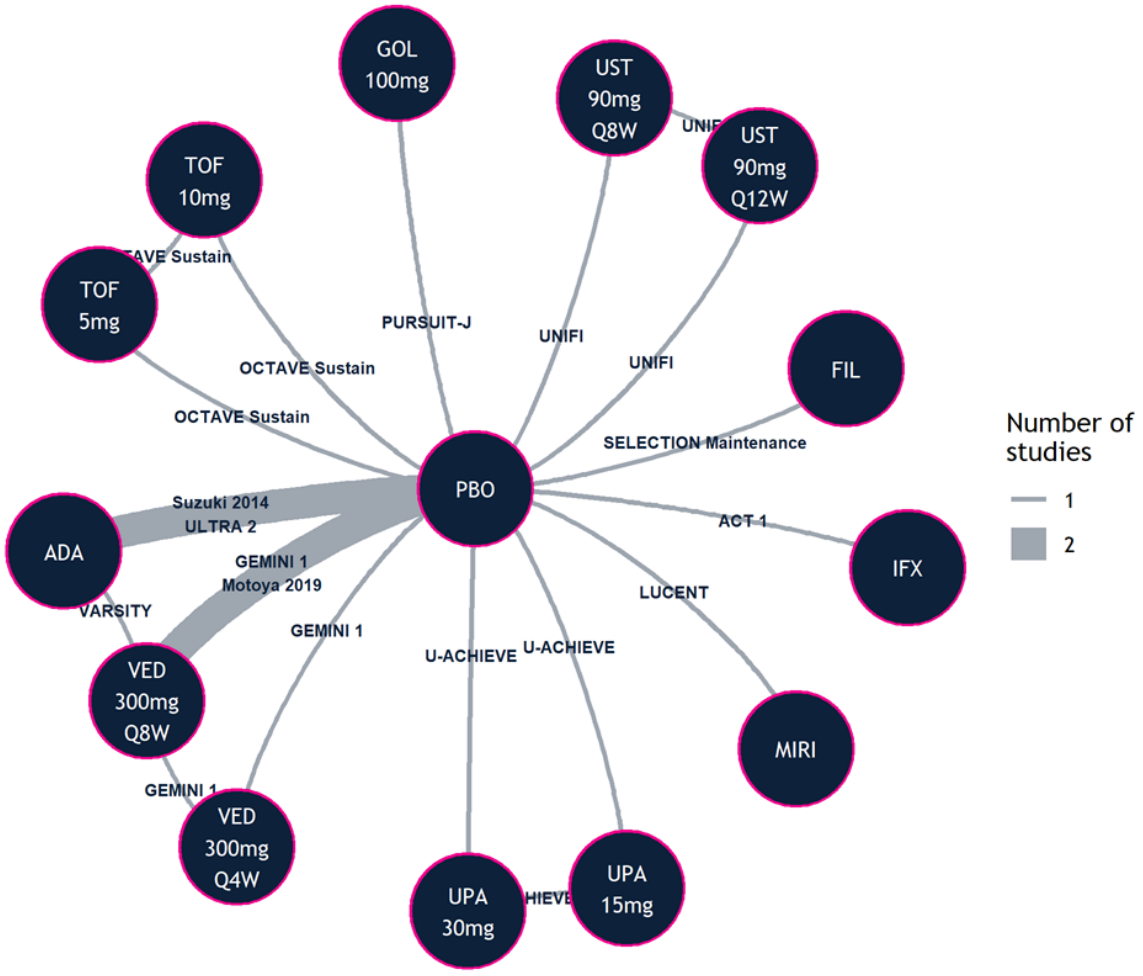
[redacted]. SUCRA values were in favour of [redacted].

Due to differences in model selection between the primary analysis (including all study designs) and the sensitivity analysis (excluding treat-through study designs, see Section 2.1.2.2 of the NMA report appendices provided in the reference pack), results cannot easily be compared. However, it should be noted that the differences in placebo response (baseline risk) observed across studies are less evident when analysing studies using the same (re-randomised) design. As a result, the unadjusted model presented a better fit to the data in the sensitivity analysis, and results for mirikizumab are less favourable than those from the primary analysis of all studies. Interpretation of the results should be made in consideration of the high placebo rate observed in the LUCENT trial (compared to comparator studies), as well as the reduced size of the network (removing 4 studies), and increased uncertainty (wider credible intervals) in results. The primary analysis results represent a more comprehensive network, with a larger number of studies and allow comparison with infliximab and adalimumab.

Section 5.3.1.4 Maintenance: Mucosal healing

Figure 34 presents the network for mucosal healing during the maintenance period for the biologic-naïve population. In total, 12 studies were included in the analysis evaluating 9 interventions (adalimumab, filgotinib, golimumab, infliximab, mirikizumab, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Table 18 presents the input data. As described in Section B.3.9.2.4 of the original Company Submission and above, terminology around mucosal healing and endoscopic improvement are often used interchangeably across studies of UC. For the purpose of this NMA, data were included in analyses of mucosal healing where outcomes were defined as “Endoscopic subscore of 0 or 1”, in line with the LUCENT trial.

Figure 34: Network plot for mucosal healing in the maintenance period and biologic-naïve population



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 18: Input data for mucosal healing in the maintenance period and biologic-naïve population

Study	Trial design	Year	Treatment	Timepoint	Number analysed	Number of patients with mucosal healing
ACT 1	TT	2005	PBO	54	121	22
ACT 1	TT	2005	IFX	54	121	55
GEMINI 1	RR	2013	PBO	52	79	19
GEMINI 1	RR	2013	VED 300mg Q8W	52	72	43
GEMINI 1	RR	2013	VED 300mg Q4W	52	73	44
LUCENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LUCENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Motoya 2019	RR	2019	VED 300mg Q8W	60	***24***	***15***
Motoya 2019	***RR***	2019	PBO	60	***28***	***10***
OCTAVE Sustain	RR	2017	PBO	60	109	15
OCTAVE Sustain	RR	2017	TOF 5mg	60	115	49
OCTAVE Sustain	RR	2017	TOF 10mg	60	104	53
PURSUIT-J	RR	2017	GOL 100mg	60	32	20
PURSUIT-J	RR	2017	PBO	60	31	5
SELECTION Maintenance	***RR***	2021	PBO	58	54	10
SELECTION Maintenance	***RR***	2021	FIL	58	107	57
Suzuki 2014	TT	2014	PBO	52	96	15
Suzuki 2014	TT	2014	ADA	52	177	51

Study	Trial design	Year	Treatment	Timepoint	Number analysed	Number of patients with mucosal healing
U-ACHIEVE	RR	2022	PBO	60	68	15
U-ACHIEVE	RR	2022	UPA 15mg	60	77	41
U-ACHIEVE	RR	2022	UPA 30mg	60	81	54
ULTRA 2	RR	2012	PBO	52	145	28
ULTRA 2	RR	2012	ADA	52	150	47
UNIFI	RR	2019	PBO	52	84	30
UNIFI	RR	2019	UST 90mg Q8W	52	79	46
UNIFI	RR	2019	UST 90mg Q12W	52	95	52
VARSITY	TT	2019	ADA	52	305	90
VARSITY	TT	2019	VED 300mg Q8W	52	304	131

Bold and italicised values have been amended from original Company Submission Appendices.
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; RR: re-randomised; TOF: tofacitinib; TT= treat-through; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.1.2.3 of the NMA report appendices in the reference pack) convergence diagnostics, and visual assessment of model performance (as described in Appendix D.1.7.6 of the original Company Submission), suggested that the fixed effects with baseline risk adjustment was associated with an improved fit relative to other models. In the random effects models fitted using meta-regression adjusting for baseline risk the 95% CrI for the interaction term β did include the possibility of no interaction (i.e., zero), however the coefficient was marginally insignificant, therefore ruling these models from contention. The network of evidence (Figure 34) is primarily a “star” shaped network with only two loops of indirect evidence, thus making it hard to estimate the value of the between-study heterogeneity parameter, although the random effect model would be preferred given the network composition the fixed effect model can be deemed reasonable.

As presented in Figure 6 in Section 2.1.2, [redacted] (Figure 35).

Absolute predictions, all pairwise comparisons of risk ratios, risk differences, and number needed to treat, along with the cumulative rank probabilities and SUCRA values, are presented in Section 2.1.2.3 of the NMA report appendices provided in the reference pack. [redacted].

Figure 35: Odds ratios versus placebo with fixed treatment effects with baseline risk meta-regression: mucosal healing, maintenance, biologic-naïve population

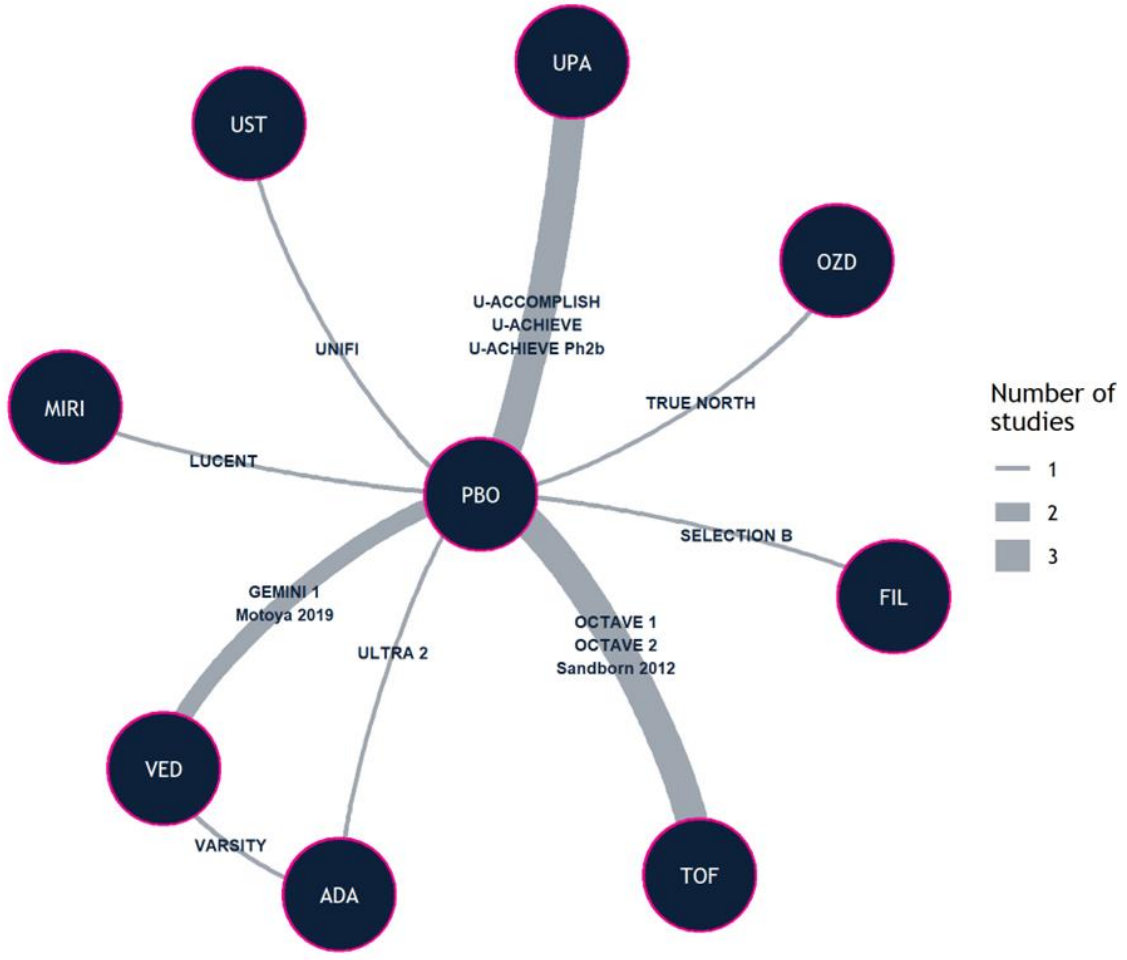
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 5.3.2 Efficacy outcomes: biologic-failed population: amended from Appendices Section D.1.10.2

Section 5.3.2.1 Induction: Clinical response and remission

Figure 36 presents the network for clinical response and remission during the induction period for the biologic-failed population. In total, 14 studies were included in the analysis evaluating eight interventions (adalimumab, filgotinib, mirikizumab, ozanimod, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Of note, no data were available for golimumab and infliximab since these interventions were evaluated in entirely biologic-naïve populations. Most interventions were assessed in one or two placebo-controlled studies, with one head-to-head study comparing adalimumab and vedolizumab (VARSITY). Table 19 presents the clinical response and remission input data.

Figure 36: Network plot for clinical response and remission in the induction period and biologic-failed population



Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 19: Summary of NMA input data: clinical response and remission, induction, biologic-failed population

Study	Treatment arm	N	No Response	Response without remission	Response with remission
GEMINI 1	Placebo	63	50 (79.4%)	11 (17.5%)	2 (3.2%)
	VED 300 mg Q2W	82	50 ***(61.0%)***	24 (29.3%)	8 (9.8%)
LUCENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Motoya 2019	VED 300 mg Q2W	85	62 (72.9%)	15 (17.6%)	8 (9.4%)
	Placebo	41	29 (70.7%)	8 (19.5%)	4 (9.8%)
OCTAVE 1	Placebo	64	49 (76.6%)	14 (21.9%)	1 (1.6%)
	TOF 10 mg	243	119 (49%)	97 (39.9%)	27 (11.1%)
OCTAVE 2	Placebo	60	46 (76.7%)	14 (23.3%)	0 ***(0.0%)***
	TOF 10 mg	222	109 (49.1%)	87 (39.2%)	26 (11.7%)
Sandborn 2012	Placebo	15	10 (66.7%)	5 (33.3%)	0 ***(0.0%)***
	TOF 10 mg	10	4 ***(40.0%)***	1 ***(10.0%)***	5 ***(50.0%)***
SELECTION B	Placebo	142	117 (82.4%)	19 (13.4%)	6 (4.2%)
	FIL 200 mg QD	262	123 (46.9%)	114 (43.5%)	25 (9.5%)
TRUE NORTH	Placebo	65	53 (81.5%)	9 (13.8%)	3 (4.6%)
	OZD 1 mg QD	130	82 (63.1%)	35 (26.9%)	13 ***(10.0%)***
U-ACCOMPLISH	Placebo	89	72 (80.9%)	15 (16.9%)	2 (2.2%)
	UPA 45 mg QD	173	53 (30.6%)	69 (39.9%)	51 (29.5%)
U-ACHIEVE	Placebo	78	68 (87.2%)	10 (12.8%)	0 ***(0.0%)***

Study	Treatment arm	N	No Response	Response without remission	Response with remission
	UPA 45 mg QD	168	60 (35.7%)	78 (46.4%)	30 (17.9%)
U-ACHIEVE Ph2b	***Placebo***	***34***	***32 (94.1%)***	***2 (5.9%)***	***0 (0.0%)***
	UPA 45 mg QD	***42***	***25 (59.5%)***	***12 (28.6%)***	***5 (11.9%)***
ULTRA 2	Placebo	101	72 (71.3%)	22 (21.8%)	7 (6.9%)
	ADA 160/80/40 mg Q2W	98	62 (63.3%)	27 (27.6%)	9 (9.2%)
UNIFI	Placebo	161	117 (72.7%)	42 (26.1%)	2 (1.2%)
	UST 6 mg	166	71 (42.8%)	74 (44.6%)	21 (12.7%)
VARSITY	ADA 160/80/40 mg Q2W	81	55 (67.9%)	16 (19.8%)	10 (12.3%)
	VED 300 mg Q2W	79	35 (44.3%)	26 (32.9%)	18 (22.8%)

Bold and italicised values have been amended from original Company Submission Appendices. [a] Response data by prior therapy subgroup is not available in the published literature identified in the SLR for the OCTAVE 1 and 2 trials independently (only as a pooled analysis). However, this data was reported in the committee papers for TA792 Filgotinib for treating moderately to severely active ulcerative colitis and has been extracted for use in the NMA. [b] Remission data by prior therapy subgroup is not available in the published literature identified in the SLR for this study. However, this data was reported in the appendix documents (Table 89 and Table 90) supporting the company submission for TA547 Tofacitinib for previously treated active ulcerative colitis and has been extracted for use in the NMA (TNF exposed subgroup).
Abbreviations: ADA: adalimumab; FIL: filgotinib; NMA: network meta-analysis; MIRI: mirikizumab; OZD: ozanimod; QD: once daily; Q2W: every 2 weeks; Q4W: every 4 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.2.1.1 of the NMA report appendices provided in the reference pack), convergence diagnostics, and visual assessment of model performance (as described in Appendix D.1.7.6 of the original Company Submission), suggested that the fixed effect model (without baseline risk adjustment) was associated with an improved fit relative to other models. In all models fitted using meta-regression adjusting for baseline risk the 95% CrI for the interaction term β included the possibility of no interaction (i.e., includes zero). Reviewing the unadjusted models, the residual deviance for the random effects model using a half-Normal prior was slightly lower than the fixed effect model ([redacted] versus [redacted]), however, the DIC was higher due to the higher number of effective parameters in the random effects model. The posterior estimate of the between study standard deviation (tau) was uncertain (95% CrI: [redacted]) in the random-effects model. Although clinical heterogeneity (as discussed in Section B.3.9.2 of the original Company Submission) favours the random effects model, the reduced network of evidence available in the biologic-failed population introduced highly uncertain results under the random effects model [redacted]. A review of inconsistency (as described in Appendix D.1.7.8 of the original Company Submission) determined there to be little evidence of inconsistency between direct and indirect estimates for either model. Therefore, primary results for clinical response and remission during the induction period for the biologic-failed population described in this section were derived from the fixed effect model (without baseline risk adjustment). Complementary results with baseline risk adjustment and results under the random effects models have been provided in the reference pack (Section 3.1.2 of the NMA report appendices).

As presented in Section 2.2.1, [redacted]

[redacted] (Figure 37 and Figure 38). Absolute predictions, all pairwise comparisons of risk ratios, risk differences, and number needed to treat, along with the cumulative rank probabilities and SUCRA values are presented in Section 2.2.1.1 of the NMA report appendices provided in the reference pack. [redacted]

Figure 37: Odds ratios versus placebo with fixed treatment effects: clinical response, induction, biologic-failed population

Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

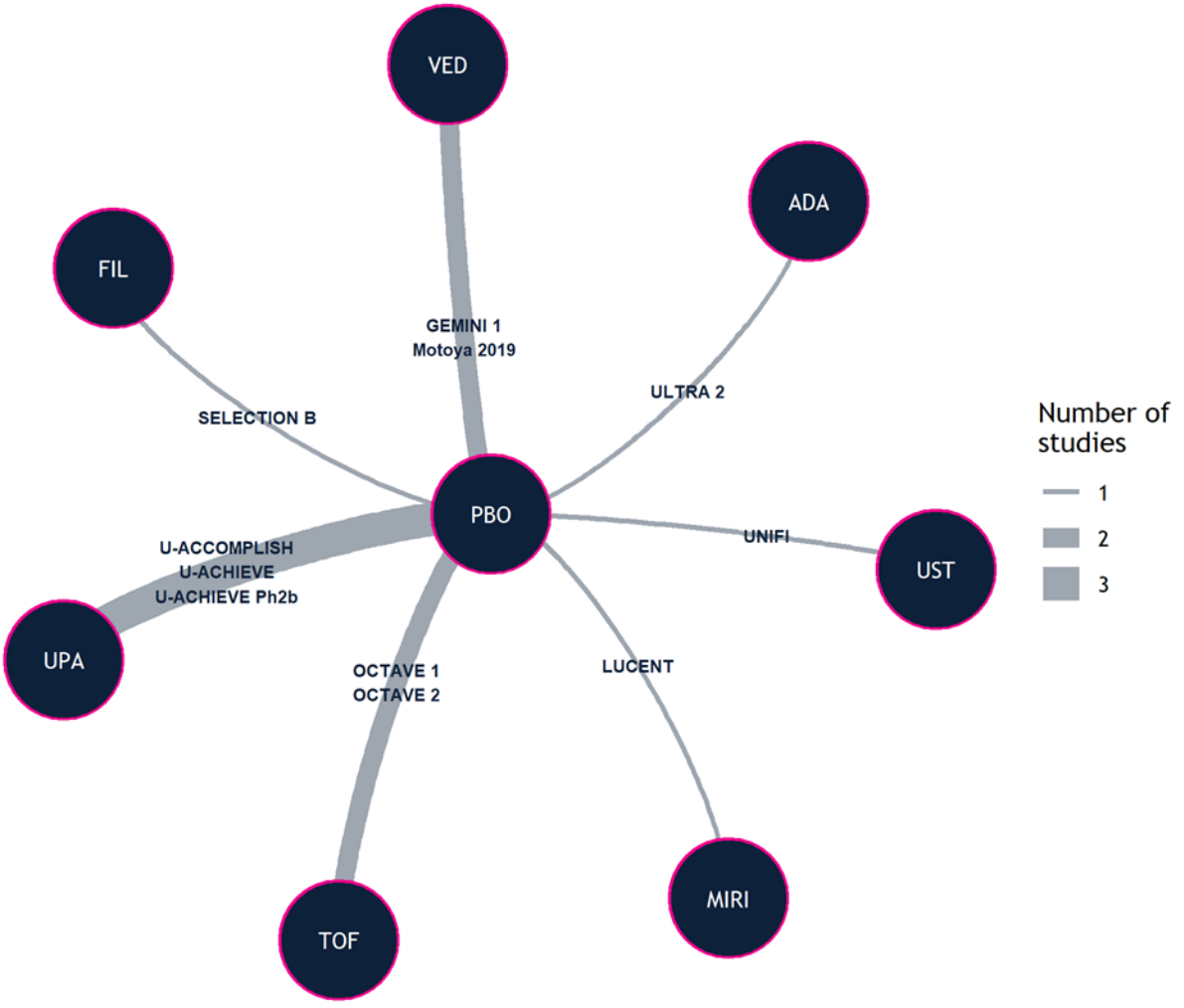
Figure 38: Odds ratios versus placebo with fixed treatment effects: clinical remission, induction, biologic-failed population

Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; OZD: ozanimod; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 5.3.2.2 Induction: Mucosal healing

Figure 39 presents the network for mucosal healing during the induction period for the biologic-failed population. In total, 11 studies were included in the analysis evaluating 7 interventions (adalimumab, filgotinib, mirikizumab, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Table 20 presents the input data. As described in earlier, terminology around mucosal healing and endoscopic improvement are often used interchangeably across studies of UC. For the purpose of this NMA, data were included in analyses of mucosal healing where outcomes were defined as “Endoscopic subscore of 0 or 1”, in line with the LUCENT trial.

Figure 39: Network plot for mucosal healing in the Induction period and biologic-failed population



Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 20: Input data for mucosal healing in the induction period and biologic-failed population

Study	Year	Treatment	Timepoint	Number analysed	Number of patients with mucosal healing
GEMINI 1	2013	PBO	6	63	13
GEMINI 1	2013	VED	6	82	25
LUCENT	2022	PBO	[redacted]	[redacted]	[redacted]
LUCENT	2022	MIRI	[redacted]	[redacted]	[redacted]
Motoya 2019	2019	PBO	10	41	12
Motoya 2019	2019	VED	10	85	22
OCTAVE 1	2017	PBO	8	***65***	4
OCTAVE 1	2017	TOF	8	***254***	***61***
OCTAVE 2	2017	PBO	8	***65***	4
OCTAVE 2	2017	TOF	8	***234***	***51***
SELECTION B	2021	PBO	10	142	11
SELECTION B	2021	FIL	10	262	45
U-ACCOMPLISH	2022	PBO	8	89	4
U-ACCOMPLISH	2022	UPA	8	173	64
U-ACHIEVE	2020	PBO	8	78	1
U-ACHIEVE	2020	UPA	8	168	45
U-ACHIEVE Ph2b	***2020***	***PBO***	***8***	***34***	***0***
U-ACHIEVE Ph2b	***2020***	***UPA***	***8***	***42***	***11***
ULTRA 2	2012	PBO	8	101	27
ULTRA 2	2012	ADA	8	98	28
UNIFI	2019	PBO	8	161	11
UNIFI	2019	UST	8	166	35

Bold and italicised values have been amended from original Company Submission Appendices.
Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.2.1.2 of the NMA report appendix in the reference pack), convergence diagnostics, and visual assessment of model performance, suggested that the fixed effects model with baseline risk adjustment was associated with an improved fit relative to other models. Adjusting for baseline response rates for this outcome seems most appropriate as the response rates across studies did appear to differ, as shown in the top left panel of Figure 1 of the NMA report appendices provided in the reference pack. In

both random effects models fitted using meta-regression adjusting for baseline risk the 95% CrI for the interaction term β did not include the possibility of no interaction (i.e., zero) and the random effect models were inherently less interpretable due to the larger amount of imprecision from the wider credible intervals. Therefore, results for mucosal healing during the induction period for the biologic-failed population were derived from the fixed effects model (with baseline risk adjustment).

As shown in the pairwise OR plot in Figure 8 in Section 2.2.1, [redacted]

[redacted]

(Figure 40). Absolute predictions, all pairwise comparisons of risk ratios, risk differences, and number needed to treat, along with the cumulative rank probabilities and SUCRA values, are presented in Section 2.2.1.2 of the NMA report appendices found in the reference pack. [redacted]

Figure 40: Odds ratios versus placebo with fixed treatment effects with baseline risk meta-regression: mucosal healing, induction, biologic-failed population

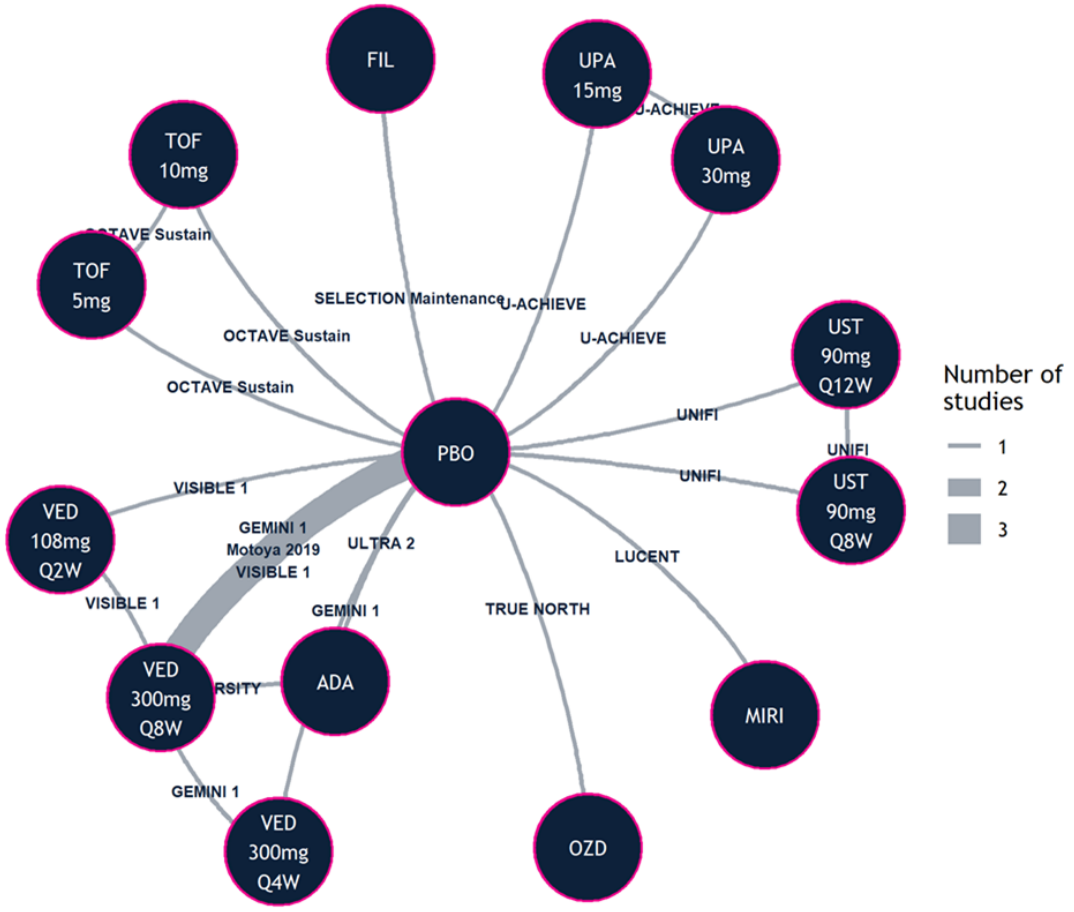
Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 5.3.2.3 Maintenance: Clinical response and remission

Base case analysis

Figure 41 presents the network for clinical response and remission during the maintenance period for the biologic-failed population. As in the induction period NMA, the network of evidence for the biologic-failed population was smaller in size than that for the biologic-naïve population. In total, 11 studies were included in the analysis evaluating 8 interventions (adalimumab, filgotinib, mirikizumab, ozanimod, tofacitinib, upadacitinib, ustekinumab, and vedolizumab), across 13 dosing regimens, and placebo. Again, as in the induction period, data were not available for infliximab and adalimumab as those interventions are evaluated only in biologic-naïve populations. Most interventions were assessed in one placebo-controlled study, with one head-to-head study comparing adalimumab and vedolizumab (VARSITY). Table 21 presents the clinical response and remission input data. Table 22 presents a summary of the recalculation of treat-through studies to obtain inputs for the NMA, as described previously in Appendix D.1.7.7 of the original Company Submission.

Figure 41: Network plot for clinical response and remission in the maintenance period and biologic-failed population.



Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 21: Summary of NMA input data: clinical response and remission, maintenance, biologic-failed population

Study	Treatment arm	N	No Response	Response without Remission	Response with Remission
Treat-through trials					
ULTRA 2	Placebo	**29**	**23 (79.3%)**	**3 (10.3%)**	**3 (10.3%)**
	ADA 40 mg Q2W	**36**	**21 (58.3%)**	**7 (19.4%)**	**8 (22.2%)**
VARSITY	ADA 40 mg Q2W	**26**	**NR**	**NR**	**13 (50%)**
	VED 300 mg Q8W	**44**	**NR**	**NR**	**16 (36.4%)**
Re-randomised trials					
GEMINI 1	Placebo	38	32 (84.2%)	4 (10.5%)	2 (5.3%)
	VED 300 mg Q8W	43	23 (53.5%)	4 (9.3%)	16 (37.2%)
	VED 300 mg Q4W	40	23 (57.5%)	3 (7.5%)	14 (35%)
LUCENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Motoya 2019	Placebo	***14***	***9 (64.3%)***	***2 (14.3%)***	***3 (21.4%)***
	VED 300 mg Q8W	***17***	***6 (35.3%)***	***1 (5.9%)***	***10 (58.8%)***
OCTAVE Sustain	Placebo	89	76 (85.4%)	3 (3.4%)	10 (11.2%)
	TOF 5 mg BID	83	46 (55.4%)	17 (20.5%)	20 (24.1%)
	TOF 10 mg BID	93	38 (40.9%)	21 (22.6%)	34 (36.6%)
SELECTION Maintenance	Placebo	44	34 (77.3%)	8 (18.2%)	2 (4.5%)
	FIL 200 mg QD	92	39 (42.4%)	31 (33.7%)	22 (23.9%)
TRUE NORTH	Placebo	69	52 (75.4%)	10 (14.5%)	7 (10.1%)

Study	Treatment arm	N	No Response	Response without Remission	Response with Remission
	OZD 1 mg QD	76	34 (44.7%)	20 (26.3%)	22 (28.9%)
U-ACHIEVE	Placebo	71	60 (84.5%)	6 (8.5%)	5 (7.0%)
	UPA 15mg	64	25 (39.1%)	13 (20.3%)	26 (40.6%)
	UPA 30mg	66	21 (31.8%)	13 (19.7%)	32 (48.5%)
UNIFI	Placebo	88	54 (61.4%)	19 (21.6%)	15 (17%)
	UST 90 mg Q8W	91	32 (35.2%)	23 (25.3%)	36 (39.6%)
	UST 90 mg Q12W	70	31 (44.3%)	23 (32.9%)	16 (22.9%)
VISIBLE 1	Placebo	19	NR	NR	1 (5.3%)
	VED 108 mg Q2W	39	NR	NR	13 (33.3%)
	VED 300 mg Q8W	22	NR	NR	6 (27.3%)

Bold and underlined values correspond to re-calculated input data for treat-through studies that was used in the NMA, corresponding calculations are provided in Table 22.
Bold and italicised values have been amended from original Company Submission Appendices.
Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; NMA: network meta-analysis; NR: not reported; OZD: ozanimod; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UST: ustekinumab; VED: vedolizumab.

Table 22: Summary of trial design adjustments for treat-through study designs: clinical response and remission, maintenance, biologic-failed population

Study	Tx arm	Raw Data				Calculated Data			Description
		MAIN N	IND response, n (%)	Durable/ sustained response at MAIN, n (%)	Remission at MAIN, n (%)	Assumed patients re-randomised[a]	Assumed patients response MAIN[b]	Assumed patients remission MAIN[c]	
ULTRA 2	Placebo	101	29 (28.7%)	6 (5.9%)		29	6	3	Response is number of durable responders. Remission is the number of clinical remitters at the end of maintenance.
	ADA 40 mg Q2W	98	36 (36.7%)	15 (15.3%)		36	15	8	Response is number of durable responders. Remission in induction phase responders was reported directly in a secondary publication for this trial (Sandborn et al., 2013).
VARSITY	ADA 40 mg Q2W	81	26 (32.1%)	NR	NR	26	NR	13	Remission is the number of clinical remitters at the end of maintenance.
	VED 300 mg Q8W	79	44 (55.7%)	NR	NR	44	NR	16	Remission is the number of clinical remitters at the end of maintenance.

[a] The total numbers of responders in the treat-through trials during the induction phase provides a proxy for the number of patients who enter maintenance. [b] Clinical response for maintenance from the treat-through trials was based on the proportion achieving sustained clinical response during the maintenance phase (this mitigates the risk of counting maintenance phase responders who were induction phase non-responders). [c] Clinical remission for maintenance from the treat-through trials is based on the reported number of remitters at end of maintenance (from TT) based on the assumption that maintenance phase remitters achieved response at induction and therefore were used as a proxy when estimating the re-randomised maintenance remission proportions.
Abbreviations: ADA: adalimumab; IND: induction; MAIN: maintenance; NR: not reported; Q2W: every 2 weeks; Q8W: every 8 weeks; Tx: treatment; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.2.2.1 of the NMA report appendices in the reference pack), convergence diagnostics, and visual assessment of model performance (as described in Appendix D.1.7.6 of the original Company Submission), suggested that the fixed effect model without baseline risk adjustment was associated with an improved fit relative to other models. In the fixed effect model fitted using meta-regression adjusting for baseline risk the 95% CrI for the interaction term β included the possibility of no interaction (i.e., includes zero), suggesting the association between baseline risk and treatment effect should not be adjusted for. The fixed effect model had reasonable fit in terms of DIC and residual deviance, further the 95% CrI for the posterior estimate of the between study standard deviation (tau) was wide for both the unadjusted models and baseline risk adjusted models. Although clinical heterogeneity, discussed in Section B.3.9.2 of the original Company Submission, favours the random effects model, the reduced network of evidence available in the biologic-failed population introduced highly uncertain results under the random effects model and the upper bound of the pairwise odds ratio 95% CrI's in some instances exceeding 100. A review of inconsistency (as described in Appendix D.1.7.8 of the original Company Submission) determined there to be little evidence of inconsistency between direct and indirect estimates for either model. Therefore, primary results for clinical response and remission during the maintenance period for the biologic-failed population described in this section were derived from the fixed effect model without baseline risk adjustment. Complementary results with baseline risk adjustment and results under random effects models have been provided in the reference pack (Section 3.3.1 of the NMA report appendices).

As presented in Figure 9 and Figure 10 in Section 2.2.2, [redacted]

[redacted] (Figure 42 and Figure 43). Absolute predictions, all pairwise comparisons of risk ratios, risk differences, and number needed to treat, along with the cumulative rank probabilities and SUCRA values, are presented in Section 2.2.2.1 of the NMA report appendices provided in the reference pack. [redacted]

Figure 42: Odds ratios versus placebo with fixed treatment effects: clinical response, maintenance, biologic-failed population

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OZD: ozanimod; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Figure 43: Odds ratios versus placebo with fixed treatment effects: clinical remission, maintenance, biologic-failed population

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; MIRI: mirikizumab; OZD: ozanimod; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Sensitivity analysis

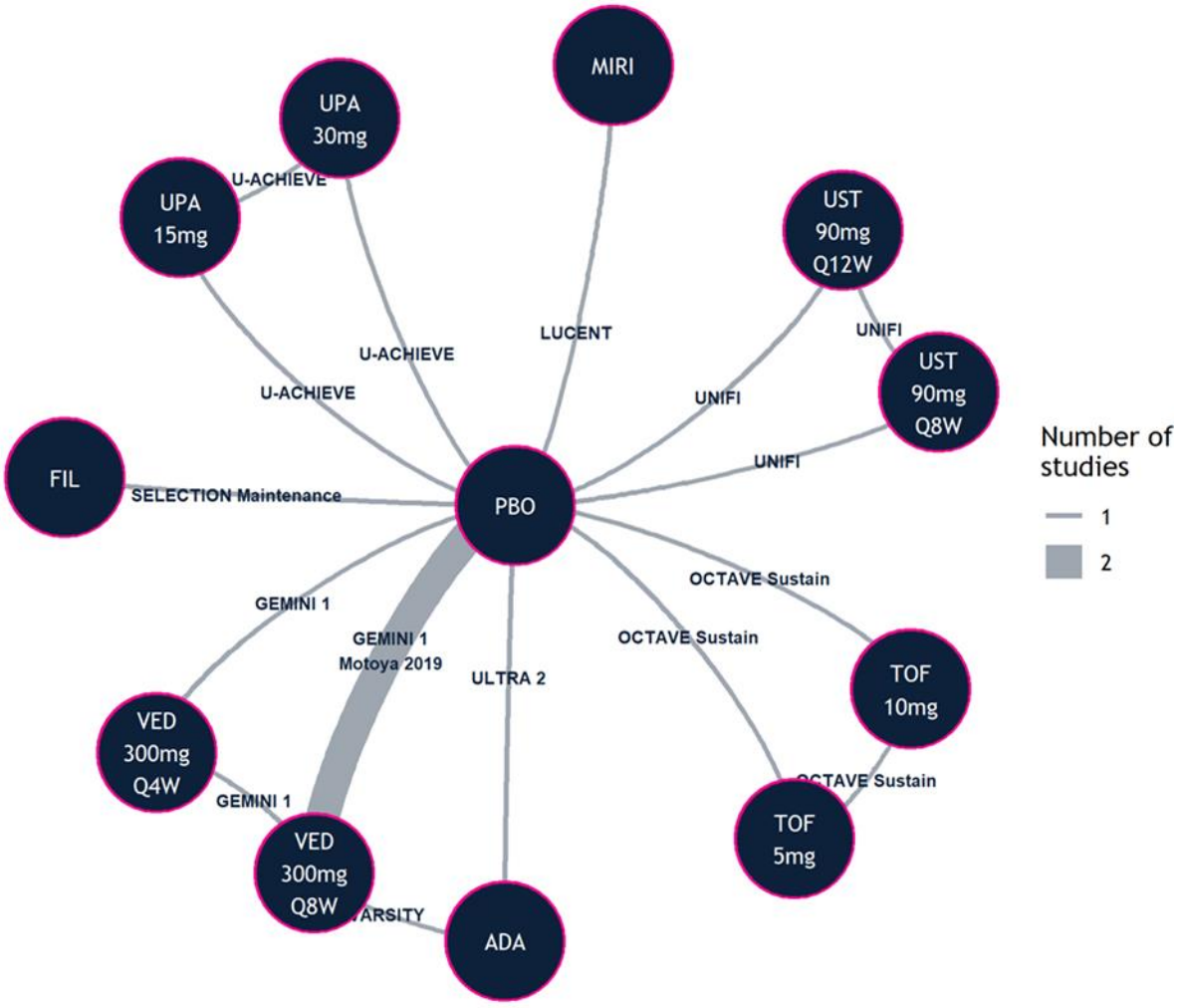
Complete results for the sensitivity analysis of clinical response and remission including only re-randomised studies of the biologic-failed population at maintenance are presented in Section 2.2.2.2 of the NMA report appendix, provided in the reference pack. The reduced network of evidence included 11 studies, notably this network excluded adalimumab which was evaluated only in treat-through trials. As for the network pooling both treat-through and re-randomised studies, the best fitting model for the NMA with only re-randomised studies was the fixed effect model without meta-regression adjusting for baseline risk Some small differences in placebo response are remain observed across re-randomised studies (see Appendix D.1.6.2 of the original Company Submission), although, the 95% CrI for the interaction term β the fixed effect model fitted using meta-regression adjusting for baseline risk includes the possibility of no interaction (i.e. includes zero) (95% CrI: [redacted]).

In line with results from the network pooling both study types, [redacted]. As for the network pooling study designs, SUCRA values were in favour of [redacted].

Section 5.3.2.4 Maintenance: Mucosal healing

Figure 44 presents the network for mucosal healing during the induction period for the biologic-failed population. In total, 9 studies were included in the analysis evaluating 11 interventions (adalimumab, filgotinib, mirikizumab, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Table 23 presents the input data. As described earlier, terminology around mucosal healing and endoscopic improvement are often used interchangeably across studies of UC. For the purpose of this NMA, data were included in analyses of mucosal healing where outcomes were defined as “Endoscopic subscore of 0 or 1”, in line with the LUCENT trial.

Figure 44: Network plot for mucosal healing in the maintenance period and biologic-failed population



Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 23: Input data for mucosal healing in the maintenance period and biologic-failed population

Study	Trial design	Year	Treatment	Timepoint	Number analysed	Number of patients with mucosal healing
GEMINI 1	RR	2013	PBO	52	38	3
GEMINI 1	RR	2013	VED 300mg Q8W	52	43	18
GEMINI 1	RR	2013	VED 300mg Q4W	52	40	19
LUCENT	RR	2022	[redacted]	[redacted]	[redacted]	[redacted]
LUCENT	RR	2022	[redacted]	[redacted]	[redacted]	[redacted]
Motoya 2019	RR	2019	PBO	60	***14***	***4***
Motoya 2019	RR	2019	VED 300mg Q8W	60	***17***	***11***
OCTAVE Sustain	RR	2017	PBO	60	89	11
OCTAVE Sustain	RR	2017	TOF 5mg	60	83	25
OCTAVE Sustain	RR	2017	TOF 10mg	60	93	37
SELECTION Maintenance	***RR***	2021	PBO	58	44	5
SELECTION Maintenance	***RR***	2021	FIL	58	92	24
U-ACHIEVE	RR	2022	PBO	60	81	6
U-ACHIEVE	RR	2022	UPA 15mg	60	71	31
U-ACHIEVE	RR	2022	UPA 30mg	60	73	41
ULTRA 2	TT	2012	PBO	52	***101***	10
ULTRA 2	TT	2012	ADA	52	***98***	15
UNIFI	RR	2019	PBO	52	88	20
UNIFI	RR	2019	UST 90mg Q8W	52	91	41
UNIFI	RR	2019	UST 90mg Q12W	52	70	18
VARSITY	TT	2019	ADA	52	81	***17***

Study	Trial design	Year	Treatment	Timepoint	Number analysed	Number of patients with mucosal healing
VARSITY	TT	2019	VED 300mg Q8W	52	79	***21***

Bold and italicised values have been amended from original Company Submission Appendices.
Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; RR: re-randomised; TOF: tofacitinib; TT: treat-through; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.2.2.3 of the NMA report appendices in the reference pack), convergence diagnostics, and visual assessment of model performance (as described in Appendix D.1.7.6 of the original Company Submission), suggested that the fixed effects without baseline risk adjustment was associated with an improved fit relative to other models. In all models fitted using meta-regression adjusting for baseline risk, the 95% CrI for the interaction term β included the possibility of no interaction (i.e., zero), and therefore ruled out these models from consideration. Estimates from the unadjusted RE models returned very imprecise estimates and little could be deduced form the results. The network of evidence contains primarily only one trial per treatment comparison, thus making it hard to estimate the value of the between-study heterogeneity parameter. Although the random effect model would be preferred, given observed clinical heterogeneity, the network composition deems the fixed effect model should provide reasonable estimates, noticeably the point estimates for the relative effects did not differ between models (without adjusted baseline risk).

As shown in Figure 11 in Section 2.2.2, [redacted]

[redacted] Absolute predictions, all pairwise comparisons of risk ratios, risk differences, and number needed to treat, along with the cumulative rank probabilities and SUCRA values, are presented in Section 2.2.2.3 of the NMA report appendices, provided in the reference pack. In terms of SUCRA ranking, [redacted]

Figure 45: Odds ratios versus placebo with fixed treatment effects: mucosal healing, maintenance, biologic-failed population

Abbreviations: ADA: adalimumab; FIL: filgotinib; MIRI: mirikizumab; PBO: placebo; Q12W: every 12 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

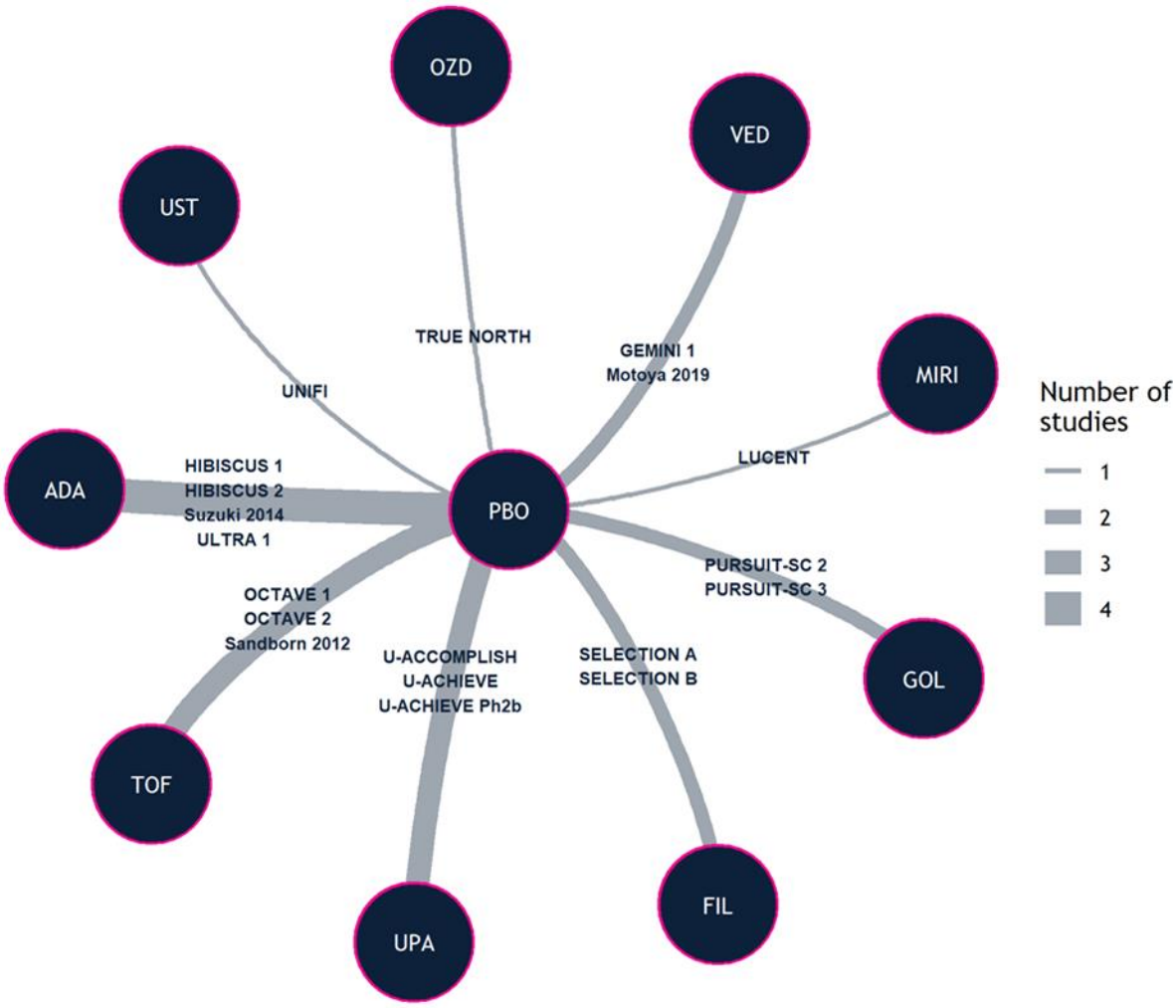
Section 5.3.3 Safety outcomes: overall population: amended from Appendices Section D.1.10.3

Section 5.3.3.1 Induction: All cause discontinuation

All cause discontinuation

Figure 46 presents the network for all cause discontinuation during the induction period for the overall mixed population. In total, 19 studies were included in the analysis evaluating ten interventions (adalimumab, filgotinib, golimumab, mirikizumab, ozanimod, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Table 24 presents the discontinuation input data.

Figure 46: Network plot for all cause discontinuation in the induction period and mixed population



Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 24: Input data for all cause discontinuation during the induction period for the mixed population

Study	Year	Treatment	Timepoint	Number analysed	Number of patients who discontinued
GEMINI 1	2013	PBO	6	149	14
GEMINI 1	2013	VED	6	225	7
HIBISCUS 1	2021	PBO	10	72	1
HIBISCUS 1	2021	ADA	10	142	1
HIBISCUS 2	2021	PBO	10	72	2
HIBISCUS 2	2021	ADA	10	143	2
LUCENT	2022	PBO	[redacted]	[redacted]	[redacted]
LUCENT	2022	MIRI	[redacted]	[redacted]	[redacted]
Motoya 2019	2019	ADA	10	82	4
Motoya 2019	2019	VED	10	164	9
OCTAVE 1	2017	PBO	8	122	4
OCTAVE 1	2017	TOF	8	476	31
OCTAVE 2	2017	PBO	8	112	15
OCTAVE 2	2017	TOF	8	429	32
PURSUIT-SC 2	2014	GOL	6	***42***	***1***
PURSUIT-SC 2	2014	PBO	6	***42***	***2***
PURSUIT-SC 3	2014	GOL	6	***258***	***6***
PURSUIT-SC 3	2014	PBO	6	***258***	***6***
Sandborn 2012	2012	PBO	8	48	13
Sandborn 2012	2012	TOF	8	33	2
SELECTION A	2021	FIL	10	245	8
SELECTION A	2021	PBO	10	137	9
SELECTION B	2021	FIL	10	262	20
SELECTION B	2021	PBO	10	142	14
Suzuki 2014	2014	ADA	8	90	4
Suzuki 2014	2014	PBO	8	96	4
TRUE NORTH	2021	OZD	10	429	28
TRUE NORTH	2021	PBO	10	216	24
U-ACCOMPLISH	2022	PBO	8	177	13

Study	Year	Treatment	Timepoint	Number analysed	Number of patients who discontinued
U-ACCOMPLISH	2022	UPA	8	345	11
U-ACHIEVE	2020	PBO	8	155	19
U-ACHIEVE	2020	UPA	8	319	12
U-ACHIEVE Ph2b	2020	PBO	8	46	5
U-ACHIEVE Ph2b	2020	UPA	8	56	6
ULTRA 1	2011	ADA	8	223	24
ULTRA 1	2011	PBO	8	223	19
UNIFI	2019	PBO	8	319	***12***
UNIFI	2019	UST	8	322	***2***

Bold and italicised values have been amended from original Company Submission Appendices.
Abbreviations: ADA: adalimumab; FIL: filgotinib; GOL: golimumab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.3.1.1 of the NMA report appendices provided in the reference pack), convergence diagnostics, and visual assessment of model performance suggested that the fixed effects model and random effects models were associated with similar fit relative to each other, the fixed effect model was selected for inference based on parsimony and the uncertain estimates provided by the random effects model. The observed difference in the DICs between models was [redacted] Results under the fixed effect model and random effects models with a flat prior have been provided as supplementary results figures and tables.

As presented in Figure 12 in Section 2.3.1, [redacted] (Figure 47). [redacted]

All pairwise comparisons of risk ratios and risk differences, as well as the cumulative ranking and SUCRA plots, are presented in Section 2.3.1.1 of the NMA report appendix, provided in the reference pack. [redacted]

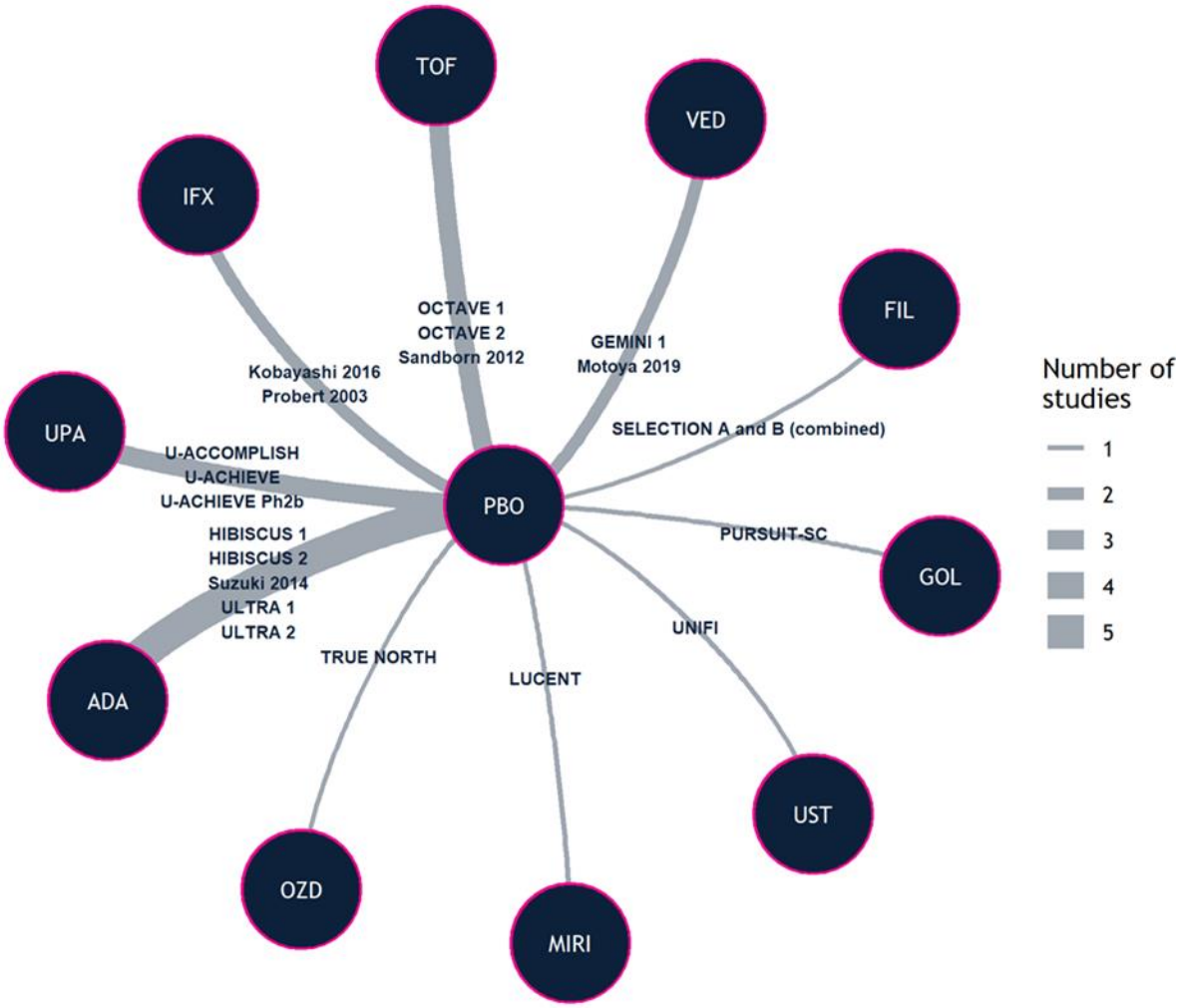
Figure 47: Odds ratios versus placebo with fixed treatment effects: all cause discontinuation, induction, mixed population

Abbreviations: ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Section 5.3.3.2 Induction: Serious adverse events

Figure 48 presents the network for serious AEs during the induction period for the overall mixed population. In total, 20 studies were included in the analysis evaluating ten interventions (adalimumab, filgotinib, golimumab, infliximab, mirikizumab, ozanimod, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) and placebo. Table 25 presents the input data for the number of patients who experienced a serious AE during induction.

Figure 48: Network plot for serious AEs in the induction period and mixed population



Abbreviations: ADA: adalimumab; AE: adverse event; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Table 25: Input data for serious AEs during the induction period for the mixed population

Study	Year	Treatment	Timepoint	Number analysed	Number of patient with serious AE
GEMINI 1	2013	PBO	6	149	10
GEMINI 1	2013	VED	6	225	5
HIBISCUS 1	2021	PBO	10	72	2
HIBISCUS 1	2021	ADA	10	142	3
HIBISCUS 2	2021	PBO	10	72	5
HIBISCUS 2	2021	ADA	10	143	3
Kobayashi 2016	2016	IFX	***14***	104	9

Study	Year	Treatment	Timepoint	Number analysed	Number of patient with serious AE
Kobayashi 2016	2016	PBO	***14***	104	13
LUCENT	2022	MIRI	[redacted]	[redacted]	[redacted]
LUCENT	2022	PBO	[redacted]	[redacted]	[redacted]
Motoya 2019	2019	PBO	10	***82***	***4***
Motoya 2019	2019	VED	10	***164***	***10***
OCTAVE 1	2017	PBO	8	122	5
OCTAVE 1	2017	TOF	8	476	16
OCTAVE 2	2017	PBO	8	112	9
OCTAVE 2	2017	TOF	8	429	18
Probert 2003	2003	IFX	6	23	***0***
Probert 2003	2003	PBO	6	20	2
PURSUIT-SC	2014	GOL	6	331	9
PURSUIT-SC	2014	PBO	6	330	20
Sandborn 2012	2012	PBO	12	48	4
Sandborn 2012	2012	TOF	12	33	2
SELECTION A and B (combined)	***2021***	***PBO***	***10***	***279***	***13***
SELECTION A and B (combined)	***2021***	***FIL***	***10***	***507***	***22***
Suzuki 2014	2014	ADA	8	90	4
Suzuki 2014	2014	PBO	8	96	7
TRUE NORTH	2021	OZD	10	429	17
TRUE NORTH	2021	PBO	10	216	7
U-ACCOMPLISH	2022	PBO	8	177	8
U-ACCOMPLISH	2022	UPA	8	344	11
U-ACHIEVE	2020	PBO	8	155	9
U-ACHIEVE	2020	UPA	8	319	8
U-ACHIEVE Ph2b	2020	PBO	8	46	5
U-ACHIEVE Ph2b	2020	UPA	8	56	3
ULTRA 1	2011	ADA	8	223	9

Study	Year	Treatment	Timepoint	Number analysed	Number of patient with serious AE
ULTRA 1	2011	PBO	8	223	17
ULTRA 2	***2012***	***PBO***	***8***	***246***	***21***
ULTRA 2	***2012***	***ADA***	***8***	***247***	***15***
UNIFI	2019	PBO	8	319	22
UNIFI	2019	UST	8	322	11

Bold and italicised values have been amended from original Company Submission Appendices.
Abbreviations: ADA: adalimumab; AE: adverse event; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

Inspection of model fit statistics (presented in Section 2.3.1.2 of the NMA report appendices provided in the reference pack), convergence diagnostics, and visual assessment of model performance suggested that the fixed effects fitted the data just as well as the random effects model. The random effects model using a half-Normal prior demonstrated slightly worse fit, [redacted]. Due to observed clinical heterogeneity between the studies included, the random effects model seems most appropriate for inference as this better captures the uncertainty in the estimates.

As presented in Figure 13 in Section 2.3.1, [redacted] (Figure 49). All pairwise comparisons of risk ratios and risk differences, as well as the cumulative ranking and SUCRA plots, are presented in Section 2.3.1.2 of the NMA report appendices provided in the reference pack. [redacted]

Figure 49: Odds ratios versus placebo with random treatment effects and a half-Normal (location: 0, scale: 5) prior for the between-trial standard deviation: serious adverse events, induction, mixed population

Abbreviations: ADA: adalimumab; CrI: credible interval; GOL: golimumab; IFX: infliximab; MIRI: mirikizumab; OZD: ozanimod; PBO: Placebo; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab; VED: vedolizumab.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost comparison

Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]

Clarification questions

January 2023

File name	Version	Contains confidential information?	Date
[ID3973] Mirikizumab - EAG questions for company_18Jan23	1.0	Yes	18th January 2023

CQ 1. CS Section B.4.2.1 Efficacy. In CS Tables 37 (Page 115, CS Document B) and in Section B.4.2.1.5 (Page 116, CS Document B), the company reports the calculated absolute probabilities of response (including remission) in the induction and maintenance phases for the two sub-groups viz Biologic-naïve and Biologic-failed, respectively. These probabilities (highlighted in **BLUE** in **Table 1** below) are hard-coded in the excel model within *Sheet!Efficacy Data*.

Table 1: Probabilities (per cycle) used in the company model (base case)

Sub-group	Induction		Maintenance	
	Response	***Non-response (estimated as 1-response)***	***Response***	***Non-response (Estimated as 1-response)***
Biologic-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]	[redacted]

a. Please provide reference of the appropriate NMA results tables in the company submission that inform the calculations.

b. PRIORITY QUESTION: Please provide step-by-step calculations for how these probabilities were obtained from the response rates.

Lilly wish to clarify that for all outcomes in both the induction and maintenance phases, the odds ratios (ORs) presented in the NMA results tables in Section B.3.9.4 of the Company Submission were not directly modelled in the multinomial models. Rather, as described below, the absolute probabilities were calculated first, and all ORs were subsequently calculated based on these absolute probabilities. For all comparisons throughout the submission, the absolute probabilities have not been presented, with ORs presented instead for ease of interpretation. The exception to this is probabilities which directly inform the economic model, as presented below.

Induction

The proportion of patients achieving clinical 'Remission' and 'Response No Remission' at the end of the initial induction period was informed from the network meta-analysis (NMA) of induction periods of clinical trials using a multinomial model with a probit link. The response rates in the induction period were estimated in two steps, as follows:

- First, the modelled probabilities of response for placebo (the reference treatment from the NMA) were estimated in line with the baseline natural history model from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 5 (program 1), using all placebo arms.[1]
- Subsequently, the response probability for mirikizumab (and by extension, all treatments) was estimated by applying the relative treatment effect versus placebo, as estimated in the NMA.

Specifically, the probability p of achieving a threshold j (response or remission) on treatment k was calculated as:

$$p_{k,j} = \Phi(A + z_j + d_k)$$

Where:

- A is a normally distributed random variable with parameters estimated from the baseline model (the mean and sd of the predictive distribution of mu), or the anchor
- z is the cut-offs for the response and remission effects
- d is the treatment effects on the probit scale
- Φ is the normal cumulative distribution function

For the CODA output, the probability of response (p) was calculated for 20,000 NMA samples (4 chains with 5,000 post-warmup iterations) of z and d. For each sample, a random baseline effect was drawn from A. The calculated (mean) absolute probabilities of response are presented in Table 2. Note that Table 2 is an updated reproduction of Table 37 in Section B.4.2.1.4 of the Company Submission.

Subsequently, based on these absolute probabilities (p), the ORs were calculated for each of the 20,000 samples. This was calculated as:

$$OR = \frac{p_1}{(1-p_1)} \Big/ \frac{p_2}{(1-p_2)}$$

Where p_1 and p_2 represent the probabilities of response of the two treatments being compared.

The resulting calculated median ORs, and the 95% credible intervals, are presented in Table 2. These ORs for the biologic-naïve and biologic-failed populations correspond to the mirikizumab versus placebo OR in Figure 16 and Figure 22 in Section B.3.9 of the Company Submission, respectively.

Table 2: Clinical response and response at the end of induction (updated and corrected version of Table 37 in Section B.4.2.1.4 of the Company Submission)

Treatment	Response (including remission)	
	Median OR relative to placebo (95% CrI)	**Calculated mean absolute probability**
Mirikizumab (for all treatments)		
Biologic-naive subgroup	[redacted]	[redacted]
Biologic-failed subgroup	[redacted]	[redacted]

Values in **bold** have been corrected (see response to Clarification Question 2 below). In addition, for accuracy, the labelling of the presented measure of uncertainty has been updated to credible intervals, rather than confidence intervals as originally presented.
Abbreviations: CrI: credible interval; OR: odds ratio.

Maintenance

Per-cycle probabilities of response in the maintenance phase were calculated as follows:

- The mean absolute probabilities of response were calculated as described above for the induction phase (presented in Table 3, alongside the subsequently calculated median ORs for the biologic-naïve and biologic-failed populations, which correspond to the mirikizumab

versus placebo OR in Figure 19 and Figure 24 in Section B.3.9 of the Company Submission, respectively).

- The complement to the derived probability is the probability of loss of response during the maintenance period. As such, the probabilities of loss of response during the maintenance phase for the biologic-naïve and biologic-failed populations were calculated as 1 minus the probability of response in that phase.
- Subsequently, the probability of loss of response during the duration of the maintenance trial was transformed to per cycle probabilities based on a fixed maintenance period of 40 weeks for all treatments using the formulae presented in Section B.4.2.1.3 of the Company Submission:
    - The probability of response in the maintenance phase was converted into an instantaneous rate:

$$r = -\ln(1 - P_{maintenance})$$

    - This rate was converted back to a probability for the relevant duration:

$$P_{12\ week\ cycle} = 1 - e^{-r/(\frac{40}{12})}$$

In this way, the probability of loss of response per 12-week cycle was calculated as [redacted] and [redacted] for biologic-naïve patients and biologic-failed patients, respectively, as presented in Section B.4.2.1.5 of the Company Submission. Therefore, the probability of continued response per cycle was 93.3% and 87.7%, respectively.

Table 3: Response in the maintenance phase

Treatment	Response (including remission)	
	Median OR relative to placebo (95% CrI)	Calculated mean absolute probability
Mirikizumab (for all treatments)		
Biologic-naive subgroup	[redacted]	[redacted]
Biologic-failed subgroup	[redacted]	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio.

CQ 2. The EAG has noted the following inconsistencies (highlighted in **BLUE** in **Table 4** below) in the confidence intervals for the response rate for Biologic-naïve subgroup. Please clarify why there is this inconsistency and which confidence intervals are correct.

Table 4: Inconsistencies in the Response rates at the end of induction

Treatment (for all treatments)	Response (including remission) OR (95% CI relative to placebo)	
Company base case	**Company reported**	**EAG check**
Biologic-naïve	[redacted] (CS Table 37)	[redacted] (CS Section B.3.9.4 Figure 16 and Appendix D.1.10 Figure 16)
Biologic-failed	[redacted]	Same as company (from CS Fig 22)

Lilly apologise that the noted inconsistency in the confidence intervals for the ORs for response (including remission) for the biologic-naïve subgroup at the end of induction is due to a typographical error in the Company Submission. Lilly can confirm that as highlighted by the EAG, the correct values for the confidence intervals are those stated in Figure 16 of Section B.3.9.4 of the Company Submission and in Figure 16 of Appendix D.1.10. The correct values are presented in Table 2 above, with updated values bolded.

Lilly can further confirm that since response probabilities for the induction period that inform the economic analysis were calculated directly from the NMA rather than from the ORs of the NMA (as described further in in response to Clarification Question 1 above), this minor typographical error does not impact the cost-comparison results presented in the Company Submission.

References

1. S. Dias NJW, A. J. Sutton and A. E. Ades. NICE DSU Technical Support Documents. Evidence synthesis in the baseline natural history model. Available at: https://www.ncbi.nlm.nih.gov/books/NBK310368/. [Accessed 23 November 2022]. 2012.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]

Patient Organisation Submission

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Crohn's & Colitis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's & Colitis UK is the UK's leading charity for everyone affected by Crohn's and Colitis. We're working to improve diagnosis and treatment, and to fund research into a cure; to raise awareness and to give people hope, comfort, and confidence to live freer, fuller lives. We want: • To drive world-class research that improves lives today and brings us closer to a world free from Crohn's and Colitis tomorrow • Everyone to understand Crohn's and Colitis • To support and empower everyone to manage their conditions • To drive high-quality and sustainable clinical care • Early and accurate diagnosis for all. Founded as a patients' association in 1979, we now have almost 48,000 members across the UK. Our members include people living with the conditions, their families and friends, health professionals and others who support our work. We have 50 Local Networks which arrange educational meetings, generate publicity and organise fundraising.

Living with the condition **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?**	Ulcerative Colitis is one of the two main forms of Inflammatory Bowel Disease (IBD) alongside Crohn's Disease. It requires tight monitoring and management, often over several decades from the age of diagnosis. If left untreated, poorly managed or in cases of severe disease, Crohn's and Colitis can cause serious complications, which require emergency medical and/or surgical intervention. The symptoms of Ulcerative Colitis, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of
comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; and research - our own and that of external organisations.

	medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships.[1] [2] For patients with moderate to severe Ulcerative Colitis the condition is more challenging, frequently overwhelming and detrimentally life-altering. This cohort are likely to experience more severe flares, weight loss, fever and constitutional symptoms.[3] [4] They are also more likely to have experienced a lack of or loss of response to treatment options. Mirikizumab could therefore offer an additional option where others have failed. **Risk of comorbidities** Patients with Ulcerative Colitis are more likely to experience several comorbidities including rheumatoid arthritis, asthma, chronic obstructive pulmonary disorder and chronic liver disease.[5] **Disease complications and mortality** Research suggests that people with Ulcerative Colitis are at a higher risk of mortality. Acute severe Colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy).[6] Between 15-25% of patients with Ulcerative Colitis will need to be hospitalised due to an acute severe flare-up at some stage. Often this will be the first presentation of their disease.[7] When a flare occurs in acute severe Colitis, deterioration can occur rapidly. Patients will require close monitoring and review by appropriate specialists. It's also vitally important to make decisions quickly to avoid severe complications.

[1] Crohn's and Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards
[2] IBD UK (2019) IBD Standards
[3] NICE (2019) NICE Guideline on Ulcerative Colitis: Management (NG130) https://www.nice.org.uk/guidance/ng130/chapter/Recommendations
[4] Dignass, A,. Second European evidence-based consensus on the diagnosis and management of Ulcerative Colitis Part 1: Definitions and diagnosis. Journal of Crohn's and Colitis Vol 6. Issue 10 https://www.sciencedirect.com/science/article/pii/S1873994612004047#t0020
[5] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *Evidence-based mental health*, **24**(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.
[6] BSG (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://gut.bmj.com/content/60/5/571.long
[7] BSG (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://gut.bmj.com/content/60/5/571.long

	The very real risks associated with acute severe Colitis include: • Life-threatening haemorrhage • Toxic megacolon - can occur in up to 1 in 40 people with Colitis[8] • Perforation of the bowel[9] Additional complications of chronic, uncontrolled, active Ulcerative Colitis also include: • Osteoporosis and vitamin D deficiency. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity[10] • Anaemia[11]. • Increased risk of cancer[12] **Impact on quality of life** Education, employment, personal relationships, social and family life may all be disrupted by the unpredictable occurrence of Ulcerative Colitis flare-ups. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect self-esteem and social functioning, particularly among the young and newly diagnosed. Emotional wellbeing can be significantly affected by difficulty in coping with personal lives and feelings of anger, embarrassment, frustration, sadness and fears of needing surgery or developing cancer.[13] Stigma and lack of wider understanding of the condition exacerbate the impact. Anxiety and depression are higher in people with Ulcerative Colitis, with mood disorders at least in part a

[8][8] Parray, F. Q. et al. (2012). Ulcerative Colitis: a challenge to surgeons. Int. J. Prev. Med. 3, 749–63.
[9] IBDUK (2019) IBD Standards 2019: Homepage | IBD UK
[10] Mowat C, Cole A, Windsor A et al. (2011) Guidelines for the management of inflammatory bowel disease in adults. Gut, 60, 571-607.
[11] Crohn's and Colitis Foundation.(2020) Anaemia. https://www.crohnscolitisfoundation.org/sites/default/files/2020-03/anemia.pdf
[12] The British Society of Gastroenterology (2019) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html
[13] Cosnes J, et al., (2011). Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology, 140 (6), 1785-94.

	consequence of the condition itself and its medical treatment (e.g., corticosteroid therapy).[14] Additionally, most reports indicate that stress may be involved in triggering flare ups.[15] Social functioning can be impaired leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. In fact, 45% of respondents in our Quality-of-Life survey reported that IBD had stopped them reaching their full potential in life in general.16 Research shows that young people aged 16-25 with Ulcerative Colitis who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. Over half (56%) of young people responding to our survey said they ruled out career options due to the impact of their condition.17 The experience of caring for someone with Ulcerative Colitis can be especially difficult given that it is an invisible condition, the unpredictable nature of the symptoms, which many also find extremely uncomfortable to talk about, and the effects of treatment. For parents of young people, there are challenges around providing support, while enabling independence and seeing lives and aspiration affected by their child's condition. Here are a selection of quotes that highlight what living with Ulcerative Colitis is like: *"Life with UC has been difficult, as I was constantly ill over a period of years, I had my relationship break down. I have been lucky that my previous line manager at work had a daughter of his own who suffered from UC, so any hospital stays weren't a problem and he allowed me to work from home on particularly bad days."* **Quote from a person living with Ulcerative Colitis.** *"I had 3 blood transfusions, multiple steroids, sleepless drained nights, cannula paracetamol, Iron deficiency, stomach ulcers and multiple drugs and many blood tests, not being able to eat and losing*

[14] Graff L. A. et al., (2009). Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflamm Bowel Dis, 15 (7), 1105-18.
[15] Sun, Y., Li, L., Xie, R., et al., (2019). Stress Triggers Flare of Inflammatory Bowel Disease in Children and Adults. *Frontiers in pediatrics*, **7**, 432. https://doi.org/10.3389/fped.2019.00432
[16] Crohn's & Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards.
[17] Crohn's & Colitis UK (2013). IBD in young people, the impact on education and employment.

	a huge amount of weight over 2 and a half stone in just 2 weeks wasn't expected out the blue in my life." **Quote from a person living with Ulcerative Colitis.** "*The last 9 months have been really quite horrible for me dealing with my UC and I went through a really low point in my life, feeling very anxious and depressed. I took 5 months off work and only recently started a new job. My UC really affected my social life and confidence especially with getting out of the house and carrying out simple tasks."* **Quote from a person living with Ulcerative Colitis.** "*The isolation I have felt has been overwhelming. I can't take my children to the park, for a walk or play date or any of the other simple things that I used to take for granted. I do not have any kind of social life myself as it is simply not possible for me to go out when I may need to open my bowels with no warning."* **Quote from a person living with Ulcerative Colitis.** *"When I am unwell the constant anaemia make everyday life feel like wading through treacle, the pain can be crippling. The very real concern of faecal incontinence gives me physical symptoms of stress as well as affecting me emotionally and mentally."* **Quote from a person living with Ulcerative Colitis.** "*He was struggling to maintain a healthy weight, was constantly feeling sick, rushing to the toilet and in pain and missing a great deal of his work at a stage in his career that was very important to him. He was unable to continue his sport and his social life was negligible*." **Quote from the parent of a person living with Ulcerative Colitis.** *"During the majority of my time living with UC and the ever-changing drugs, I had no quality of life. I was off sick from work for 8 months. I was unable to drive my children to or from school or make them their breakfast as this was the time, usually until about midday, that I could not leave the toilet. There was no fun time with my 3 wonderful children or my husband, I was always in bed, in pain or on the toilet. We did not cuddle or play, because if any of them touched my tummy, it would be so sore. This period of illness really affected my confidence. My friends gave up coming around as I was so poorly. My quality of work really dropped. I continuously made mistakes because of the side effects from all the drugs."* **Quote from a person living with Ulcerative Colitis.**

	“Making plans means I always have to caveat with 'if I can' so that's annoying and I have to plan sleep days if I know I have a busy week coming.” **Quote from a person living with Ulcerative Colitis.**

Current treatment of the condition in the NHS **7. What do patients or carers think of current treatments and care available on the NHS?**	The IBD UK national repot revealed that 28% of patients with IBD rated the quality of their care as fair or poor.[18] Patients express dissatisfaction with many of the current treatment options. The effects of steroids are extremely unpleasant and long-term safety profile of other treatments, including biologics, are of some concern. **Steroids** Corticosteroids are commonly used a first line treatment. However, there are significant short and long-term side effects with these, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis.[19] Therefore, they do not represent a therapeutic option as a maintenance treatment. The BSG guidelines set out clear stipulations on the best practice of prescribing steroid therapies given their diminishing returns, harsh side effects and risk of dependency.[20] *"My 'moon face' from the constant use of prednisolone was depressing and because of my ill health my hair became really thin. Prednisolone also affected my mood. I was so angry and unhappy. This also kept me awake at night, so I took sleeping pills."* **Quote from a person living with IBD** **Surgery** For many patients with Ulcerative Colitis, the prospect of surgery is one they face with considerable anxiety, and it can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. Clinical outcomes after pouch surgery remain variable and fertility in women can be significantly affected by any pelvic surgery. *"Surgery would have been a massive emotional and psychological barrier for our son at this stage in his life*." **Quote from a person living with IBD** *"Personally I'm not prepared for the drastic surgery of having my colon removed*." **Quote from a person living with IBD**

	"I'd had enough of being ill and hospital admissions and blood transfusions and requested surgery to remove my colon. The surgeon said it disintegrated as he was taking it out it was in such a bad state. I now have a j-pouch and while life is a lot better it isn't the cure that was promised and it impacts on my life considerably." **Quote from a person living with IBD**

[18] IBD UK (2021). *Crohn's and Colitis Care in the UK: The Hidden Cost and a Vision for Change*. CROJ8096-IBD-National-Report-WEB-210427-2.pdf
[19] Blackwell J, Selinger C, Raine T, *et al* (2021). Steroid use and misuse: a key performance indicator in the management of IBD. *Frontline Gastroenterology* , **12**, p.207-213.
[20] BSG (2019) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html

8. Is there an unmet need for patients with this condition?	There is currently no medical or surgical cure for Ulcerative Colitis. Current available treatments are aimed at inducing and maintaining remission and improving quality of life. The range of options available for treating Ulcerative Colitis remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies. **Immunosuppressants** Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them.[21] [22] In most patients who do respond, the benefits take three to six months to appear. Significant risks of thiopurines including non-Hodgkin's lymphoma (as high as 4-5-fold compared with unexposed IBD patients and further increased when used in combination with anti-TNFs). Other side effects include early hypersensitivity reactions such as fever and pancreatitis, bone marrow suppression and hepatotoxicity requiring frequent lab monitoring during treatment. [23] [24] **Anti-TNFs** These are increasingly being used earlier in the treatment pathway and can have a significant and positive effect on quality of life for patients. However, up to 40% of patients treated with anti-TNF therapy do not respond to induction therapy.[25] In the approximately one-third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time.[26] Overall, there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with Ulcerative Colitis to resume their lives and restore their quality of life. "*I have suffered with UC for 13 years. It's always been moderate to severe. I have tried all drugs including all biologics. All failed after a while. The best was Infliximab, I had my first ever remission for 2 years. However, it came to an end in Aug 2017. I had 18 months of pain and blood, countless hospital admissions, yet I was still pushed to try yet another biologic, Vedolizumab then Golimumab. None of it worked. 6 weeks later I had an emergency op and my colon was removed. My recovery is slow as I was ill for quite some time before and I'm building up my stamina now."* **Quote from a person living with Ulcerative Colitis.**

	"*Vedolizumab, when I first started it, was my wonder drug. It was difficult spending so much time in hospital but worth it to be completely symptom free. I was in remission for nearly 4 months.* *I was then given Golimumab which was a lot more convenient, and I liked having the control of self-administering. This however never gave me remission and my CRP worsened over the period I was taking it. I am now being offered Tofacitinib but have been told this is my final option*." **Quote from a person living with Ulcerative Colitis.** *"I was steroid dependent and all conventional UC therapies failed – including anti TNF (Infliximab). Long term steroid use resulted in osteoporosis at age 28. I was housebound for many years due to UC and was unable to work. Quality of life was zero."* **Quote from a person living with Ulcerative Colitis.**

[21] Fraser, A.G, Orchard, T.R, Jewell, D.P. (2002). The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut*, **50**: 485–9.
[22] Candy, S, Wright, J, Gerber, M, *et al.,* (1995) A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut*, **37**: 674–8.
[23] Siegel, C.A, Marden, S.M, Persing, S.M, *et al.,* (2009). Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*, **7**:874–881
[24] Jorquera, A, Solari, S, Vollrath, V. et al., (2012). Phenotype and genotype of thiopurine methyltransferase in Chilean individuals. *Rev Med Chil*, **140**:889–895
[25] Rutgeerts, P, Van Assche, G, Vermeire S. (2004). Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology*, **126**(6):1593-610.
[26] Roda, G. (2016). Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*, **7** (1), e135.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients most likely to benefit from this drug are those for whom currently available therapies are ineffective, contraindicative or they develop an intolerance. In this group, it is likely that individuals, without further choice, will return to treatment/s which have already been established to be inadequate. This may include highly undesirable long-term steroid use or unproven unconventional therapy. It is also likely that patients in this group who exhaust all other treatment options would be forced to have a colectomy, either elective or as an emergency. *"I am well aware that these drugs have a very significant cost but without them, the last 12 years would have been very different for me. Even with them I have had to have 2 lots of surgery to remove scarred bowel but without them I think I would have had to have more extensive surgery and possibly not even be here to send this email. I am also well aware that I am on my last chance here with current available drugs having taken everything the NHS has to offer; if the vedo [Vedolizumab] stops working then I have nowhere else to go with medication. New drugs and options for medication will be vital for my health going forward."* **Quote from a person living with IBD, in which drug treatments have not been effective.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Prescription costs faced people living with long-term and chronic conditions, including Ulcerative Colitis, in England, are shown to contribute to economic disadvantage, which can impact adherence and lead to complications and increased cancer risks and cost to the NHS.[27] However, the disadvantage is not specific to Mirkizumab, and the value of an additional treatment option may will remain beneficial as it will reduce the risk of loss of response.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who have had little or no success with currently available medical treatment options, and wish to avoid or delay surgery, are likely to benefit. This would include young people wishing to complete studies and those for whom surgery would be considered unacceptable due to cultural or religious factors.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For certain religious groups, the impact of active disease and the effects of surgery may interfere with religious practices and cause distress, which could be alleviated by an additional medical therapeutic option. Although not specific to Mirikizumab, prescription costs may also be a factor associated with lower income.

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The symptoms of Ulcerative Colitis, and their unpredictable nature, together with the side effects of medications, can have a profound and devastating impact on all aspects of a person's life. • There is significant unmet need within the moderate to severe cohort. Current treatments remain far from optimal for patients, a substantial number of whom experience a lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety. • Mirikizumab offers a novel treatment option and increases choice for both clinicians and patients (in the context of shared decision making). • Mirikizumab may delay or prevent surgery in Ulcerative Colitis patients. This is particularly important for patients who have exhausted all over treatment options and wish to avoid or delay surgery (e.g. to complete studies.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

CONFIDENTIAL UNTIL PUBLISHED

External Assessment Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Mirikizumab for treating moderately to severely active ulcerative colitis

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Karen Pickett, Senior Research Fellow, SHTAC Neelam Kalita, Senior Research Fellow, SHTAC Emma Maund, Research Fellow, SHTAC Jaime Peters, Senior Research Fellow, University of Exeter Marcia Takahashi, Research Fellow, SHTAC Joanna Picot, Senior Research Fellow, SHTAC
Correspondence to	Dr Karen Pickett Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	20/03/2023

Source of Funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number NIHR135730.

Acknowledgements

We thank Professor Alan Lobo, Consultant Gastroenterologist, Inflammatory Bowel Disease Centre, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, for providing clinical advice to the project team through commenting on a draft version of this report.

We also thank Lorna Hazell, Senior Research Assistant, Southampton Health Technology Assessments Centre (SHTAC), for providing a quality assurance review of the draft report. We additionally thank Lois Woods, Senior Research Assistant, SHTAC, for critically appraising the systematic literature review search strategies.

Declared competing interests of the authors and advisors

The authors report none. Prof Alan Lobo reports the following financial relationships with a company associated with this appraisal in the previous 12 months: receipt of consulting fees from Takeda UK and being a virtual advisory board Chair for Takeda UK in relation to vedolizumab for Crohn's disease and in relation to aspects of the management of Crohn's disease. Prof Lobo also reports contributing to a non-promotional virtual policy summit and a subsequent report, organised and funded by Takeda UK, on care for people with inflammatory bowel disease.

Rider on responsibility for report

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

This report should be referenced as follows:

Pickett, K; Kalita, N; Maund, E; Peters, J; Takahashi, M; Picot, J. Mirikizumab for treating moderately to severely active ulcerative colitis*: A Single Technology Appraisal.* Southampton Health Technology Assessments Centre, 2023.

Contributions of authors

Karen Pickett critically appraised the company's decision problem and network meta-analysis, drafted the report, project managed the review, and is the project guarantor; Neelam Kalita critically appraised the company's economic evaluation, and drafted the report; Emma Maund critically appraised the clinical efficacy evidence from the company's trials, and the network meta-analysis, and drafted the report; Jaime Peters critically appraised the company's network meta-analysis and drafted the report; Marcia Takahashi critically appraised the company's economic evaluation, and drafted the report; Joanna Picot critically appraised the company's background information, the decision problem, the clinical efficacy evidence from the company's trials, and the network meta-analysis, and drafted the report.

Table of Contents

LIST OF TABLES

LIST of FIGURES

LIST of APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse event
BNF	British National Formulary
CRD	Centre for Reviews and Dissemination
CrIs	Credible intervals
CS	Company submission
CSR	Clinical study report
DIC	Deviance information criteria
EAG	External Assessment Group
eCOA	Electronic clinical outcome assessment
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
FDA	Food and Drug Administration
IBDQ	Inflammatory Bowel Disease Questionnaire
ITT	Intention-to-treat
IV	Intravenous
JAK	Janus kinas
MIMS	Monthly Index of Medical Specialities
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ONS	Office for National Statistics
OR	Odds ratio
PATT	Proportionate approach to technology appraisals
PAS	Patient access scheme
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
RCT	Randomised controlled trial
SAP	Statistical analysis plan
SC	Subcutaneous
SLR	Systematic literature review
SP	Sphingosine 1-phospate
TA	Technology appraisal

TNFi	Tumour necrosis factor alpha inhibitor
TSD	Technical Support Document
UC	Ulcerative colitis

1 Executive summary

The company (Eli Lilly) submitted evidence to NICE for mirikizumab, in the treatment of people with moderately to severely active ulcerative colitis (UC), to be considered under NICE's proportionate approach to technology appraisals (PATT) streamlined cost-comparison process. This report is the external assessment group's (EAG's) critique of the company's submission (CS). It identifies the strengths and weaknesses of the CS. This summary provides a brief overview of the issues identified by the EAG as being potentially important for decision making. All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

During the EAG's evaluation of the CS, the company submitted an addendum to the CS to NICE, in which the company amended input errors identified in the network meta-analysis (NMA) presented in their original CS. We refer to this document as the 'CS addendum' in this report. The company also submitted a revised cost-comparison model as part of the addendum.

The company is using the PATT streamlined cost-comparison process for this appraisal as they argue a case in the company submission (CS) that mirikizumab has similar or better clinical efficacy for treating moderately to severely active UC than the company's two chosen comparators, ustekinumab and vedolizumab, in the induction and maintenance phases of UC treatment. The EAG is overall satisfied that the company's argument is supported by the evidence in the CS.

1.1 Overview of the EAG's key issues

The EAG has identified no critical issues with the evidence included in the CS that, in our opinion, would prevent a cost-comparison approach proceeding. Below, however, we detail uncertainties we identified with an aspect of the company's decision problem and with the evidence base they present.

1.2 The decision problem: summary of the EAG's critique

The company's decision problem overall appears appropriate and the EAG suggests, based on advice from our clinical expert and based on NICE committee discussions in previous appraisals, that the company's selection of vedolizumab and ustekinumab as comparators for the cost-comparison is reasonable.

The only uncertainty we have identified with the decision problem is that, from the information supplied in the CS, it is not fully clear what the company mean when they state they are partly positioning mirikizumab for managing moderately to severely active UC in biologic-naïve patients (that is, people for whom conventional treatment cannot be tolerated or is not working well enough) in whom "*other biologic treatment is not suitable*" (CS section B.1.1).

1.3 The clinical effectiveness evidence: summary of the EAG's critique

The company conducted a network meta-analysis (NMA) to provide support for their claim that mirikizumab has similar clinical efficacy to ustekinumab and vedolizumab. We judged that the methodology of the NMA was overall appropriate, but we had some concerns about the NMA. These included that:

- the searches for the systematic literature review that informed the NMA were performed over six months ago, meaning that there is a risk that there may have been relevant studies published recently that will not have been included in the NMA;
- the study eligibility criteria of the systematic literature review that informed the NMA focused on a broad population of "*adult patients (≥18 years) with moderate to severe UC*" (CS Appendix D, section D.1.3, Table 19); eligibility was not limited to studies of only adults with moderately to severely active UC who were intolerant of, or whose disease has had an inadequate response, or loss of response to previous biologic therapy or conventional therapy, as per the population of interest specified in the NICE scope. As a consequence of this, the biologic-naïve subgroup analyses in the NMA (of people "*who had not received any prior biologic, including a JAKi [Janus kinas inhibitor]*", CS section B.3.9.3.1) do not fully reflect the population of interest in the NICE scope, as the participants included in these analyses were not necessarily intolerant of, or had had an inadequate response to or loss of response to conventional therapy. The NMA biologic-naïve subgroup also does not fully reflect the biologic-naïve population in whom the company is partly positioning mirikizumab (that is, those in whom "*Conventional treatment cannot be tolerated or is not working well enough and other biologic treatment is not suitable ("biologic-naïve")*", CS section B.1.1);
- the company did not model baseline effect using representative UK-specific data as is recommended in Technical Support Document (TSD) 5[1] and the impact of this on the results is unclear;
- the company's NMA network was broad, including a range of approved targeted therapies and emerging therapies for UC. There was considerable statistical and

clinical heterogeneity in the analysis. We suggest this may have been reduced through using a narrower network, with fewer comparators included (i.e. by limiting the NMA to the treatments of interest in the cost-comparison: mirikizumab, ustekinumab, vedolizumab and placebo). Reduced heterogeneity would provide more confidence in the potential clinical efficacy equivalence of the drugs (through providing more precise credible intervals).

We also note that the similarity of the treatment effects and safety of mirikizumab versus ustekinumab and vedolizumab is based on findings of statistical significance in the NMA. Non-inferiority and equivalence have not been statistically assessed in the available evidence in the CS (e.g. through an equivalence or non-inferiority trial).

The concerns we detail above, however, are not, in our opinion, critical issues affecting the robustness of the NMA efficacy and safety results.

1.4 The cost-effectiveness evidence: summary of the EAG's critique

The company conducted a cost-comparison analysis of mirikizumab versus ustekinumab and vedoluzimab. The EAG conclusions are as follows:

- The company's cost comparison analyses considered two patient cohorts: biologic-naïve and biologic failed. The patients' characteristics, based on the pivotal mirikizumab LUCENT trials' intention-to-treat (ITT) populations, are consistent with a previous NICE appraisal (TA633;[2] ustekinumab for treating moderately to severely active UC).
- The comparators included in the analysis are appropriate and consistent with the NICE scope.
- The company's model structure and assumptions are appropriate and consistent with a previous NICE appraisal (TA633). Overall, the model was well-implemented, although we identified two errors in the company's scenario analyses.
- The model assumes equal clinical efficacy for mirikizumab, ustekinumab and vedolizumab based on the NMA results. While there are uncertainties with the NMA, none of these are critical. Hence, we view it is reasonable to assume equal clinical efficacy for all three drugs.
- At the list price, mirikizumab is [redacted] – ustekinumab and vedolizumab. This applies for the company's base case analysis and for all the company and EAG scenario analyses.

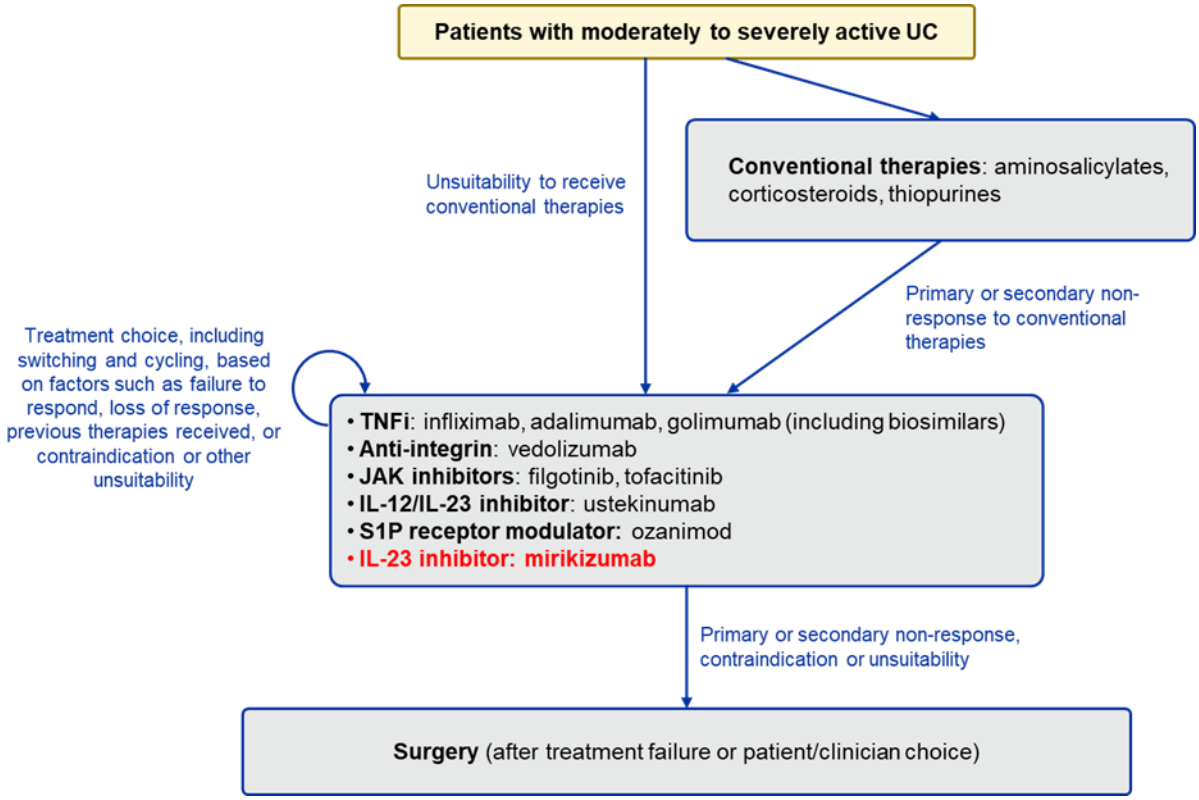
- The cost difference between mirikizumab and the two comparators is most sensitive to assumptions about re-induction rates and delayed response assessment.

2 Background

Mirikizumab for treating moderately to severely active ulcerative colitis (UC) is being considered using cost-comparison methodology as part of the recently introduced proportional approach to technology appraisals (PATT) process. This is because:

- at the time the final scope was produced NICE had already released technology appraisal (TA) guidance for similar medicines used for the same indication: TA329[3] (the TNF inhibitors infliximab, adalimumab and golimumab), TA342[4] (vedolizumab), TA547[5] (tofacitinib) and TA633 (ustekinumab).[2] TA828[6] on ozanimod for treating moderately to severely active UC, TA792[7] on filgotinib for treating moderately to severely active UC and TA856[8] on upadacitinib for treating moderately to severely active UC were released after the final scope for this appraisal.
- The CS states that mirikizumab has similar or better efficacy for treating moderately to severely active UC than the company's two chosen comparators, ustekinumab and vedolizumab, in the induction and maintenance phases of treatment (CS section B.1.1). Relative efficacy was estimated by an indirect treatment comparison that compared mirikizumab to the full range of comparators specified in the final scope.

The company provides a succinct and accurate description of the disease area in CS section B.1.3.1 covering the primary and secondary symptoms of UC, epidemiology and diagnosis, disease staging (severity and extent). Burden of disease is summarised in CS section B.1.3.2. The clinical pathway of care, focussing on patients with moderately to severely active UC, is provided in CS section B.1.3.3 and summarised in CS Figure 2 which is reproduced below as Figure 1. As Figure 1 shows, first-line treatment for suitable patients is conventional therapies (e.g. aminosalicylates, corticosteroids, thiopurines). If conventional therapies are not suitable for a patient, or when a patient has an inadequate response to or loses response to conventional therapies a variety of biological therapies form the next (second-line) treatment options. The company show the intended positioning of mirikizumab is at the same step of the pathway as the biological therapies, Janus kinas (JAK) inhibitors and sphingosine 1-phospate (SP) receptor modulator. As stated in the figure, the biologic ustekinumab (a comparator in this appraisal) is restricted for use only where a tumour necrosis factor alpha inhibitor (TNFi) has failed or cannot be tolerated. The final treatment option available either for patients unable to receive biological therapies, or for patients who experience inadequate disease control despite receipt of a biological therapy, is surgery to remove the colon.



Patients with a response or in remission remain on the same therapy with a 12-month review. In the biologic-naïve setting, ustekinumab is restricted for use only where a TNFi has failed (that is, the disease has responded inadequately or has lost response to treatment) or cannot be tolerated, and ozanimod is for use where conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable.

Figure 1 Current treatment pathway for moderately to severely active UC in UK clinical practice and the anticipated positioning of mirikizumab within it.

Source: reproduction of CS Figure 2
IL, interleukin; JAK, Janus kinase; S1P, sphingosine-1-phosphate; TNFi, tumour necrosis factor alpha inhibitors, UC: ulcerative colitis.

Mirikizumab's mechanism of action is shown in CS Figure 1 (this is within CS Table 2). Mirikizumab is a recombinant humanised IgG4 monoclonal antibody that selectively binds to the p19 subunit of the IL-23 cytokine. When mirikizumab is bound to the p19 subunit, the interaction of the IL-23 cytokine with the IL-23 receptor is inhibited, thereby reducing the inflammatory processes driven via IL-23 that contribute to the inflammatory processes underlying UC. Mirikizumab is administered by intravenous (IV) infusion during induction and thereafter by subcutaneous injection for maintenance. Mirikizumab does not yet hold a license in the UK.

As summarised in Appendix 1 mirikizumab's mechanism of action is most similar to that of ustekinumab, one of the company's chosen comparators. Ustekinumab also inhibits the inflammatory cascade underlying UC via inhibition of the IL-23 cytokine but because

ustekinumab binds to the p40 subunit, it also inhibits the IL-12 cytokine which shares this subunit (whereas mirikizumab targets the p19 subunit of the IL-23 cytokine). Additionally, mirikizumab and ustekinumab share a similar method of administration (initially IV infusion for induction, followed by subcutaneous injection for maintenance). The other eight therapies recommended by NICE and listed as potential comparators in the final scope (including the company's other chosen comparator, vedolizumab) have different mechanisms of action. Two can also be administered by IV infusion for induction, followed by subcutaneous injection for maintenance (infliximab and vedolizumab, infliximab can be administered solely by IV infusion), two are administered subcutaneously (adalimumab, golimumab) and four orally (tofacitinib, filgotinib, ozanimod, upadacitinib).

3 Critique of the decision problem in the company's submission

CS Table 1 outlines the decision problem addressed by the company in the CS in relation to the final scope issued by NICE. The table shows deviations from the scope, as highlighted by the company. Here we provide a critique of the company's deviations from the NICE scope and the company's stated reasons for these.

3.1 Population

The population addressed in the company's decision problem is "*Adults with moderately to severely active ulcerative colitis for whom conventional treatment cannot be tolerated or is not working well enough and other biologic treatment is not suitable, or biological treatment cannot be tolerated or is not working well enough*" (CS Table 1). The population specified by the company (see CS Table 1) broadly matches that specified in the NICE scope, but differs in that among people who cannot tolerate conventional treatment or in whom conventional treatment has not worked well enough, the company is positioning mirikizumab treatment only in the subgroup for whom other biologic treatments are not suitable. This population is referred to by the company as "biologic-naïve"; see CS section B.1.1. The company state this is a sub-population of the proposed marketing authorisation (see CS Table 1). In the CS, the population in whom biological treatment cannot be tolerated or is not working well enough is also addressed in the company's decision problem and is referred to by the company as "biologic-failed".

From the information supplied in the CS, the EAG is not fully clear about what the company mean when they state mirikizumab is partly positioned for managing UC in biologic-naïve patients in whom "*other biologic treatment is not suitable*" (CS Table 1). We note that none of the comparator drugs specified in the NICE scope, for which NICE recommendations have been published,[2-7] have the same restriction as proposed by the company for mirikizumab. Ustekinumab (TA 547) is more specifically recommended as an option when conventional treatment or a biologic cannot be tolerated, or the disease has not responded adequately or lost response to treatment, only if a TNFi has failed, cannot be tolerated or is unsuitable.[2] Ozanimod (TA 828) is more specifically recommended as an option when conventional treatment cannot be tolerated or is not working well and infliximab is unsuitable (as well as being recommended for as a treatment option when a biologic cannot be tolerated or is not working well enough).[6]

The clinical expert advising the EAG stated that they thought clinicians would want to have the option of using mirikizumab to treat patients who cannot tolerate either conventional or existing available biologic treatments. The expert also estimated that the proportion of patients for whom other biologic treatment would be unsuitable would be low – around 10% to 15% of patients. They commented that the criteria clinicians would use to judge unsuitability would be subjective and not clearly defined (the judgement might be based on, for example, cancer risk or patient preference).

3.2 Intervention

The intervention specified by the company in their decision problem (mirikizumab) matches the NICE scope.

3.3 Comparators

In a cost-comparison NICE appraisal, companies are not expected to provide a comparison of the intervention against all the comparators specified in the NICE scope.[9] Only one of the scoped comparators needs to be selected, which should represent NICE recommended treatments as a whole in terms of costs and effects, and which has a significant market share. In the company's decision problem for this appraisal, they have selected ustekinumab and vedolizumab as comparators, for the reasons outlined in CS Table 1 and in CS section B.1.1, which include that the company state that their NMA shows that mirikizumab has a similar or possibly greater efficacy than ustekinumab and vedolizumab. The company state ustekinumab and vedolizumab are the relevant comparators for the biologic-failed subgroup (CS section B.1.1; see section 3.1 above for how this subgroup is defined). The company does not explicitly state the relevant comparator(s) for biologic-naïve population in whom other biologic treatments are not suitable (see section 3.1 above for how this subgroup is defined).

The company does not provide an estimate in the CS of the market share for either ustekinumab or vedolizumab in treating people with moderately to severely active UC who are intolerant of, or have failed treatment with, prior biologic therapy. Clinical expert advice to the EAG is that ustekinumab and vedolizumab are used extensively in these patients. The expert notes that the treatment landscape is currently changing and would also include tofacitinib, filogotinib and (if recommended by NICE) upadacitinib. The EAG's expert estimated that the market share of vedolizumab is 40%, tofacitinib 35%, ustekinumab 20% and surgery or other treatments 5%.

We consider the company's selection of ustekinumab and vedolizumab as comparators for mirikizumab in this cost-comparison appraisal is reasonable based on Committee meeting discussions in previous NICE appraisals of treatments for moderately to severely active UC, the NICE recommended indications for these drugs in moderately to severely active UC,[4,10] and based on clinical expert advice to the EAG for this appraisal. The EAG's clinical expert noted that treatment options are changing rapidly for moderately to severely active UC. They noted that vedolizumab and ustekinumab are reasonable comparators to choose, but that tofacitinib, filgotinib and ozanimod would also be treatment options. The expert noted that tofacitinib is quite frequently used, but that its use is variable due to differing familiarity with it and some concern about side effects. The EAG's expert commented that there is considerable uncertainty about how the various treatments for moderately to severely active UC should be positioned and sequenced.

Regarding the use of TNF-alpha-inhibitors in treating moderately to severely active UC, we note that in the NICE appraisals of ustekinumab, filgotinib and ozanimod (TA633, TA792 and TA828, respectively), clinical experts informed the NICE Committees that, in practice, TNF-alpha inhibitors are typically offered as a first biologic treatment after failure on or due to intolerance of conventional therapy,[2,6,7] with infliximab commonly used at this stage.[2,6] The clinical experts advising the Committee on the ustekinumab appraisal, for which guidance was published 17 June 2020, stated that if a patient produces antibodies to a TNF-alpha inhibitor and loses response, another TNF-alpha inhibitor may be tried.[2] If the patient has produced no antibodies and the condition has not responded adequately or lost response to the first TNF-alpha inhibitor, the patient may be offered vedolizumab or tofacitinib.[2] The expert advising us in this appraisal agreed with this depiction of the use of TNF-alphas in clinical practice.

3.4 Outcomes

The company has included all the outcomes specified in the NICE scope in the CS, except for rates of and duration of relapse. The company, however, models loss of response in the cost comparison model (CS section B.4.2.1.5). The expert advising the EAG confirmed that loss of response is clinically the same as relapse. The company provide a definition of loss of response in CS Table 12. The EAG's expert was of the opinion that the definition is appropriate.

Mortality is not reported as an efficacy outcome in the CS, but is reported as an adverse effect.

The outcomes of clinical response and clinical remission were measured in the comparator vedolizumab and ustekinumab pivotal trials (GEMINI I[11] and UNIFI,[12] respectively) and were outcomes used in the cost-effectiveness economic models that informed the NICE appraisals of these drugs.[2,4] We note that the definitions of these outcomes used in the mirikizumab pivotal trials (LUCENT-1 and LUCENT-2) differ to those used in the previous appraisals. This is discussed further in section 4.5.4.3, where we note that the expert advising the EAG confirmed that the way these outcomes had been defined in the pivotal mirikizumab trials was appropriate.

3.5 Economic analysis

The company has submitted a cost comparison analysis for the reasons outlined in section 2. The company's base case analysis uses a 10-year time horizon (CS section B.4.2.2). The expert advising the EAG was of the opinion that this time horizon would be sufficient for capturing any differences in costs between mirikizumab and ustekinumab and vedolizumab. The CS details that a patient access scheme (PAS) discount has been submitted to the Patient Access Schemes Liaison Unit and provides details of the proposed discount (CS Table 2). The company provides base case and scenario analyses results using both the list and PAS prices (CS sections B.4.3 and B.4.4.2, and updated in sections 3.2 and 3.3 of the CS addendum). We note confidential commercial arrangements are in place for ustekinumab and vedolizumab.

3.6 Subgroups to be considered

Two patient subgroups are specified in the company's decision problem: 'biologic-failed' and 'biologic-naïve' (these subgroups are defined in CS Table 1). The company's definitions of these groups broadly align with those of the subgroups specified in the NICE scope, except that the company includes tofacitinib (which is a small molecule JAK inhibitor) in addition to biologics. The clinical expert advising the EAG, confirmed it is reasonable to group tofacitinib with biologics, as, collectively, these therapies are now sometimes described as 'advanced therapies'. The expert additionally noted that while grouping tofacitinib with the biologics was reasonable, there is sparse information available about whether people who fail on tofacitinib differ in an important way to those who fail on a TNF-alpha inhibitor. This is partly because tofacitinib is not often used as a first-line treatment. The expert notes that general clinical experience is that there are higher response rates in biologic naïve patients than those who have been biologic exposed, but it is unclear if the same pattern of response would be observed in people who have received tofacitinib but who have not been exposed to a biologic.

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Overview of the clinical effectiveness evidence submitted by the company

The company identified the submitted clinical effectiveness evidence by conducting a systematic literature review (SLR) and by including data on their own pivotal Phase III trials (LUCENT-1 and LUCENT 2) which were not published when searches for the SLR were conducted. The final evidence included comprises:

- LUCENT-1.[13] The company's phase III randomised controlled trial (RCT) of mirikizumab versus placebo designed to evaluate the safety and efficacy of mirikizumab over a 12-week induction period.
- LUCENT-2.[14] The company's phase III RCT of mirikizumab versus placebo designed to evaluate the safety and efficacy of mirikizumab in maintaining a treatment response to Week 40, with the primary study population comprising of LUCENT-1 participants who were randomised to mirikizumab and who achieved a clinical response at week 12.
- 35 additional studies included in the company's NMAs that compare mirikizumab with a broader range of comparators than that listed in the NICE scope for this appraisal.

The company's two pivotal studies of mirikizumab are described and critiqued in sections 4.2 to 4.4 of this report and the company's NMAs in section 4.5 below.

4.2 Description of pivotal studies of mirikizumab

CS sections B.3.2 and B.3.3 provide details of the design and methodology of the company's two pivotal mirikizumab studies, LUCENT-1 and LUCENT-2. Patients who completed the 12-week induction period of LUCENT-1 were eligible to enrol in the LUCENT-2 study, which was a 40-week maintenance study. Treatment received in LUCENT-2 was based on the patient's randomised treatment arm and clinical response in LUCENT-1 and whether they experienced loss of response in LUCENT-2. These studies are discussed individually in sections 4.2.1 and 4.2.2 below.

4.2.1 LUCENT-1

LUCENT-1 was a multi-national, phase III, randomised, double-blind placebo-controlled study evaluating the superiority of mirikizumab versus placebo in inducing clinical remission at 12 weeks in patients with moderately to severely active UC whose prior treatment with either conventional therapy or with biologic therapy had failed.

- Moderately to severely active UC was defined as a modified Mayo score of 4 to 9 out of a possible total score of 9 (i.e. a score based on three of four total Mayo subscores (Stool frequency subscore (0–3), Rectal bleeding subscore (0–3), and Endoscopic subscore (0–3) but excluding the Physician's global assessment subscore (0-3) (CS Table 12)),[15] and an endoscopic subscore of ≥2. The EAG agree with the company that the modified Mayo score has been shown to highly correlated with the full Mayo score and the exclusion of the Physician's Global Assessment subscore is in line with guidance published by the Food and Drug Administration (FDA).[16]
- Conventional-failed ("biologic-naïve") patients were defined as having had an inadequate response to, loss of response to, or intolerance to corticosteroids or immunomodulators and having never failed nor demonstrated an intolerance to a biologic medication (TNFis, anti-integrins) indicated for the treatment of UC. [redacted]
- Biologic-failed patients were defined as having had an inadequate response to, loss of response to, or intolerance to biologic (TNFis, anti-integrins) or JAK inhibitors (e.g. tofacitinib). Further details of medication failure criteria are in CS Appendix J. [redacted]

The EAG notes that the LUCENT-1 trial definition of the conventional-failed subgroup encompasses people who are biologic-naïve who have not failed on or are intolerant to a biologic. It is not clear if these people were not suitable for treatment with a biologic. This LUCENT trial subgroup therefore does not fully reflect biologic-naïve subgroup stated to be of interest in the company's decision problem ("*adult patients with moderately to severely active ulcerative colitis for whom: Conventional treatment cannot be tolerated or is not working well enough and other biologic treatment is not suitable ("biologic-naïve)"*; CS section B.1.1 and Table 1).

The study design is shown in Figure 2. The study had a screening period of up to 28 days followed by double-blind treatment for 12 weeks. Patients who completed 12 weeks of treatment were eligible to enrol in LUCENT-2. Patients who discontinued LUCENT-1 before week 12 or completed LUCENT-1 but did not enrol in LUCENT-2, completed a post-treatment follow-up period for 16 weeks after their last visit.

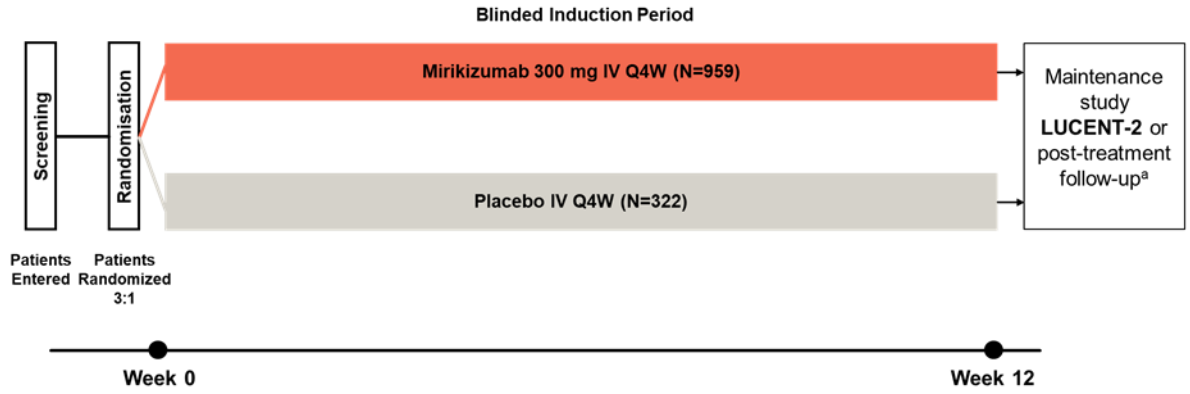


Figure 2 Trial design of LUCENT-1

[a] Patients who completed LUCENT-1 through Week 12 either completed post-treatment follow-up within the study or were eligible to participate in the maintenance study LUCENT-2.
IV: intravenous; Q4W: every 4 weeks.
Source: reproduced from CS Figure 3

In the LUCENT-1 trial, 1281 patients were randomised 3:1 to IV mirikizumab 300 mg every 4 weeks or IV placebo every 4 weeks stratified by biologic-failed status, baseline corticosteroid use, baseline disease activity (modified Mayo score of 4–6 or 7–9) and region. Patients received visually identical IV treatment by blinded personnel at weeks 0, 4 and 8 and were allowed to continue ongoing therapy with stable doses of protocol specified non-biologic treatments (CS Table 6, LUCENT-1 Trial Protocol point 9).

Eligibility criteria for LUCENT-1 are shown in CS Table 6 and CS Appendix J, with baseline characteristics shown in CS Tables 8 and 9. The company states that baseline characteristics were well-balanced across treatment groups (CS section B.3.3.2.1); the EAG agrees with this.

The primary outcome of LUCENT-1 was the proportion of patients in clinical remission at week 12 defined using the modified Mayo score (i.e. Stool frequency subscore = 0 or 1, with ≥1-point decrease from baseline, Rectal bleeding subscore = 0, Endoscopic subscore = 0 or 1 (excluding friability), CS Table 12). Major secondary outcomes are listed in CS Table 6, defined in CS Table 12, adverse reactions in CS Appendix F and additional secondary outcomes in Appendix M and the clinical study report (CSR).

Electronic clinical outcome assessment (eCOA) devices were used to record patient reported outcomes, including the Stool frequency and Rectal bleeding subscore components of the modified Mayo score. During the trial, errors in the Turkish and Polish wording of these two components on the eCOA devices were discovered (LUCENT-1 statistical analysis plan (SAP) section 4.3). One hundred and seventeen patients from Turkey and

Poland therefore had baseline data collected using incorrect questions (CSR section 3.1.2.2). As a result, and in agreement with the FDA, the primary efficacy analysis for all endpoints was based on a modified intention to treat population (LUCENT-1 SAP section 5.4). This population (n=1162, 90.7% of randomised patients) included all randomised patients who received any amount of study treatment, regardless of whether they received the correct treatment, or otherwise did not follow the protocol, but excluded those 117 patients impacted by the eCOA wording errors in Turkey and Poland (CS Table 13, LUCENT-1 SAP section 5.4). Sensitivity analyses that included impacted patients from Turkey and Poland by using methods of imputation were performed (LUCENT-1 SAP section 5.3.4); results were presented in the CSR only. In contrast, the primary analysis of adverse events was based on the safety population (n=1279) which included impacted patients from Turkey and Poland. Descriptions of trial populations used in the analysis of LUCENT-1 outcomes are presented in CS Table 13 and a summary of the statistical analyses undertaken for LUCENT-1 is provided in CS Table 15. The EAG note that to account for multiple testing a two-sided alpha of 0.00125 was used for all primary and major secondary endpoints. For all other endpoints, a significance level of 0.05 was used (LUCENT-1 SAP section 5.1.4).

4.2.2 LUCENT-2

LUCENT-2 was a multi-national, phase III, 40 week-long maintenance study comprising five treatment arms (n=1177, LUCENT 2 CSR Table 8.1). Patients in LUCENT-1 who received at least one dose of study drug and completed assessments at week 12 were eligible to enrol in LUCENT-2; eligibility criteria are detailed in CS Table 7 and CS Appendix K. The study design is shown in Figure 3.

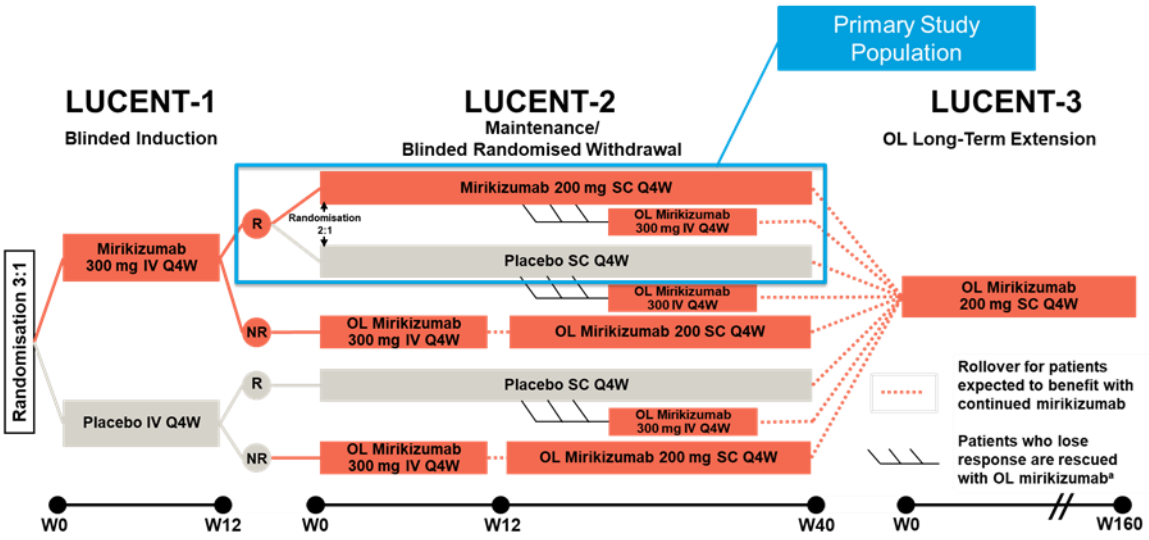


Figure 3 The trial design of LUCENT-2

[a] Patients for whom re-induction ("rescue therapy") with open-label mirikizumab was not deemed to demonstrate clinical benefit discontinued treatment and were not eligible to enter the open-label extension.
IV: intravenous; NR: non-responder OL: open-label; Q4W: every 4 weeks; R: responder; SC: subcutaneous; W: week.
Source: reproduced from CS Figure 4

The primary study population of LUCENT-2 (the two study arms within the blue box in Figure 3) were patients randomised to mirikizumab in LUCENT-1 and who achieved clinical response at week 12 of LUCENT-1, i.e. mirikizumab responders. In LUCENT-2, these patients (n= 581, LUCENT-2 CSR Table AMAG.8.1) were re-randomised (stratified by biologic-failed status, induction remission status, baseline corticosteroid use, and region) 2:1 to blinded subcutaneous mirikizumab 200mg maintenance treatment or blinded subcutaneous placebo every 4 weeks (weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, and 36). Patients were allowed to continue ongoing therapy with stable doses of protocol specified non-biologic treatments (CS Table 7). If patients experienced loss of response to either mirikizumab or placebo at or after week 12 of LUCENT-2, they received open-label IV mirikizumab 300mg treatment every 4 weeks for three doses and no subcutaneous injections. Loss of response was defined as:

- ≥2-point increase in the combined stool frequency and rectal bleeding subscores (relative to LUCENT-1 baseline)
- ≥4 points combined stool frequency and rectal bleeding subscores on 2 consecutive visits
- Confirmation of negative Clostridium difficile testing (from week 8)

And

- Confirmed by a centrally read endoscopic subscore of 2 or 3 from week 12 and no later than week 28 (CS Table 12).

Patients who, in the investigator's opinion, received clinical benefit (not further defined in the CS or CSR) from IV mirikizumab were considered for a longer-term extension study (LUCENT-3) but were discontinued from LUCENT-2. Patients who did not receive clinical benefit from IV mirikizumab discontinued study treatment and went into post-treatment follow up.

The three remaining treatment arms in LUCENT-2 were not assigned by randomisation. These were:

- Patients randomised to placebo in LUCENT-1 who achieved clinical response at week 12 of LUCENT-1, i.e. placebo responders. These patients received subcutaneous blinded placebo every 4 weeks in LUCENT-2. Loss of response and subsequent procedures were the same as those defined for those patients in the primary study population.
- Patients randomised to mirikizumab in LUCENT-1 who did not achieve clinical response at week 12 of LUCENT 1, i.e. mirikizumab non-responders. These patients received open-label extended induction therapy, i.e. IV mirikizumab 300 mg every at Weeks 0, 4 and 8 of LUCENT-2. At Week 12, these patients were assessed for clinical response, i.e. delayed clinical response. Patients who achieved delayed clinical response, as compared with LUCENT-1 baseline, received open-label subcutaneous mirikizumab 200 mg every four weeks from Week 12. Patients who did not achieve delayed clinical response discontinued the study.
- Patients randomised to placebo in LUCENT-1 who did not achieve clinical response at week 12 of LUCENT-1, i.e. placebo non-responders. These followed the same procedures in LUCENT-2 as for mirikizumab non-responders, described above.

The primary outcome of LUCENT-2 was the proportion of patients in the primary study population who achieved clinical remission at week 40, using the modified Mayo score. Major secondary outcomes are listed in CS Table 7 with additional secondary outcomes detailed in CS Appendix N and in the CSR.

Inferential statistics were only carried out for the primary study population (CS section B.3.4.1). As in LUCENT-1, due to the issue with eCOA devices described in section 4.2.1, primary efficacy analyses were based on the modified intention-to-treat population and

included patients who were deemed as mirikizumab induction responders (n=544). Safety analyses were performed for this “mirikizumab induction responders” subset of the overall safety population (n=581).” Baseline characteristics, shown in CS Tables 10 and 11, were balanced between the two arms of the primary study population. A summary of the statistical analyses undertaken for LUCENT-2 is provided in CS Table 15. A statistical significance level of 0.05 was used for all primary and major secondary endpoints.

4.3 Key results from pivotal studies of mirikizumab

Key results for LUCENT-1 and LUCENT-2 are presented individually in sections 4.3.1 and 4.3.2 below. Caution is required in the interpretation of subgroup results given that neither trial was powered to demonstrate statistically significant treatment differences according to subgroups (LUCENT-1 CSR section 5.1.2 and LUCENT-2 CSR section 5.1.2). Although we note that the LUCENT-2 trial protocol states an expected 80% power to assess clinical remission among biologic-failed participants who were induction remitters (LUCENT-2 protocol, page 15).

4.3.1 LUCENT-1 trial results

4.3.1.1 Primary outcome - Proportion of patients in clinical remission at week 12

A statistically significant greater percentage of patients achieved clinical remission at week 12 (defined using the modified Mayo score), in the mirikizumab group compared to the placebo group (24.2% versus 13.3%, p=0.00006). A statistically significant difference in favour of mirikizumab versus placebo was also seen in the biologic-naïve subgroup (30.9% versus 15.8%, p= <0.001) but not in the biologic-failed subgroup (15.2% versus 8.5%, p=0.065; CS.B.3.6.1.1).

4.3.1.2 Key secondary outcomes

Results using the alternative definition of clinical remission at week 12 were consistent with those of the primary outcome (CS B.3.6.1.2).

For the following efficacy outcomes there was [redacted] for the whole trial population, and for both the biologic-naïve and biologic-failed subgroups:

- Clinical response at week 12 (CS B.3.6.1.3)
- Endoscopic remission at week 12 (CS B.3.6.1.4)
- Symptomatic remission at week 12 (CS B.3.6.1.5)
- Bowel urgency numeric rating scale improvement at week 12 (CS B.3.6.1.6)

- Histologic-endoscopic mucosal improvement at week 12 (CS B.3.6.1.7)

The health-related quality of life outcomes of the European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) total score at week 12 (CS Appendix M.1) and the Inflammatory Bowel Disease Questionnaire (IBDQ) total score change from baseline at week 12 (CS Appendix M.2) were reported for the whole trial population only. Both were statistically significantly in favour of mirikizumab versus placebo.

Data on adverse events in LUCENT-1 were presented in CS Appendix F and in the CSR. Overall, the safety and tolerability of mirikizumab appeared similar to or better than placebo:

- Treatment-emergent adverse events were similar between the two treatment groups (44.5% in the mirikizumab group versus 46.1% in the placebo group). However, the proportion of severe adverse events was approximately three times greater in the placebo group compared to mirikizumab (7.2% versus 2.2%)
- There were no deaths in the 12-week induction period of LUCENT-1. However, two patients randomised to mirikizumab died during the 16 week follow up period. Both deaths (sudden cardiac death and disseminated intravascular coagulation) were considered unrelated to study drug or protocol procedures (LUCENT-1 CSR section 5.2.3).
- Serious adverse events in the placebo group were nearly double that of the mirikizumab group (5.3% versus 2.8%). Ulcerative colitis, pneumonia and cytomegalovirus colitis were the only serious adverse events to occur in more than one patient.
- The proportion of patients discontinuing due to adverse events was over four times greater in the placebo group compared to the mirikizumab group (7.2% versus 1.6%). The most common adverse event leading to discontinuation in both groups was ulcerative colitis (5.9% in the placebo group versus 0.5% in the mirikizumab group), the second most common adverse event leading to discontinuation was infusion-related hypersensitivity reaction in the mirikizumab group (0.3% versus none in the placebo group).

4.3.2 LUCENT-2 trial results

4.3.2.1 Primary population study

The following results relate to the primary study population only of LUCENT-2; that is, patients who were mirikizumab responders at week 12 of LUCENT-1 and were subsequently re-randomised to mirikizumab or placebo in LUCENT-2.

4.3.2.1.1 Primary outcome – clinical remission

A statistically significant greater percentage of patients achieved clinical remission at week 40 (defined using the modified Mayo score), in the mirikizumab group compared to the placebo group (49.9% versus 25.1% of patients, p<0.001). [redacted] was also seen in both the biologic-naïve subgroup (51.5% versus 30.7% of patients, p<0.001) and in the biologic-failed subgroup (46.1% versus 15.6% of patients, p<0.001; CS B.6.2.1).

4.3.2.1.2 Key secondary outcomes

Results using the alternative definition of clinical remission at week 12 were consistent with the primary outcome (CS B.3.6.2.2). [redacted] in both the primary study population and in the biologic-failed subgroup only (CS B.3.6.2.3).

For the following efficacy outcomes there was [redacted] for the primary study population, and for both the biologic-naïve and biologic-failed subgroups:

- Endoscopic remission at Week 40 (CS B.3.6.2.4)
- Corticosteroid-free remission without surgery at Week 40 (CS B.3.6.2.5)
- Histologic-endoscopic mucosal remission rates at Week 40 (CS B.3.6.2.6)
- Bowel urgency numeric rating scale improvement at Week 40 (CS B.3.6.2.7)
- Bowel urgency remission at Week 40 among clinical responders with urgency numeric rating scale ≥3 at induction baseline (CS B.3.6.2.8)

Data for symptomatic remission were reported for the primary study population only (CS Appendix N.3). There were statistically significant differences in favour of mirikizumab versus placebo for symptomatic remission rates at week 40 and stable maintenance of symptomatic remission at Week 40.

During the 40-week randomised phase of LUCENT-2 (CS Appendix N.6):

- [redacted] patients in the placebo group and [redacted] patients in the mirikizumab group had UC-related hospitalisation.
- [redacted] underwent UC-related surgery

The health-related quality of life outcomes of EQ-5D-5L total score at week 40 (CS Appendix N.1) and IBDQ total score change from baseline at week 40 (CS Appendix N.2) were reported for the primary study population only. Both were statistically significantly in favour of mirikizumab versus placebo.

Data on adverse events in LUCENT-2 were presented in CS section B.3.10 and in the CSR. Overall, the safety and tolerability of mirikizumab appeared similar or better than placebo:

- The proportion of patients who experienced a treatment-emergent adverse event (TEAE) was similar between the two treatment groups as was the proportion who experienced severe adverse events (CS Table 31). Nasopharyngitis was the most frequently reported TEAE in the mirikizumab group (7.2% compared with 5.7% in the placebo group), while ulcerative colitis was the most frequent event in the placebo group (20.8% versus 6.7% in the mirikizumab group).
- There was one death, in the placebo group, during LUCENT-2.
- Serious adverse events in the placebo group were more than double that of the mirikizumab group (7.8% versus 3.3%), with ulcerative colitis the most frequent event in the placebo group (3.1% versus 0% in the mirikizumab group). (CS Table 33)
- The proportion of patients discontinuing due to adverse events was over five times greater in the placebo group compared to the mirikizumab group (8.3% versus 1.5%, respectively), with ulcerative colitis the most frequent event in both groups.

However, the EAG note that in the mirikizumab group four patients experienced depression and one patient experienced “depression suicidal”, which were adverse events of special interest. No patients in the placebo arm experienced such events (CS Tables 33 and 35). Our clinical expert noted that depression is more frequent in people with IBD and is probably associated with disease activity. They were unaware of depression as an adverse event of other treatments of UC, therefore the occurrence of these events in the mirikizumab arm only of LUCENT-2 were of potential concern.

4.3.2.2 Placebo or mirikizumab non-responders in LUCENT-1

In patients who were placebo or mirikizumab non-responders in LUCENT-1 and subsequently received three initial doses of 300 mg, open-label IV mirikizumab therapy in LUCENT-2 (CS B.3.6.2.10):

- [redacted] of patients previously treated with placebo in LUCENT-1 achieved clinical remission versus [redacted] previously treated with mirikizumab
- [redacted] of patients treated with placebo in LUCENT-1 achieved a clinical response versus [redacted] of patients previously treated with mirikizumab

- [redacted]% of patients treated with placebo in LUCENT-1 achieved endoscopic remission versus [redacted]% of patients previously treated with mirikizumab.

4.4 Critique of the company's risk of bias assessment of the pivotal studies of mirikizumab

The company assessed the LUCENT studies for risk of bias with results reported in Appendix D.3.5 of the CS. The EAG agree with the company's assessment and is not concerned with the risk of bias of either study. (The EAG's full risk of bias assessment is available in Appendix 2.)

4.5 Critique of the network meta-analyses (NMAs) submitted by the company

The company carried out NMAs to compare the efficacy and safety of mirikizumab with a wide range of approved targeted therapies for UC, including ustekinumab and vedolizumab, as well as emerging therapies (see CS Appendix D, Table 19). They carried out the NMA due to an absence of RCTs directly comparing mirikizumab with comparators (CS section B.3.9). The company stated they conducted a wide NMA, comparing mirikizumab with comparators other than just ustekinumab and vedolizumab, for "completeness" (CS section B.3.9); the EAG has found no other justification in the CS for the wide network. The EAG suggests that such a broad network may introduce greater heterogeneity.

The outcomes of main interest in the NMA were clinical response and remission (both in the induction and maintenance phases of treatment), for the reasons described in CS section B.3.9.2.4. The NMA additionally focused on mucosal healing (also both during the induction and maintenance periods) for the reasons outlined in CS section B.3.9.2.4. The safety outcomes of all cause discontinuation during induction and serious adverse events during the induction phase only were also analysed; see CS section B.3.9.2.4 for the company's reason for only analysing AEs in the induction period.

Separate clinical efficacy analyses were conducted in the NMA for the biologic-naïve and biologic-failed subgroups. In the NMA, the biologic-naïve group was defined as "*patients who had not received any prior biologic, including a JAKi*" (CS section B.3.9.3.1). The biologic-failed group was defined as "*patients who had failed previous biologic therapy, including with a JAKi*" (CS section B.3.9.3.1). This is in line with definition of the biologic-failed subgroup used in the LUCENT trials and in line with where the company is partly positioning mirikizumab treatment in their decision problem (see CS section B.1.1). The NMA subgroup

definitions also broadly match the subgroups specified to be of interest in the NICE scope. Safety analyses were conducted for the total trial populations.

4.5.1 How the NMA results are used in the company's cost-comparison model

The company used the following efficacy parameters derived from the NMA results in their cost-comparison model (see CS sections B.4.2.1.4 and sections B.4.2.1.5 and section 5.3.1 of this report):

- the distributions of the response status (response, including remission) at the end of the induction period, and,
- loss of response estimates, calculated from the NMA maintenance phase clinical response results, to model treatment discontinuation during maintenance treatment.

4.5.2 Identification and selection of studies included in the NMA

A systematic literature review was carried out to identify relevant RCTs to include in the NMA (CS B.3.9.1). The methodology of the review is detailed in CS Appendix D. Reflecting the broad scope of the review, the study eligibility criteria were wide (CS Appendix D, Table 19) and included a range of approved targeted therapies (including all eight comparators listed in the NICE scope) and emerging therapies for UC, which could be either the intervention or comparator drugs in the screened studies. These drugs could either be used alone or in combination with conventional drugs (as shown in the company's inclusion criteria in: CS Appendix D, Table 19; Table 3 in the NMA report appendices accompanying the CS;[17] and, CS Addendum, Appendix 1.3, Table 3). Clinical expert advice to the EAG is that the use of concomitant medications in clinical practice depends on the drug. Patients might receive a steroid alongside vedolizumab and ustekinumab until a drug effect is observed. Adalimumab and infliximab are usually used in combination with thiopurine/methotrexate. Tofacinib, ozanimod and filgotinib tend to be used alone.

The stated population in the study eligibility criteria for the NMA was "*adult patients (≥18 years) with moderate to severe UC*" (CS Appendix D, Table 19). The population was not limited to those who were intolerant of, or whose disease has had an inadequate response, or loss of response to previous biologic or conventional therapy, as specified by the NICE scope. Therefore, the NMA population does not fully reflect the population of interest in this appraisal (the implications of this are discussed in our summary of our critique of the company's NMA presented in section 4.5.6 below). The company do not explain why the inclusion criteria population differs to the population specified in the NICE scope. The company state that separate clinical efficacy analyses were conducted in the NMA for the

biologic-naïve and biologic-failed subgroups (CS section B.3.9; also see section 4.5.4.2 below).

Overall, the EAG has no other concerns with how the systematic literature review was carried out, but we note that the review searches were last updated in June 2022 (CS section B.3.9.1). This means that there is a risk that there may be recently published, relevant studies available that have not been included.

4.5.3 Studies included in the NMAs and the company's feasibility assessment of the studies

A total of 71 RCTs were included in the company's systematic literature review, including the mirikizumab phase III LUCENT trials (see CS section B.3.91 and CS Appendix D, section D.1.4.1 for details). The company included the 71 RCTs in an NMA feasibility assessment before the NMAs were conducted, to assess if any important heterogeneity in the study populations, interventions, outcomes and methodology was present (CS section B.3.9.2). At this stage, the company included only studies that used European Medicines Agency (EMA) and FDA approved dosing regimens in the NMA (CS section B.3.9.2.3) (thus effectively applying another inclusion criteria to the review by excluding studies that did not use the approved regimens). We note that EMA and FDA approved doses for ustekinumab and vedolizumab are the same for induction treatment, but there are some differences in the recommended dosing regimens for these two drugs in the maintenance treatment period, as shown in CS Appendix D, Table 27, and as highlighted in bold in Table 1 here. We note, however, that the FDA approved maintenance doses match part of the maintenance doses clinicians can opt to use as outlined by the EMA (see Table 1), so it appears to be appropriate to include data from studies using the FDA approved doses. Different dosing regimens of the same drug were used as separate comparators in the NMA (CS section B.3.9.2.3 and CS Appendix D, Table 33) and this also appears appropriate.

Table 1 Comparison of EMA and FDA approved dosing regimens for ustekinumab and vedolizumab

Drug	EMA approved dose and regimen		FDA approved dose and regimen	
	Induction	Maintenance	Induction	Maintenance
Ustekinumab	Approx. 6mg/ kg (260 mg (IV) or 390 mg (IV) or 520 mg (IV) based on weight, single dose	**90 mg (SC) Q12W** (or Q8W if needed)	260 mg (IV) or 390 mg (IV) or 520 mg (IV) based on weight single dose	90 mg (SC) Q8W from week 8

Vedolizumab	300 mg (IV) week 0, 2 and 6	300 mg (IV) Q8W **(or Q4W if needed)** **108 mg (SC) Q2W**	300 mg (IV) week 0, 2 and 6	300 mg (IV) Q8W

Source: this is a shorted, reproduced version of CS Appendix D, section D.1.6.1, Table 27. Bold text shows where the EMA approved maintenance dosing regimen differs to that specified by the FDA. EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; Q2W, once every two weeks; Q4W, once every four weeks; Q8W, once every eight weeks; Q12W, once every 12 weeks; SC, subcutaneous.

After the feasibility assessment, 34 studies were excluded from the NMA (CS section B.9.2.5) and the exclusions appear appropriate based on the reasons supplied by the company (CS Appendix D, Table 26). Of the 71 originally identified studies, 28 assessed an EMA or FDA approved UC treatment in the induction period and 21 assessed an EMA or FDA approved treatment in the maintenance period (CS section B.3.9.2.2). When the LUCENT trials were added to these numbers (mirikizumab is currently undergoing regulatory consideration; CS Table 2), along with the included PUSUIT SC study being split into two separate studies, there were 30 induction and 22 maintenance studies considered for the NMAs.

4.5.4 Clinical heterogeneity assessment

As with the NMA conducted for the ustekinumab NICE appraisal (TA633),[18] we and the company have identified a number of sources of potential heterogeneity across the studies included in the NMA, as we detail below (sections 4.5.4.1 to 4.5.4.4). The company discusses heterogeneity in CS section B.3.9.2 and CS Appendix D, section D.1.6.1.

4.5.4.1 Treat-through and re-randomised responder trials

As detailed in CS Appendix D, section D.1.6.1, the studies included in the maintenance treatment phase NMAs were of either a 'treat-through' or 're-randomised responder' design. The differences between these two types of trial designs are described in CS Appendix D, section D.1.6.1, and so are not repeated here for brevity. Nine of the maintenance studies were of a treat-through design, while 13 were re-randomised studies. As pointed out in CS Appendix D, section D.1.6.1, participants entering the maintenance phases therefore differ from each other in each of these trial designs in terms of their exposure to the study drug. Those who have received active treatment during induction who are re-randomised to placebo may show a better response during maintenance than those who have remained on placebo in the treat-through trials. To account for this source of heterogeneity (e.g. in patients' potential level of response to treatment), statistical adjustments were carried out to make the populations more comparable (CS Appendix D, section D.1.6.1) – see section

4.5.5.1 below for the EAG's explanation and critique of this. The company carried out a sensitivity analysis of clinical response and remission in the maintenance phase in which studies with a treat-through design were excluded (CS Appendix D.1.6.3).

4.5.4.2 Subgroup definitions

There was some heterogeneity between studies in how the groups of patients from which the company used data to inform their 'biologic-naïve' and 'biologic-failed' subgroup analyses in the NMA were defined (see CS Addendum, Appendix 1.5, Table 8). The EAG, however, has no concerns about this.

4.5.4.3 Outcome definitions

There was heterogeneity across the studies included in the NMA in how clinical response and remission were defined, as we outline below. It should be noted that the outcome of response encompasses patients in clinical remission.

4.5.4.3.1 Clinical response in the induction and maintenance phases

Five different definitions of clinical response in the induction and maintenance phases were used across the studies included in the NMA, where definitions were reported (see CS Appendix D, section D.1.6.1, Tables 28 and 29). We note that 22 studies in the NMA used the same definition as used in the GEMINI I and UNIFI pivotal trials of vedolizumab and ustekinumab, respectively (see Table 2 below for definitions) in the induction phase and 10 studies used this definition in the maintenance phase. The definition in the LUCENT trials in the maintenance and induction phases differs to this, as is also shown in Table 2 and as is detailed in CS Appendix D, section D.1.6.1. The LUCENT-1 trial is the only study included in the NMA that uses this definition in the induction phase NMA and the LUCENT-2 trial is one of only two studies that uses this definition in the maintenance phase NMA (as assumed by the EAG from information provided in CS Appendix D, section D.1.6.1, Tables 28 and 29). The clinical expert advising the EAG confirmed the definition of clinical response used in the LUCENT trials is not used in clinical practice *per se*, but is appropriate and reflects FDA guidance. The expert also felt the differences in the definitions used by the GEMINI I and UNIFI trials (and thus the majority of the other studies in the NMA) and the LUCENT trials were unlikely to be important, as the differing elements would make little difference to whether or not a patient would be classed as having responded or not.

4.5.4.3.2 Clinical remission in the induction and maintenance phases

Similarly to the discussion above about the definition of clinical response, the majority of the studies included in the NMA used the same definition of clinical remission in the induction (n = 17) and maintenance (n = 15) phases as used in the ustekinumab and vedolizumab pivotal trials (see Table 2 below for the definition used in these studies, and see CS Appendix D, section D.1.6.1, Tables 30 and 31, for the definitions used in the studies included in the NMA). The LUCENT trials, however, used a different definition, and so did the remaining NMA studies (where the definition was reported). Again, the clinical expert advising the EAG confirmed the definition used in the LUCENT trials does not reflect clinical practice as such, but is appropriate and in line with FDA guidance, and that missing elements from the definition would not impact on whether or not patients would be classed as being in clinical remission.

Table 2 Definitions of clinical response and clinical remission used in the mirikizumab, vedolizumab and ustekinumab pivotal clinical trials

Trials (intervention)	Definition of clinical response	Definition of clinical remission
LUCENT-1 and -2 trials (mirikizumab)	• ≥2-point and ≥30% decrease in the modified Mayo score from baseline • Rectal bleeding subscore = 0 or 1, or ≥1 point decrease from baseline	Definition 1: • Stool frequency subscore = 0 or 1, with ≥1-point decrease from baseline • Rectal bleeding subscore = 0 • Endoscopic subscore = 0 or 1 (excluding friability) Definition 2: RBS of 0, stool frequency score ≤1 and decrease from baseline ≥1, and endoscopy subscore ≤1 (excluding friability)
GEMINI I (vedolizumab) and UNIFI (ustekinumab) trials	Reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point	Complete Mayo score of ≤ 2 points and no individual subscore > 1 point.

Source: the LUCENT-1 and -2 trials' outcome definitions are reproduced from CS Table 12. The GEMINI and UNIFI trials' outcome definitions were sourced from the company submissions to NICE in the associated NICE appraisals.[2,4]

4.5.4.4 Other sources of heterogeneity

In Table 3 below, we outline some of the other potential sources of heterogeneity in the company's NMAs. In addition to these, we note, as was highlighted by the EAG in the filgotinib NICE appraisal (TA792) and as discussed at the NICE Committee meeting for that appraisal,[7] that due to including trial designs in the NMA in which participants have been re-randomised, there is heterogeneity in the maintenance networks in the treatments patients in the common comparator placebo arms received during induction and their response to those treatments. For example, those who were re-randomised to placebo after responding to mirikizumab or other comparator drugs during the induction phase will be included in the placebo comparator of the NMA. There is therefore heterogeneity between the participants based on how they responded to treatment in the induction phase.

4.5.4.5 Risk of bias assessment for studies included in the NMA

The company assessed the risk of bias associated with studies included in the NMA using the Centre for Reviews and Dissemination (CRD)'s[19] quality assessment checklist for RCTs and presents their judgements on each of the CRD checklist domains in CS Appendix D, section D.3, Table 46. The company's critical appraisal of the LUCENT trials is available in CS section B.3.5, and the EAG and the company's assessments are summarised in section 4.4 of this report. The company does not provide an overall conclusion about the risk of bias associated with the NMA studies. Based on the company's judgements, the EAG notes the studies were generally rated to be of a low risk of bias across most of the risk of bias domains assessed, but with most of the studies having one or more unclear or high risk of bias judgements on some of the domains.

Table 3 Other potential sources of heterogeneity in the company's NMA

Study aspect	Heterogeneity across studies	EAG comments
Induction timepoint of assessment	Varied from 6 to 14 weeks (CS Appendix D, section D.1.5)	The EAG suggests that studies with a shorter assessment timepoint in the induction period may be at risk of not identifying patient clinical response or remission that may have occurred at later timepoints.
Maintenance phase assessment timepoint	Ranged from 30 to 60 weeks. To address this the company restricted inclusion of studies in the maintenance NMAs to those with assessment points between 52 and 60 weeks (CS Appendix D, section D.1.6.1).	The EAG considers this reasonable. The EAG report for the ustekinumab NICE appraisal[18] notes that inclusion of studies with a shorter maintenance assessment timepoint may bias results in favour of the treatment (e.g. there may be less loss of response than if the outcome had been measured at a later timepoint). [redacted]
Baseline risk adjustment (i.e. placebo response rate)	Please see discussion in CS Appendix D, section D.1.6.2 about this. The Company addressed potential heterogeneity through carrying out baseline risk adjustment NMAs, using an exploratory analysis utilising meta-regression to adjust for baseline risk. The results of the adjusted and unadjusted NMAs were compared and the adjusted or unadjusted results were chosen for use in the CS based on goodness-of-fit statistics and covariate coefficient statistics (CS Appendix D, section D.1.6.2).	As we critique further in section 4.5.5.2 below, the company has used placebo-arm data from all included RCTs and has not used representative UK-specific data as is recommended in the NICE Decision Support Unit (DSU) Technical Support Document 5.[1]

Source: The information in this table was synthesised from CS Appendix D, sections D.1.5 D.1.6.1 and D.1.6.2 by the EAG. CS, company submission; EAG, External Assessment Group; NMA, network meta-analysis; UC, ulcerative colitis.

4.5.5 Critique of the NMA modelling approach and statistical procedures

4.5.5.1 Data inputs to the NMA

The company report the data inputs from RCTs included in the NMA for each outcome analyses (CS Appendix sections D.1.10.1, D.1.10.2 and D.1.10.3). As with similar TAs in UC, relevant trials include treat-through RCTs and re-randomised RCTs (as described above in section 4.5.4.1). This difference in study design only impacts on the analysis of outcomes in the maintenance phase. To deal with these differences, the company have taken a similar approach to that reported in previous TAs, in particular TA792[7] (filgotinib). Raw data are calculated for the treat-through RCTs to reflect the results that would have been seen had these been re-randomised RCTs (CS Appendix D.1.7.7). The company assume that 1) the total number of responders at the end of the induction phase in the treat-through RCTs is a proxy for the total number of patients entering the maintenance phase, 2) the number of patients with a durable or sustained response at maintenance from the treat-through RCTs can be used to estimate the number of patients with a response at the end of the maintenance phase, and 3) the proportion of patients in remission at the end of the maintenance phase in the treat-through RCTs is a proxy for the number of those with a response in remission. Where such data are not reported in the relevant treat-through RCTs, the company make assumptions to enable estimation. As LUCENT-1 and LUCENT-2 are re-randomised RCTs, no adjustments are made to their results. The four RCTs affected are ACT1 for infliximab, Suzuki 2014 and ULTRA 2 for adalimumab, and VARSITY which compared adalimumab with vedolizumab (CS Appendix D Table 37 and Table 42). There are two points to note in the company's calculations. The first relates to the number of remitters in the placebo arm of ACT1 for the biologic-naïve population. The company use a weighted average of the percentage of responders who were remitters across all placebo arms of the re-randomised trial, which is appropriate in the circumstances. However, we could not replicate the weighted average in the original CS (57.7%; CS Appendix D, Table 37) unless we assumed that 100% of responders were remitters in TRUE NORTH and VISIBLE1, and then a weighted average of 57.8% was obtained. For TRUE NORTH and VISIBLE1, the number of responders without remission in the placebo arm is not reported, and the company do not state how they dealt with this when estimating the weighted average for ACT1, e.g. whether or not they assumed 100% were remitters or excluded these RCTs from the calculations. In the CS Addendum the number of responders without remission is reported for TRUE NORTH (CS Addendum Table 16) and the weighted average reported, and applied, is 78.7% (CS Addendum Table 17), yet the EAG could not replicate this figure regardless of whether it is assumed that all responders were remitters in VISIBLE1 or data from VISIBLE1 are excluded from calculations. The second point relates to

the placebo arm of ULTRA2. For the biologic-naïve subgroup there is a difference in the raw data calculated by the company compared to that reported by Lu et al 2022[20] (a publication based on TA792). However, the company have followed their own described approach, which the EAG agree with. As stated in section 4.5.4.1 above, for clinical response and remission in the maintenance phase, the company undertook sensitivity analyses which excluded all treat-through study designs.

4.5.5.2 Statistical methods for the NMA

The company used a Bayesian framework, implemented in Stan,[21] for their NMAs (CS Appendix section D.1.7.2). The statistical models chosen followed recommendations made in NICE DSU TSD 2:[22] a multinomial model with probit link function to estimate clinical response and remission (accounting for correlation between these outcomes); and a binomial model with logit link to estimate mucosal healing (CS Appendix section D.1.7.4). The company undertook fixed and random effects modelling, assessed the impact of assuming different prior distributions on the between-trial heterogeneity parameter in the random effects models (CS Appendix section D.1.7.3), and explored the use of meta-regression to adjust for different levels of baseline risk across studies, as recommended in TSD 3[23] (CS Appendix section D.1.7.4). The statistical models chosen for the different outcomes were appropriate, and addressed limitations noted in previous TAs on this topic.

To model the baseline effect, the company incorporated placebo-arm data from all included RCTs rather than using representative UK-specific data as is recommended in TSD 5.[1] In related TAs, reporting of the data used to inform the baseline effects does not appear to be stated explicitly (e.g. TA792 and TA633). This could suggest that the same approach was taken, as there is no statement of other UK-relevant data being used instead. In TA828[6] (ozanimod), the company used placebo-arm data from all RCTs, and the EAG conducted an additional analysis limiting the placebo-arm data to RCTs that were deemed to be more generalisable to the UK. The EAG reported that this led to lower response rates observed in the placebo arms, and in many of the active treatment arms. It is not clear how the results for mirikizumab would change had the baseline effects been more representative of the UK. We therefore highlight this as an additional source of uncertainty in the NMA results.

Methods reported by the company for assessing model convergence (CS Appendix section D.1.7.6) are appropriate. Homogeneity was assessed by noting the value of tau (as recommended in TSD3[23]), and where there were closed loops in the network, consistency was assessed and reported (as recommended in TSD 4[24]), CS Appendix section D.1.7.8.

The company summarise the posterior distributions from the NMA using the mean and 95% credible intervals (CS section B.3.9.4, CS Appendix sections D.1.10.1, D.1.10.2 and D.1.10.3). When the posterior distribution is asymmetric, reporting the median is preferred. It is unclear whether the posterior distributions from the company NMAs are asymmetric, so whether different estimates would be seen had the medians been reported instead of the means. Given that the credible intervals would remain the same, and treatment rankings, which are reported for the different outcomes and population subgroups, also contribute to an assessment of whether mirikizumab can be considered to have similar, or greater, effectiveness than ustekinumab and vedolizumab, it is unlikely that reporting of posterior medians would have led to different conclusions.

4.5.5.3 Choice between NMA models

The company conduct fixed effects and random effects models with and without adjustment for baseline risk (CS Appendix sections D.1.7.3 and D.1.7.4). To help choose between fixed or random effects models for each outcome and population subgroup (biologic-naïve or biologic-failure), the company report using goodness-of-fit statistics, in particular the deviance information criteria (DIC), and also refer to the magnitude of heterogeneity within the network. In deciding whether the base case model should include adjustment for baseline risk or not, the company consider goodness of fit and evidence on whether differences in baseline risk are observed. Thus, the base case models are not the same across each outcome and population subgroup.

There is some inconsistency in justification of whether a fixed effects or random effects model is the most appropriate. For instance, for induction of clinical response and remission in a biologic-naïve population and for serious adverse events in induction, the DIC is lowest for the fixed effects model (indicating a better fitting model), however a random effects model is preferred by the company due to the heterogeneity observed across the network. In other analyses (sensitivity analyses for maintenance of clinical response and remission in the biologic-naïve population and all cause discontinuation, although the DIC indicates the random effects model would be preferred, and there is evidence of a great deal of heterogeneity across the network, a fixed effects model is chosen by the company. The company justify the choice of fixed effects over random effects models for all cause discontinuation on the basis of "*parsimony and the uncertain estimates provided by the random effects model*" (CS Addendum Section 5.3.3.1). Although not explicitly stated by the company, it is assumed that their argument follows that these very wide credible intervals

lead to NMA results that have limited usefulness in determining the comparative effectiveness of treatments. Given limitations in available data when a network is sparse (as in these cases), use of vague prior distributions can lead to estimates of heterogeneity that are unrealistically high (TSD3[23]). The use of more informative prior distributions for the between-trial parameters has been recommended, however the EAG believes that use of the fixed effects model in the company's submission is reasonable, especially given the small difference in DIC values between models in the Company NMA (≤3); any difference in DIC values between models of <5 is not considered to be important (TSD 3[23]). The EAG note that fixed effects NMA models were deemed appropriate in similar analyses for ustekinumab (TA633[2]) and filgotinib (TA792[7]).

Where results of baseline risk adjusted models indicate evidence of differences in baseline risk across trials, the company have chosen to report results from these adjusted models. The EAG agrees with this approach. However, for mucosal healing in the maintenance period for the biologic-naïve population a baseline risk adjusted model is preferred by the company when the DIC suggests an unadjusted model is a better fit and there is no evidence from the meta-regression that this coefficient should be included. No appropriate justification is given by the company for this decision.

Comparison of results from the base case NMA models chosen by the company, with results from models with the lowest DIC tends to show a slightly more favourable finding from the company chosen models, in terms of the magnitude of the mean of the posterior distribution for mirikizumab. As expected, where a fixed effects model is chosen over a random effects model, the credible intervals are generally much narrower. However, the overall conclusions across the outcomes and populations do not change depending on the model selected, except for the outcome of all cause discontinuation: results from the fixed effects model (the company preferred model) are more favourable to mirikizumab compared to placebo (OR [redacted]) than results from the random effects model (OR [redacted]) due the narrower 95% credible intervals.

4.5.6 Summary of EAG critique of the NMA

- Overall, the EAG does not have any major concerns about the studies selected for inclusion in the NMA, but we note the following:
    - The range of treatments that studies could examine to be included in the NMA was broad. As with other appraisals of treatments for moderately to severely active UC,[18,25] many sources of heterogeneity across the included

studies were identified. As there is no justification for analysing such a broad network (other than for completeness), a smaller network may have resulted in less heterogeneity observed in the network. Reduced heterogeneity could provide more confidence in the NMA results through providing more precise credible intervals.

- The NMA study eligibility criteria did not limit inclusion of studies to only people with moderately to severely active UC *who were intolerant of, or whose disease has had an inadequate response, or loss of response to previous biologic therapy or conventional therapy*, as per the population of interest specified in the NICE scope. This does not affect the interpretation of the results for the biologic-failed subgroup, as the studies that contributed data to these subgroup analyses included various populations of people who had had an inadequate response, loss of response, or intolerance to TNF antagonists, biologic therapy or specified biologics, or treatment failure on TNF or biologic. It does mean, however, that the biologic-naïve subgroup analyses do not fully reflect the population of interest in the NICE scope. This is because the studies contributing evidence to these analyses included people who had mainly just not previously received a TNF inhibitor therapy or biologic (CS Addendum, Appendix 1.5, Table 8) (i.e. they were not intolerant of, or had had an inadequate response to or loss of response to conventional therapy).
- The searches for the systematic literature review informing the network meta-analysis were performed over six months ago and there is a risk that there may have been relevant studies published recently that will have been missed.

- Regarding how the NMA was conducted, the general approach to imputation of data used in NMA maintenance phase analyses from RCTs with a treat-through design was described as used in TA792[7] (filgotinib). However, there is an inconsistency in the weighted average applied to the placebo arm of ACT1 in the CS Addendum, and a difference in the raw data calculated from the company compared to that reported by Lu et 2022[20] (publication based on TA792[7]). The impact of these on the results for mirikizumab are likely to be minimal and the company conducted sensitivity analyses removing these 4 RCTs.
- The statistical models chosen for the different outcomes are appropriate and addressed limitations noted in previous TAs on this topic. Reporting of methods is generally clear.

- To model the baseline effect, the company incorporated placebo-arm data from all included RCTs rather than using representative UK-specific data as is recommended in TSD 5. The impact of this on the results is unclear.
- Justification for base case model choice was not consistent across the outcomes and subgroups. However, given limitations of a sparse network, the degree of heterogeneity observed and the small differences in estimates of model fit (DIC), the EAG believes the company's approach is reasonable

4.5.7 Results from the NMAs

Results of the NMA are presented below by treatment phase (induction phase, maintenance phase). Summaries of analyses, statistical models used and results, by subgroup (biologic-naïve, biologic-failed), are presented in Table 4 (induction phase) and Table 5 (maintenance phase), with statistically significant results highlighted in bold.

4.5.7.1 Induction phase

Results of the NMA for the induction phase are described below and presented in Table 4.

4.5.7.1.1 Clinical response – biologic-naïve and biologic-failed subgroups

For clinical response in the induction period, results of the biologic-naïve base case multinomial probit random effects model unadjusted for baseline risk show [redacted] (odds ratio (OR) [redacted]; Table 4; CS Addendum Figure 1). These findings are [redacted] (OR [redacted]; Table 4; CS Addendum Figure 7). For both the biologic-naïve subgroup and biologic-failed subgroup, [redacted] (Table 4; CS Addendum Figure 1 and 7). Exploratory analyses, which were adjusted for baseline risk, [redacted] (Table 4; CS Addendum, Appendix 3.1.1, Figure 114), but [redacted]; Table 4; CS Addendum, Appendix 3.1.2, Figure 124).

4.5.7.1.2 Clinical remission – biologic-naïve and biologic-failed subgroups

NMA results of clinical remission for the biologic-naïve subgroup and for the biologic-failed subgroup [redacted] respectively; Table 4; CS

Addendum Figure 2 and Figure 7), but [redacted]

(Table 4; CS Addendum Figure 2 and Figure 7). Results of exploratory analyses, i.e. with baseline risk adjustment, showed [redacted] (Table 4; CS Addendum, Appendix 3.1.1, Figure 115), but [redacted],Table 4; CS Addendum, Appendix 3.1.2, Figure 124).

4.5.7.1.3 Mucosal healing – biologic-naïve and biologic-failed subgroups

In both the biologic-naïve subgroup and biologic-failed subgroups, NMA results of mucosal healing show [redacted] respectively; Table 4; CS Addendum Figure 3 and Figure 8), but [redacted] (Table 4; CS Addendum Figure 3 and Figure 8).

4.5.7.1.4 All-cause discontinuation and serious adverse events – overall population

For the outcome of all cause discontinuation for the overall population (i.e. biologic-naïve and biologic-failed), [redacted]; Table 4; CS Addendum Figure 12), but [redacted]. However as we have previously noted (section 4.5.5.3 above) the company's results come from the fixed effect model whereas the model with the lowest DIC was the random effects model and this produced [redacted].

NMA results of serious adverse events for the overall population (i.e. biologic-naïve and biologic-failed), showed [redacted] (Table 4; CS Addendum Figure 13).

Table 4 Summary of NMA analyses and results for the induction phase

OUTCOME	ANALYSIS	STATISTICAL MODEL FEATURES		MIRI vs. PBO OR (95% CrI)	MIRI vs. VED OR (95% CrI)	MIRI vs. UST OR (95% CrI)
		FIXED/ RANDOM EFFECTS	BASELINE RISK ADJUSTMENT			
BIOLOGIC-NAÏVE INDUCTION PHASE						
Clinical response	Base case	Random[a]	No	[redacted]	[redacted]	[redacted]
	Exploratory	Random[a]	Yes	[redacted]	[redacted]	[redacted]
Clinical remission	Base case	Random[a]	No	[redacted]	[redacted]	[redacted]
	Exploratory	Random[a]	Yes	[redacted]	[redacted]	[redacted]
Mucosal healing	Base case	Random[b]	Yes	[redacted]	[redacted]	[redacted]
BIOLOGIC-FAILED INDUCTION PHASE						
Clinical response	Base case	Fixed[a]	No	[redacted]	[redacted]	[redacted]
	Exploratory	Fixed[a]	Yes	[redacted]	[redacted]	[redacted]
Clinical remission	Base case	Fixed[a]	No	[redacted]	[redacted]	[redacted]
	Exploratory	Fixed[a]	Yes	[redacted]	[redacted]	[redacted]
Mucosal healing	Base case	Fixed[b]	Yes	[redacted]	[redacted]	[redacted]
OVERALL/MIXED POPULATION INDUCTION PHASE						
All cause discontinuation	Base case	Fixed[b]		[redacted]	[redacted]	[redacted]
SAEs	Base case	Random[b]		[redacted]	[redacted]	[redacted]

[a] Multinomial model with ordered categories and probit link; [b] Binomial model with logit link
CrI: credible interval; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; SAEs: serious adverse events; UST: ustekinumab; VED: vedolizumab.
For efficacy outcomes OR > 1 is in favour of mirikizumab. For safety outcomes OR <1 is in favour of mirikizumab.
Bold text: an OR and 95% CrIs which show a statistically significant result in favour of mirikizumab
Source: CS Appendices Table 32; CS Addendum Figures 1, 2, 3, 7, 8, 12 and 13; CS Addendum section 2.3.1; CS Addendum, Appendix 3.1.1, Figures 114 and 115; CS Addendum, Appendix 3.1.2, Figure 124

4.5.7.2 Maintenance phase

Results of the NMA for the maintenance phase are described below and presented in Table 5.

4.5.7.2.1 Clinical response – biologic-naïve and biologic-failed subgroups

For clinical response in the maintenance phase, results of the biologic-naïve base case multinomial probit fixed effect model adjusted for baseline risk show [redacted]; Table 5; CS Addendum Figure 4) and [redacted]. However, there was [redacted]. Exploratory analyses, unadjusted for baseline risk, also show [redacted]; Table 5; CS Addendum, Appendix 3.2.1, Figure 133). There was however [redacted] (Table 5; CS Addendum, Appendix 3.2.1, Figure 133).

Results of the biologic-failed base case multinomial probit fixed effect model unadjusted for baseline risk, also show [redacted]; Table 5; CS Addendum Figure 9). There was however [redacted] (Table 5; CS Addendum Figure 9). Exploratory analyses adjusted for baseline risk showed [redacted] Table 5; CS Addendum, Appendix 3.3.1, Figure 145).

The company note that results for maintenance phase clinical response (and clinical remission) should be interpreted with caution due to the imputation of data to account for the differing RCT designs. The EAG agree with the company. Results of sensitivity analyses (including re-randomised RCTs only) show that in the biological-naïve subgroup for clinical response for mirikizumab versus placebo [redacted] (Table 5; CS Addendum Figure 4 and CS Addendum, Appendix 2.1.2.2, Figure 42). However, this difference is also likely to be affected by the fact that these results are from a different base case NMA model (the sensitivity analysis results are from a model not adjusted for baseline

risk, while the analysis including the imputed data are from a model where baseline risk is included). The company have not reported results for the sensitivity analysis using a model with adjustment for base line risk. In the biologic-failed subgroup for maintenance phase clinical response, [redacted]. The same model (not including baseline risk adjustment) is used in both analyses.

4.5.7.2.2 Clinical remission – biologic-naïve and biologic-failed subgroups

For clinical remission in the maintenance phase, results of the biologic-naïve base case multinomial probit fixed effect model adjusted for baseline risk show [redacted]; Table 5; CS Addendum Figure 5) and [redacted]. However, there was [redacted]. Exploratory analyses, which were unadjusted for baseline risk, [redacted] Table 5; CS Addendum, Appendix 3.2.1, Figure 134). Furthermore, there was [redacted] (Table 5; CS Addendum, Appendix 3.2.1, Figure 134).

Results of the biologic-failed base case multinomial probit fixed effect model unadjusted for baseline risk, also show [redacted]; Table 5; CS Addendum Figure 10). [redacted] (Table 5; CS Addendum Figure 10). [redacted] (Table 5; CS Addendum, Appendix 3.3.1, Figure 145)

As stated earlier, the above results for clinical remission in the maintenance phase should be interpreted with caution due to the imputation of data to account for the differing RCT designs. Results of sensitivity analyses (including re-randomised RCTs only) for remission in the maintenance phase [redacted]:

- in the biologic-naïve subgroup there are [redacted]

[redacted] (Table 5; CS Addendum Figure 5 and CS Addendum, Appendix 2.1.2.2, Figure 43).

- in the biologic-failed subgroup, results of sensitivity analysis for clinical remission are [redacted] (Table 5; CS Addendum, Appendix 2.2.2.2, Figure 86).

4.5.7.2.3 Mucosal healing – biologic-naïve and biologic-failed subgroups

In the biologic-naïve subgroup, NMA results of mucosal healing in the maintenance phase showed [redacted]; Table 5; CS Addendum Figure 6), but [redacted] (Table 5; CS Addendum Figure 6). In the biologic-failed subgroup, NMA results of mucosal healing showed [redacted] Table 5; CS Addendum Figure 11).

4.6 Summary

In the absence of a trial directly comparing mirikizumab against vedolizumab and ustekinumab, the evidence for the comparability of mirikizumab with these drugs comes from the company's NMA results and is based on the statistical significance of the results only. There are no data available in the CS to directly show whether mirikizumab may be statistically equivalent to or non-inferior to ustekinumab and vedolizumab (i.e. there are no data from equivalence or non-inferiority trials). Acknowledging this limitation as an area of uncertainty, the EAG observes that based on the results reported in the NMA, mirikizumab appears to result in [redacted] (CS Addendum Figures 1, 2, 7 and 12). There is evidence from the base case NMA that mirikizumab results in [redacted] (CS Addendum Figures 4 and 5). [redacted] (CS Addendum Figures 4, 5, 9 and 10).

Table 5 Summary of NMA analyses and results for the maintenance phase

OUTCOME	ANALYSIS	STATISTICAL MODEL FEATURES		MIRI vs. PBO OR (95% CrI)	MIRI vs. VED OR (95% CrI) (108mg Q2W; 300mg Q4W; 300mg Q8W)	MIRI vs. UST OR (95% CrI) (90mg Q8W; 90mg Q12W)
		FIXED/ RANDOM EFFECTS	BASELINE RISK ADJUSTMENT			
BIOLOGIC-NAÏVE MAINTENANCE PHASE						
Clinical response	Base case	Fixed[a]	Yes	[redacted]	[redacted]	[redacted]
	Sensitivity[b]	Fixed[a]	No	[redacted]	[redacted]	[redacted]
	Exploratory	Fixed[a]	No	[redacted]	[redacted]	[redacted]
Clinical remission	Base case	Fixed[a]	Yes	[redacted]	[redacted]	[redacted]
	Sensitivity[b]	Fixed[a]	No	[redacted]	[redacted]	[redacted]
	Exploratory	Fixed[a]	No	[redacted]	[redacted]	[redacted]
Mucosal healing	Base case	Fixed[c]	Yes	[redacted]	[redacted]	[redacted]
BIOLOGIC-FAILED MAINTENANCE PHASE						
Clinical response	Base case	Fixed[a]	No	[redacted]	[redacted]	[redacted]
	Sensitivity[b]	Fixed[a]	No	[redacted]	[redacted]	[redacted]
	Exploratory	Fixed[a]	Yes	[redacted]	[redacted]	[redacted]
Clinical remission	Base case	Fixed[a]	No	[redacted]	[redacted]	[redacted]
	Sensitivity[b]	Fixed[a]	No	[redacted]	[redacted]	[redacted]

OUTCOME	ANALYSIS	STATISTICAL MODEL FEATURES		MIRI vs. PBO OR (95% CrI)	MIRI vs. VED OR (95% CrI) (108mg Q2W; 300mg Q4W; 300mg Q8W)	MIRI vs. UST OR (95% CrI) (90mg Q8W; 90mg Q12W)
		FIXED/ RANDOM EFFECTS	BASELINE RISK ADJUSTMENT			
	Exploratory	Fixed[a]	Yes	[redacted]	[redacted]	[redacted]
Mucosal healing	Base case	Fixed[c]	No	[redacted]	[redacted]	[redacted]

[a] Multinomial model with ordered categories; [b] Re-randomised studies only sensitivity analysis; [c] Binomial model with logit link

CrI: credible interval; MIRI: mirikizumab; OR: odds ratio; PBO: placebo; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; UST: ustekinumab; VED: vedolizumab.

For efficacy outcomes OR > 1 is in favour of mirikizumab. For safety outcomes OR <1 is in favour of mirikizumab.

Bold text: an OR and 95% CrIs which show a statistically significant result in favour of mirikizumab

Source: CS Appendices Table 32; CS Addendum Figures 4, 5, 6, 9, 10 and 11; CS Addendum sections 2.1.2, 2.2.2, 5.3.1.3 and 5.3.2.3; CS Addendum, Appendix 2.1.2.2, Figures 42 and 43; CS Addendum, Appendix 2.2.2.2, Figures 86 and 87; CS Addendum, Appendix 3.2.1, Figures 133 and 134; CS Addendum, Appendix 3.3.1, Figures 145 and 146

5 Summary of the EAG's critique of the cost comparison evidence submitted

5.1 Introduction

The following sections critique:

i. the company's cost comparison evidence submitted on 8th December 2022 for this appraisal (henceforth, referred to as the 'original CS' and the 'original economic model')

ii. the new evidence, received on 15th February 2023, submitted as an addendum to the original CS and a revised economic model (henceforth, referred to as 'addendum to the CS' and 'revised economic model', respectively).

The company produced the addendum and the corresponding revised economic model to correct errors in the NMA in the original CS (as discussed earlier in Section 4.5). This amendment was in response to the EAG's correspondence with NICE, seeking further clarifications on the NMA inputs that informed the company's original economic model.

5.2 Decision Problem for the cost comparison

5.2.1 Population

The EAG has determined that the characteristics of the population used by the company in the cost-comparison analysis adequately reflects the indications in the NICE recommendations for the comparator drugs. The company's cost analyses modelled two patient cohorts with mean age of [redacted] years for biologic-naïve and [redacted] years for biologic-failed patients respectively (CS Table 39). These patient characteristics, based on the modified ITT populations of the LUCENT trials, are similar to those of the modelled cohort for the comparator appraisal TA633 (ustekinumab).[2]

5.2.2 Comparators

The analysis compares mirikizumab with ustekinumab and vedolizumab. As stated in section 3.3, the EAG consider that these comparators are appropriate for the cost-comparison analysis.

5.2.3 Cost-comparison model

The company describe their cost-comparison model in CS section B.4.2.1. The model structure is illustrated in CS Figures 29 and 30. We outline the model features and structure below.

Model features:

- Markov model with four components:
    - an induction period of up to 26 weeks comprising two-week tunnel states,
    - an on-treatment maintenance state,
    - an off-treatment state, and
    - a death state.
- Efficacy parameters (response rates) in the induction and maintenance phases are informed by the NMA results (discussed earlier in Section 4.5 of this report).
- Patients incur no costs in the off-treatment state.
- Time horizon: 10 years
- No discounting
- Perspective: National Health Service (NHS)/Personal Social Services (PSS)
- Cycle length: 2 weeks (induction phase); 12 weeks (maintenance phase)

Model structure:

Induction phase:

- Variable and treatment-specific lengths of induction periods for the treatments, varying between 2-12 weeks depending on the drug, and up to 12 additional weeks for delayed responders. For the mirikizumab arm, the induction phase is 12 weeks for the base case and a scenario was conducted to include an extended induction phase for delayed responders up to 12 weeks.
- All non-responders at the end of the induction period either enter the no-treatment state or continue to be treated for an additional 8 weeks on ustekinumab (16 weeks total induction), an additional 4 weeks on vedolizumab (10 weeks total treatment) or an additional 12 weeks on mirikizumab (24 weeks total treatment) to assess delayed response. The timepoints for delayed response are based on the pivotal trials for the respective drugs.
- At the end of the induction period, patients are classified as responders or non-responders. The responders transition to the maintenance state and the non-responders to the no-treatment state.

Maintenance phase:

- Responders at the end of induction phase enter the maintenance phase, which includes:
    - on treatment,

    - off treatment, and
    - death
- Non-responders transition to ‘no treatment’ state.
- In their base case, the company included re-induction of mirikizumab in the maintenance phase (rather than dose-escalation as modelled in the comparator arms) as this is anticipated in their marketing authorisation. The re-induction dose is 300 mg IV mirikizumab at Week 12, 16 and 20. In the base case, [redacted] of patients receiving mirikizumab were modelled to undergo re-induction (equating to [redacted] per cycle), to reflect the proportion of patients who were re-inducted in the LUCENT-2 trial. A scenario was conducted with 30% of patients undergoing re-induction, to align with the comparator arms where 30% of the patients receive dose escalation in the maintenance phase.
- Given the assumption of equal efficacy for all treatments, dose escalation and reinduction were assumed to affect only costs, not efficacy.
- The cost of re-induction was applied only to the cycle in which the patient is re-induced.

EAG conclusions:

- The model structure is a reasonable simplification. We agree with the company’s approach to exclude other states (such as surgery/ post-surgery) due to similar downstream costs driven by similar efficacy.
- The company explored the impact of varying model features in their scenario analysis. These included: increasing the model time horizon, applying discount rates, extending the induction phase for delayed responders, assuming similar proportion of patients receiving re-induction as patients in the comparator arms receiving dose-escalation. Further details are in Section 6.
- Based on our clinical expert’s advice, we view it is reasonable to assume that dose escalation and re-induction are likely to impact only costs and not efficacy of the drugs, due to the assumption of equal efficacy for all the treatments.

5.3 Model parameters

5.3.1 Efficacy

As stated earlier in section 5.1, the company corrected their NMA inputs in the original CS and submitted a revised economic model. We present a detailed critique of the revised NMA in section 4.5 of this report. The efficacy parameters discussed in the following sub-sections are obtained from the revised NMA to populate the company’s revised economic model.

Induction phase

- The model assumed similar response rates across all treatments, although the rates differed between the two sub-groups: biologic-naïve and biologic-failed.
- For their base case, the response rates were obtained from the revised NMA inputs shown in Table 2, Figure 1 (biologic-naïve) and Figure 7 (biologic-experienced), respectively, of the addendum to the CS.
- For the scenario analysis (extended induction), the absolute probability of response was obtained from the previous NICE appraisal on ustekinumab TA633 (Table 3 of the addendum to the CS).

Maintenance phase

- All treatments were assumed to have the same risk of treatment discontinuation. The odds ratio obtained for response at the end of maintenance for mirikizumab relative to placebo from the revised NMA were converted to absolute probability. Further details on the NMA are in Section 4.5 above.
- Those patients who are off treatment remained in the state until the end of the model simulation or death.

In Table 6, we present a summary of the estimated probabilities obtained from the revised NMA response rates results (as presented in the addendum to the CS) that are used in inform the revised economic model.

Table 6 Probabilities (per cycle) used in the company model for the base case

Sub-group	Induction		Maintenance	
	Response	***Non-response (estimated as 1-response)***	***Response***	***Non-response (Estimated as 1-response)***
Biologic-naïve	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-failed	[redacted]	[redacted]	[redacted]	[redacted]
Sources: Table 2 and section 3.1.1.2 of the addendum to the CS				

EAG conclusions:

- Overall, we agree with the company's assumptions which are reasonable simplifications.
- The company's methodological approach to obtain the probabilities from response rates is appropriate (further details are in company's response to EAG clarification Question 1). We did not have access to the CODA output to produce the mean

absolute probabilities of response, which was calculated for 20,000 NMA samples. Therefore, we are unable to verify the company's estimates for the probability of response.

- With respect to the efficacy inputs in the model, obtained from the revised NMA, the EAG has a few concerns including i) the broad NMA structure leading to clinical and statistical heterogeneity, ii) the lack of representative UK-specific data for modelling baseline effect; and iii) inconsistency in the population characteristics for the biologic-naïve subgroup included in the NMA and those stated in the NICE scope. For further details, see Section 4.5. However, none of these concerns are critical and we do not anticipate these to have any significant impact on the efficacy parameters.

5.3.2 Mortality

The Office for National Statistics (ONS) life tables, adjusted for age and gender, were used for mortality estimation. No increased mortality was assumed due to ulcerative colitis. This is consistent with previous NICE TAs (TA633, TA342, TA792 and TA547).

5.3.3 Costs

Acquisition costs

Details of the company's inputs and assumptions for acquisition costs of the intervention – mirikizumab – and the comparators ustekinumab and vedolizumab are summarised in CS Table 40. Drug acquisition costs, sourced from Monthly Index of Medical Specialities (MIMS) and the British National Formulary (BNF), are summarised in CS Table 41 (induction phase) and CS Table 42 (maintenance phase).

Mirikizumab patients who did not respond after initial induction therapy or who lost response in the maintenance phase received re-induction. Whereas patients in the two comparator arms who did not respond after initial induction therapy or who lost response in the maintenance phase received dose-escalation. Irrespective of patients re-induced or who received dose-escalation, drug acquisition costs took into account the proportion of patients on standard and escalated doses during the maintenance phase.

All other costs

- Drug administration costs are summarised in CS Tables 43 and 44.
- Disease management costs, costs for monitoring and tests during the induction phase, and adverse event costs are not modelled.

EAG conclusions: Overall, we agree with the company's costs estimates. Their approach for estimating acquisition costs is appropriate and that for administration costs is consistent with previous appraisals (TA633, TA547 and TA792). Based on our clinical expert's opinion, we view it is reasonable to exclude the costs associated with disease management, monitoring, and adverse events, provided the assumption that all the treatments have similar efficacy holds true. Furthermore, our expert indicated that the provision of mirikizumab is unlikely to incur any other additional costs that are not incurred in the provisions of ustekinumab and vedolizumab.

5.4 EAG model checks

The EAG conducted a range of checks on the company's original cost-comparison model submitted on 8th December 2022. These included:

- verification that all input parameters and model results matched the values cited in the CS and, where available, values in published sources.
- Inspection of formulae in the Markov trace and intermediate calculations ('white box' verification)
- checking that changes to input parameters had a plausible impact on results ('black box' verification).
- re-running all the company's sensitivity and scenario analyses. The probabilistic sensitivity analysis (PSA) was not implemented in the model, which is acceptable, as the PSA is not required for a cost-comparison model.

We conducted the following checks on the company's revised model received on 15th February 2023:

- re-produced the revised cost comparison results from the original company model (received on 8th December 2022) by applying the revised NMA estimates into the original model.
- verified no other changes have been made to the remaining model parameters including baseline characteristics, life tables, costs, and adverse events, in the revised model.
- re-ran all the company's sensitivity and scenario analyses.

We identified two inconsistencies in the company's scenario analyses:

- A minor inconsistency in the estimation of adverse event costs. The company applied adverse events costs of £4000; we estimated a slightly different AE cost of £3,898. This minor difference does not have any significant impact on the results.

- For the scenario of extended induction (when non-responders at the end of induction continue for an additional treatment phase), the company did not apply the correct treatment duration for mirikizumab which is 24 weeks in total (12 weeks of induction + 12 weeks of extended induction) (see CS Document B section B.4.2.1.1). We corrected this error (in cell K96 of Sheet!Model Settings of the company's revised mdel); the results, in Table 7 below, show that mirikizumab is [redacted] than the two comparators, in both the sub-groups.

Table 7 Corrected results from the company's scenario analysis of delayed response (extended induction) (list price)

Scenario	Incremental costs relative to mirikizumab (biologic-naive)			Incremental costs relative to mirikizumab (biologic-experienced)		
	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC	Ustekinumab	Vedolizumab IV	Vedolizumab IV/SC
Company's Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario with delayed response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG conclusions: Overall, the model is well-implemented, although we identified two errors in the company's scenario analyses, as discussed above.

6 Company and EAG cost comparison results

6.1 Company's cost comparison analysis results

The company revised base case cost comparison results are presented in Table 6 (for biologic-naïve) and Table 7 (for biologic-failed) of the addendum to the CS. These results are based on the list price and PAS price for mirikizumab, and list prices for the two comparators, respectively. We present the results of the company's analyses using the PAS prices for mirikizumab and vedolizumab and CMU price for ustekinumab in a confidential addendum.

Uncertainty over model assumptions was assessed with one-way sensitivity analyses (parameters described in Table 8 of the addendum to the CS) and scenario analyses (Table 9 of the addendum to the CS), respectively. The one-way sensitivity analysis was conducted using an outdated PAS price discount for mirikizumab and list prices for the two comparators. Hence, we have not commented on these results. We have, however, run these analyses using the list prices for all the three treatments, as discussed in the following Section 6.2. We also conducted the corresponding analyses using PAS prices for mirikizumab and vedolizumab and CMU price for ustekinumab in the confidential addendum.

Results from the company's scenario analyses using the list prices for all the three drugs (see Table 9 of the addendum to the CS) show that:

- for biologic-naïve population (Table 10 of the addendum to the CS), mirikizumab remained [redacted] than the comparators in most of the scenarios. Increasing the percentage of patients in treatment re-induction from [redacted] to [redacted] per cycle (scenario 5) had the highest impact for vedolizumab IV, [redacted] the incremental cost from [redacted] (revised base case) to [redacted]. Scenario 6 (with a delayed response assessment for mirikizumab and the comparators) had the biggest impact for ustekinumab and vedolizumab IV/SC, [redacted] the incremental cost from [redacted] (revised base case) to [redacted] for ustekinumab, and from [redacted] (revised base case) to [redacted] for vedolizumab IV/SC respectively.
- Regarding the biologic-failed population results (Table 11 of the addendum to the CS), the EAG observed similar effect as the biologic-naïve population, where mirikizumab remained [redacted] than the comparators in all scenarios, [redacted] the incremental cost from [redacted] (revised base case) to [redacted]. Scenario 6 (with a delayed response assessment for mirikizumab and the comparators) had the biggest impact for ustekinumab and vedolizumab IV/SC, [redacted] the incremental cost from

[redacted] (revised base case) to [redacted] for ustekinumab, and from [redacted] (revised base case) to [redacted] for vedolizumab IV/SC, respectively.

6.2 EAG analyses

6.2.1 Company's one-way sensitivity analysis using list prices

The EAG has run the company's one-way sensitivity analysis using the list prices for all three drugs (mirikizumab, ustekinumab and vedolizumab) for biologic-naïve and biologic-failed populations using the revised company model as the company conducted the one-way sensitivity analysis results using an outdated PAS price for mirikizumab. Tornado plots are presented in the Appendix 3 of this report (see Figure 4,

Figure 6, and

Figure 8 for the biologic-naïve population, and Figure 5, Figure 7, and Figure 9 for the biologic-failed population, respectively). For both the subgroups, the key model drivers are the response rates for the induction and the maintenance phases. Changing the proportion of patients for dose escalation also impacted the model results, but to a lesser extent.

6.2.2 Additional scenarios by EAG

We performed three additional analyses with the company's base case to complement the company's scenarios and analyse the impact of changing some of the model assumptions in the final cost-comparison results.

- Mirikizumab arm: change the re-induction rate from [redacted] to [redacted] and [redacted], and maintain dose escalation in 30% for the comparators
- Include AE costs (for completeness: £3898 EAG estimated vs company's estimate of £4000)
- Time horizon: 15 years.

Table 8 presents the results for biologic-naïve and Table 9 for biologic-failed populations. These analyses are conducted using the list prices for mirikizumab and the comparators-ustekinumab and vedolizumab. The EAG notes:

- For the biologic-naïve population, mirikizumab [redacted] than the comparators. Varying the re-induction rate to [redacted] the cost difference between mirikizumab and the comparators by [redacted], which increased to [redacted] at a [redacted] re-induction rate. Using a 15-year time horizon had a marginal impact on the cost difference between mirikizumab and vedolizumab [redacted] by [redacted] compared to the

revised base case result, by [redacted] between mirikizumab and vedolizumab (IV) and [redacted] between mirikizumab and vedolizumab (IV/Sc), respectively. The scenario including revised adverse event costs [redacted] the costs [redacted].

- For the biologic-failed population, mirikizumab remained [redacted] than the comparators in all the scenarios. Varying the re-induction rate [redacted] the cost difference between mirikizumab and the comparators by [redacted] (10% re-induction rate) and [redacted] (15% re-induction rate), respectively compared to the company's revised base case results. The scenarios including adverse event costs and time horizon [redacted] the costs negligibly ([redacted]).

Table 8 EAG scenario analysis for mirikizumab for biologic naïve population – incremental cost mirikizumab versus comparators (list price for all drugs)

EAG scenario	Treatments	Total costs	Incremental costs for Mirikizumb vs comparators
Revised company base case	Mirikizumab	[redacted]	
	Ustekinumab	£23,310	[redacted]
	Vedolizumab IV	£35,732	[redacted]
	Vedolizumab SC/IV	£26,644	[redacted]
Re-induction rate per cycle to 10%	Mirikizumab	[redacted]	
	Ustekinumab	£23,310	[redacted]
	Vedolizumab IV	£35,732	[redacted]
	Vedolizumab SC/IV	£26,644	[redacted]
Re-induction rate per cycle to 15%	Mirikizumab	[redacted]	
	Ustekinumab	£23,310	[redacted]
	Vedolizumab IV	£35,732	[redacted]
	Vedolizumab SC/IV	£26,644	[redacted]
Include adverse event costs (£3,898)	Mirikizumab	[redacted]	
	Ustekinumab	£23,521	[redacted]
	Vedolizumab IV	£35,938	[redacted]
	Vedolizumab SC/IV	£26,850	[redacted]
Time horizon 15 years	Mirikizumab	[redacted]	
	Ustekinumab	£24,090	[redacted]
	Vedolizumab IV	£37,101	[redacted]
	Vedolizumab SC/IV	£27,615	[redacted]

Table 9 EAG scenario analysis for mirikizumab considering for biologic failed population – incremental cost mirikizumab versus comparators (list price for all drugs)

EAG scenario	Treatments	Total costs	Incremental costs for Mirikizumb vs comparators
Revised company base case	Mirikizumab	[redacted]	
	Ustekinumab	£10,542	[redacted]
	Vedolizumab IV	£12,952	[redacted]
	Vedolizumab SC/IV	£10,481	[redacted]
Re-induction rate per cycle to 10%	Mirikizumab	[redacted]	
	Ustekinumab	£10,542	[redacted]
	Vedolizumab IV	£12,952	[redacted]
	Vedolizumab SC/IV	£10,481	[redacted]
Re-induction rate per cycle to 15%	Mirikizumab	[redacted]	
	Ustekinumab	£10,542	[redacted]
	Vedolizumab IV	£12,952	[redacted]
	Vedolizumab SC/IV	£10,481	[redacted]
Include adverse event costs (£3,898)	Mirikizumab	[redacted]	
	Ustekinumab	£10,609	[redacted]
	Vedolizumab IV	£13,015	[redacted]
	Vedolizumab SC/IV	£10,544	[redacted]
Time horizon 15 years	Mirikizumab	[redacted]	
	Ustekinumab	£10,543	[redacted]
	Vedolizumab IV	£12,954	[redacted]
	Vedolizumab SC/IV	£10,482	[redacted]

7 Equalities and innovation

Mirikizumab is not a particularly innovative medicine in comparison to the comparators either in terms of mechanism of action (targeting the IL-23 cytokine pathway, which is similar to ustekinumab that targets the IL-23 and IL-12 cytokine pathways as summarised in section 0) or in terms of method of administration (initially IV infusion for induction then subcutaneous injection for maintenance treatment). No equality considerations have been raised during this appraisal.

8 EAG commentary on the robustness of evidence submitted by the company

The EAG overall does not have any major concerns about how the clinical efficacy and safety estimates for mirikizumab versus ustekinumab and vedolizumab have been derived from the company's NMA. We have not identified any critical issues, that, in our opinion, would prevent progression with a cost-comparison approach. We have identified some uncertainties associated with the evidence base, however. We note that:

- with regard to results presented in the CS for the biologic-naïve population from the NMA, there is an issue that the characteristics of this group in the NMA studies do not fully reflect the exact biologic-naïve population stated in the NICE scope and the biologic-naïve group in whom the company is partly positioning mirikizumab.
- the NMA methodology on the whole appears appropriate, but the company has not modelled baseline effect using representative UK-specific data as is recommended in TSD 5.[1] The impact of this on the results is unclear.
- there was considerable clinical and statistical heterogeneity in the broad NMA network; a narrower network may have resulted in more precise estimates of clinical efficacy (i.e. through providing narrower credible intervals, and thus providing more confidence in mirikizumab having [redacted] to comparators).
- there are no data available in the CS to show whether mirikizumab may be statistically non-inferior or equivalent to ustekinumab and vedolizumab (i.e. there are no data from equivalence or non-inferiority trials).

Based on the statistical significance of the NMA findings, mirikizumab appears to have [redacted], treatment effects (i.e. clinical response and remission in the induction and maintenance treatment phases) than, and a [redacted] safety profile to, vedolizumab and ustekinumab.

The EAG's conclusions on the company's cost-comparison analysis are:

- The model structure and key assumptions of the company's cost comparison model are appropriate, and consistent with the previous NICE ustekinumab appraisal TA633.
- The model assumes equal clinical efficacy for mirikizumkab, ustekinumab and vedolizumab based on the NMA results. While there are uncertainties with the NMA (discussed in Section 4 and reiterated above), none of these are critical. Therefore, we view that it is appropriate to assume equal clinical efficacy for all three drugs.

- With the list prices for mirikizumab, ustekinumab and vedolizumab, mirikizumab is [redacted] than the two comparators. This applies for the company's base case analysis and for all the company and EAG scenario analyses.
- The cost difference between mirikizumab and the two comparators is most sensitive to assumptions about re-induction rates and delayed response assessment.

9 References

1. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Supoort Docuemnt 5: Evidence synthesis in the baseline natural history model - report by the Decision Support Unit. Sheffield: Decision Suport Unit, 2012.
2. National Institute for Health and Care Excellence (NICE). *Ustekinumab for treating moderately to severely active ulcerative colitis [TA633]*. https://www.nice.org.uk/guidance/ta633/evidence.
3. National Institute for Health and Care Excellence (NICE). *Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [TA329].* https://www.nice.org.uk/guidance/ta329.
4. National Institute for Health and Care Excellence (NICE). *Vedolizumab for treating moderately to severely active ulcerative colitis [TA342]*. https://www.nice.org.uk/guidance/ta342.
5. National Institute for Health and Care Excellence (NICE). *Tofacitinib for moderately to severely active ulcerative colitis. Technology appraisal guidance [TA547]*. https://www.nice.org.uk/guidance/ta547.
6. National Institute for Health and Care Excellence (NICE). *Ozanimod for treating moderately to severely active ulcerative colitis [TA828]*. https://www.nice.org.uk/guidance/ta828.
7. National Institute for Health and Care Excellence (NICE). *Filgotinib for treating moderately to severely active ulcerative colitis [TA792]*. https://www.nice.org.uk/guidance/ta792.
8. . *National Institute for Health and Care Excellence (NICE). Upadacitinib for treating moderately to severely active ulcerative colitis [GID-TA10866]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10866. [Accessed 05 October 2022].*
9. National Institute for Health and Care Excellence. NICE Fast track appraisals - guiding notes for ERGs: NICE, 2017.
10. National Institute for Health and Care Excellence. Single Technology Appraisal. Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]. Committee Papers. 2020.
11. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. *New England Journal of Medicine* 2013;369(8):699-710.
12. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. *New England Journal of Medicine* 2019;381(13):1201-14.
13. Eli Lilly (Data on file): LUCENT-1 Clinical Study Report.
14. Eli Lilly (Data on file). LUCENT-2 Clinical Study Report.
15. Naegeli AN, Hunter T, Dong Y, et al. Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients. *Crohn's & Colitis 360* 2021;3(1):otab007.
16. Center for Drug Evaluation and Research. Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry. Available at: https://www.fda.gov/files/drugs/published/Ulcerative-Colitis--Clinical-Trial-Endpoints-Guidance-for-Industry.pdf. [Accessed 15 November 2022].
17. Eli Lilly (Data on file). NMA report appendices.
18. Kalita N, Lord J, Pickett K, et al. Ustekinumab for treating moderately to severely active ulcerative colitis: A Single Technology Appraisal. Southampton: Southampton Health Technology Assessments Centre (SHTAC), 2019.
19. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York Publishing Services Ltd.: CRD, 2009.

20. Lu X, Jarrett J, Sadler S, et al. Comparative efficacy of advanced treatments in biologic-naïve or biologic-experienced patients with ulcerative colitis: a systematic review and network meta-analysis. *Int J Clin Pharm* 2022;Online ahead of print.
21. Stan Development Team. *Stan Modeling Language Users Guide and Reference Manual*. https://mc-stan.org.
22. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Sheffield: ScHARR, University of Sheffield, 2016.
23. Dias S, Sutton AJ, Welton NJ, et al. Evidence Synthesis for Decision Making 3: Heterogeneity—Subgroups, Meta-Regression, Bias, and Bias-Adjustment. *Medical Decision Making* 2013;33(5):618-40.
24. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU technical support document 4: inconsistency in networks of evidence based on randomised controlled trials. Sheffield: Decision Support Unit, ScHARR, University of Sheffield, 2014.
25. Essat M, Tappenden P, Ren S, et al. Vedolizumab for the treatment of adults with moderately to severely active ulcerative colitis: A Single Technology Appraisal: School of Health and Related Research (ScHARR), 2014.
26. National Institute for Health and Care Excellence. Single Technology Appraisal. Tofacitinib for previously treated active ulcerative colitis [ID1218]. Committee Papers., 2018.
27. *British National Formulary (BNF). Available at: https://bnf.nice.org.uk/. [Accessed 22 September 2022].*

10 Appendices

Appendix 1 Comparator mechanisms of action and modes of administration

Table 10 Mechanisms of action and modes of administration for the comparators listed in the NICE scope for this PATT

NICE TA	Biologic therapy	Mechanism of action	Mode of administration [a]
TA329	Infliximab [b]	Monoclonal antibodies that inhibit the activity of TNF-α which is a key component in the inflammation process.[3]	Either by intravenous infusion, or initially by intravenous infusion followed by subcutaneous injection.
	adalimumab		Subcutaneous injection
	golimumab		Subcutaneous injection
TA342	vedolizumab	A humanised monoclonal antibody that binds to the α4β7 integrin expressed on certain gut homing T helper lymphocytes. When bound to α4β7 integrin vedolizumab inhibits adhesion of these cells to mucosal addressing cell adhesion molecule-1 (MAdCAM-1). Vedolizumab therefore selectively targets the gut and reduces gut inflammation by preventing the selective migration of pathogenic gut-homing lymphocytes.[4]	Induction by intravenous infusion followed by subcutaneous maintenance doses
TA547	tofacitinib	Janus kinase (JAK) inhibitor (similar in structure to adenosine triphosphate (ATP) and competes with ATP at target sites).[26]	Oral
TA633	ustekinumab	Fully human IgG1κ monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23 cytokines thereby dampening	Induction infusion followed by

		the inflammatory cascade underlying UC.[10]	subcutaneous maintenance doses.
TA792	filgotinib	JAK1 inhibitor[27]	Oral
TA828	ozanimod	A sphingosine-1-phosphate receptor modulator thought to inhibit inflammation by preventing lymphotcyte movement to sites including the intestine.[6,27]	Oral
TA856	upadacitinib	JAK1 inhibitor[27]	Oral

[a] Information on mode of administration has been taken from the BNF[27] for each drug in the relevant indication; [b] and biosimilars

Appendix 2 EAG's risk of bias assessments of the LUCENT-1 and LUCENT-2 trials

The EAG's risk of bias assessment of the pivotal mirikizumab LUCENT-1 and LUCENT 2 trials, in comparison to the company's assessment, is shown in Table 11.

Table 11 EAG and company's risk of bias assessments of the LUCENT-1 and LUCENT-2 trials

Study question (Yes/No/Unclear)	LUCENT-1 COMPANY ASSESSMENT	LUCENT-1 EAG ASSESSMENT	LUCENT-2 COMPANY ASSESSMENT	LUCENT-2 EAG ASSESSMENT
Was randomisation carried out appropriately?	Yes	Yes Assignment to treatment groups determined by a computer-generated random sequence using an interactive web-response system (LUCENT-1 Trial Protocol section 7.2)	Yes	Yes Assignment to treatment groups for clinical responders determined by a computer-generated random sequence using an interactive web-response system (LUCENT-2 Trial Protocol section 7.2)
Was the concealment of treatment allocation adequate?	Yes	Yes Interactive web-response system used	Yes	Yes Interactive web-response system used
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes Disease location, severity (total Mayo score), endoscopic Mayo subscore of severe disease,faecal calprotectin, and prior biologic or tofacitinib failure were similar between arms (CS Table 9)	Yes	Yes Disease location, severity (total Mayo score), endoscopic Mayo subscore of severe disease,faecal calprotectin, and prior biologic or tofacitinib failure were similar between the randomised arms (CS Table 11)
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes Double-blind study. (investigator, site personnel performing assessments and patients were blinded) Blinded study personnel prepared investigational product.	Yes	Yes Double-blind study. (investigator, site personnel performing assessments and patients were blinded) Blinded study personnel prepared investigational product.

		Mirikizumab visually indistinguishable from placebo. (LUCENT-1 Trial Protocol 7.1.1 and 7.3)		Mirikizumab visually indistinguishable from placebo. (LUCENT-2 Trial Protocol 7.1.1 and 7.3)
Were there any unexpected imbalances in drop-outs between groups?	Unclear	Unclear There were imbalances, but not necessarily unexpected, with a greater proportion discontinuing due to adverse events (most common event was ulcerative colitis), withdrawal by subject and lack of efficacy in the placebo arm compared to the mirikizumab arm. (LUCENT-1 CSR Table 8.1. CS Appendix F.4)	Unclear	Unclear There were imbalances, but not necessarily unexpected, with a greater proportion discontinuing due to adverse events (most common event was ulcerative colitis), withdrawal by subject and lack of efficacy in the placebo arm compared to the mirikizumab arm (LUCENT-2 CSR Table 8.1, CS Table 36)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No Objectives and endpoints in protocol match those reported in the CSR	No	No Objectives and endpoints in protocol match those reported in the CSR
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes Analysis was based on modified intention to treat This was due to baseline errors in electronic data collection devices. This approach was agreed with FDA. Appropriate methods used to impute missing data for primary outcome (LUCENT-1 SAP 5.3.1 and 5.4)	Yes	Yes Analysis was based on modified intention to treat This was due to baseline errors in electronic data collection devices. This approach was agreed with FDA. Appropriate methods used to impute missing data for primary outcome (LUCENT-2 SAP 5.3.1 and 5.4)

Source: The company risk of bias assessments were extracted from CS Appendix D.3 Table 46.

Appendix 3 EAG update to Company's one-way sensitivity results using list prices

Figure 4 Tornado plot with results from the one-way sensitivity analysis – mirikizumab (list price) versus vedolizumab IV in the biologic-naïve population

Figure 5 Tornado plot with results from the one-way sensitivity analysis – mirikizumab (list price) versus vedolizumab IV in the biologic-failed population

Figure 6 Tornado plot with results from the one-way sensitivity analysis – mirikizumab (list price) versus vedolizumab SC/IV in the biologic-naïve population

Figure 7 Tornado plot with results from the one-way sensitivity analysis – mirikizumab (list price) versus vedolizumab SC/IV in the biologic-failed population

Figure 8 Tornado plot with results from the one-way sensitivity analysis – mirikizumab (list price) versus ustekinumab in the biologic-naïve population

Figure 9 Tornado plot with results from the one-way sensitivity analysis – mirikizumab (list price) versus ustekinumab in the biologic-failed population

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Mirikizumab for treating moderately to severely active ulcerative colitis [ID3973]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 29 March 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Corrections and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, Page 10 states: "The searches for the systematic literature review that informed the NMA were over six months out-of-date, meaning that there is a risk that there may have been relevant studies published recently that will not have been included in the NMA." Similar wording is presented on Page 33 (Section 4.5.2) and Page 43 (Section 4.5.6)	This should be amended to: "The searches for the systematic literature review that informed the NMA were **performed** over six months **ago**, meaning that there is a risk that there may have been relevant studies published recently that will not have been included in the NMA." Similar adjustment should be made to the wording on Pages 33 and 43.	The current wording could be interpreted to mean that the current searches were carried out more than six months prior to the six month cut-off (i.e., more than a year before submission), which is incorrect. This should be clarified at all instances where this wording is presented.	Thank you for highlighting this. We have now adjusted the text in section 1.3 as suggested by the company. We have similarly adjusted the text in sections 4.5.2 and 4.5.6.
Section 3.4, Pages 18 and 19 state: "The company has included all the outcomes specified in the NICE scope in the CS, except for:… Endoscopic healing…"	If this is in reference to the clinical data presented in the CS, the bullet point regarding the outcome "Endoscopic healing" should be removed. If this is reference to the clinical endpoints explicitly included in the economic model, wording should be added to clarify this.	As discussed in Section B.3.3.3 of the main Company Submission, endoscopic improvement was investigated in the LUCENT trials, with "endoscopic remission" representing a key secondary outcome in both LUCENT trials, and "histologic-endoscopic mucosal improvement" and "histologic-endoscopic mucosal remission" representing key secondary outcomes in the LUCENT-1 and LUCENT-2 trials, respectively. Results for these outcomes are presented in Sections B.3.6.1 and B.3.6.2 of the CS for LUCENT-1 and	Thank you for your comments about this. Our original text was in reference to the clinical data presented in the CS. We have now removed the bullet point regarding the 'endoscopic healing' outcome in section 3.4.

		-2, respectively. As such, it is inaccurate to state that results for endoscopic healing have not been included in the Company Submission. As such, this wording should be amended as appropriate, dependent upon whether it is in reference to the clinical data or the clinical endpoints modelled.	
Section 3.5, Page 19 states: "The company provides base case and scenario analyses results using both the list and PAS prices (CS sections B.4.3 and B.4.4.2)."	This should be amended as follows: "The company provides base case and scenario analyses results using both the list and PAS prices (CS sections B.4.3 and B.4.4.2, **and updated in Sections 3.2 and 3.3 of the CS addendum**).	Updated results were provided in the CS addendum; for clarity, reference to them should be made here.	Thank you for pointing this out. We have amended section 3.5 of the report, using the company's suggested wording.
Section 4.1, Page 21 states: "LUCENT-2.[14] The company's phase III RCT of mirikizumab versus placebo designed to evaluation the safety and efficacy of mirikizumab in maintaining a treatment response in those LUCENT-1 participants who were randomised to mirikizumab and who achieved a clinical response at week 12."	This should be amended as follows: "LUCENT-2.[14] The company's phase III RCT of mirikizumab versus placebo designed to evaluation the safety and efficacy of mirikizumab in maintaining a treatment response **to Week 40, with the primary study population of** LUCENT-1 participants who were randomised to mirikizumab and who achieved a clinical response at week 12."	As described in Section B.3.3.1.2 of the CS and depicted in Figure 4 therein (replicated as Figure 3 on Page 25 of the EAG report), all patients who completed LUCENT-1 who had received at least 1 dose of study drug, and who had all necessary evaluations to assess the modified Mayo score at the end of the study, were eligible to be recruited to the LUCENT-2 trial. Within this, distinct populations were studied. While mirikizumab responders from LUCENT-1 represented the primary study	Thank you for highlighting this. We have adjusted the text to read as follows (we have used the company's suggested alternative wording, but we have added the word 'comprising' to explain the population and corrected an error we originally made in this text; that is, we have changed 'evaluation' to 'evaluate'): "LUCENT-2.[14] The company's phase III RCT of mirikizumab versus placebo designed to evaluate the safety and efficacy of mirikizumab in maintaining a treatment response to

		population of interest, the current wording that the LUCENT-2 trial was designed to assess safety and efficacy in only those patients who received mirikizumab and responded to it in the LUCENT-1 trial is inaccurate.	Week 40, with the primary study population comprising of LUCENT-1 participants who were randomised to mirikizumab and who achieved a clinical response at week 12."
Section 4.2.2, Pages 26 and 27 state: "Inferential statistics were only carried out for the primary study population (CS section B.3.4.1). As in LUCENT-1, due to the issue with eCOA devices described in section 4.2.1, primary efficacy analyses were based on the modified intention-to-treat population (n=544) and safety analyses were based on the safety population (n=581)."	The wording here should be amended to: "Inferential statistics were only carried out for the primary study population (CS section B.3.4.1). As in LUCENT-1, due to the issue with eCOA devices described in section 4.2.1, primary efficacy analyses were based on the modified intention-to-treat population **and included patients who were deemed as mirikizumab induction responders (n=544). Safety analyses were performed for this "mirikizumab induction responders" subset of the overall safety population (n=581)."**	The current wording in the EAG report does not make it clear that the presented 'n' numbers are for the mirikizumab induction responders cohort of patients in the LUCENT-2 trial, rather than the mITT population and safety population. The Company therefore suggests this wording be amended to clarify the specific group of patients to which the sample sizes given are referring. As these patient cohort numbers are unpublished, they should also be marked as academic in confidence as provided here.	Thank you for pointing this out. We have amended the report as suggested.
Section 4.3.2.1.2, Pages 29 and 30 refer to "the whole trial population" of LUCENT-2 at four instances.	This wording should be adjusted to "the primary study population" or "mirikizumab induction responders".	The current wording could be interpreted to be referring to the mITT of the LUCENT-2 trial, which is incorrect; these data are correct for the mirikizumab induction responder population which represents the primary study	Thank you for highlighting this. We have changed the four instances of "whole trial population" to "primary study population".

		population within the LUCENT-2 trial.	
Section 4.5.5.3, Page 42 states: "The use of more informative prior distributions for the between-trial parameters has been recommended, however the EAG believes that use of the fixed effects model in the company's submission is reasonable, especially given the small difference in DIC values between models (<5, which is not considered to be important (TSD 3[23])."	The wording here should be amended to: "The use of more informative prior distributions for the between-trial parameters has been recommended, however the EAG believes that use of the fixed effects model in the company's submission is reasonable, especially given the small difference in DIC values between models **in the Company NMA ([redacted]); any difference in DIC values between models of <5** is not considered to be important (TSD 3[23])**.**	The current value stated in regards to the DIC difference could be misconstrued as being representative of the data in the Company NMA, when in actuality this is in reference to a statement made in the NICE TSD 3. Therefore, the wording here should be amended to make clear the distinction between the presented Company NMA results and the reference to the NICE TSD 3 document.	Thank you for highlighting the potential for misinterpretation here. The text has been amended as suggested. Please see Section 4.5.5.3.
Section 4.5.7.1.2, Page 45 states: "…but [redacted]…	The wording here should be amended as follows: "…but [redacted]…"	This is a minor typographical error	Thank you for highlighting this typographical error. The text has been amended as suggested.
Section 5.1, Page 53 states: "…the company's cost comparison evidence submitted on 8th December 2022 for this CDF (henceforth, referred to as the	The Company are unclear as to the use of the acronym CDF, which is not defined in the report. Please define this abbreviation, or replace it as appropriate if this represents a minor typographical error.	The acronym CDF may be confused for reference to the Cancer Drugs Fund, which is not relevant to this appraisal. As such, its use within the context of this appraisal should be clarified or edited as appropriate.	Thank you for highlighting this typographical error. We have revised the text as follows: *"…the company's cost comparison evidence submitted on 8th December 2022 for this appraisal*

'original CS' and the 'original economic model')"			*(henceforth, referred to as the 'original CS' and the 'original economic model')"*
Section 6.1, Page 60 states: "The company revised base case cost comparison results are presented in Table 6 (for biologic-naïve) and Table 7 (for biologic experienced) of the addendum to the CS."	This wording should be amended to: "The company revised base case cost comparison results are presented in Table 6 (for biologic-naïve) and Table 7 (for **biologic-failed**) of the addendum to the CS."	The wording of the subgroups should be aligned to the wording used throughout the Company submission.	Thank you for highlighting this typographical error. We have revised the wording to align with the CS.

Issue 2 Data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.5.4.3.2, Page 36 states: "…the majority of the studies included in the NMA (n = 15) used the same definition of clinical remission in the induction and maintenance phases…"	The wording here should be amended as follows: "the majority of the studies included in the NMA used the same definition of clinical remission in the induction **(n=17)** and maintenance **(n=15)** phases…"	The present wording does not make it clear which phase of the study the given n number is referring to.	Thank you for highlighting this. We have now amended the text as suggested.
Section 4.5.5.3, Page 42 states: "…than results from the random effects model (OR [redacted] (CrI [redacted])) due the narrower 95% credible intervals."	The values here should be corrected to align with those presented in Figure 27, Page 101 of the original Company Submission: "…than results from the random effects model (OR [redacted] (CrI	The data currently presented are incorrect.	The data we have presented here are taken from the Addendum NMA Report Appendices Table 28 (unadjusted RE(2)), and have been exponentiated to obtain the OR values we report. Our aim is to compare these values with those

	[redacted])) due the narrower 95% credible intervals."		obtained from the fixed effects model. None of these results relate to the Original Submission. Thus, we believe the data are correctly reported.

Issue 3 Confidentiality marking errors

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 4.2.1, Page 24	Unpublished trial details are missing academic in confidence highlighting.	"This population (n=1162, 90.7% of randomised patients) included all randomised patients who received any amount of study treatment, regardless of whether they received the correct treatment, or otherwise did not follow the protocol, but excluded those **117** patients impacted by the eCOA wording errors in Turkey and Poland (CS Table 13, LUCENT-1 SAP section 5.4)."	Thank you for bringing this to our attention. We have now marked the relevant text as academic in confidence.
Section 4.3.2.1.1, Page 29	The p-values for the data presented are from the Clinical Study Reports for the LUCENT-2 trial, the results of which are currently unpublished. They should therefore be marked as academic in confidence.	"A statistically significant greater percentage of patients achieved clinical remission at week 40 (defined using the modified Mayo score), in the mirikizumab group compared to the placebo group (49.9% versus 25.1% of patients, **p<0.001**). A statistically significant difference in favour of mirikizumab versus placebo was also seen in both the biologic-naïve subgroup(51.5% versus 30.7% of patients, [redacted]) and in the biologic-failed subgroup (46.1% versus 15.6% of patients, [redacted]; CS B.6.2.1"	Thank you for bringing this to our attention. We have now marked the p-values as academic in confidence.

Section 4.5.5.3, Page 42	The results of the all-cause discontinuation NMA are not yet published and as such should be marked as academic in confidence. In addition, as noted in Issue 2, these data should be updated for accuracy.	"…except for the outcome of all cause discontinuation: results from the fixed effects model (the company preferred model) are more favourable to mirikizumab compared to placebo (OR [redacted] (CrI [redacted])) than results from the random effects model (OR [redacted] (CrI [redacted])) due the narrower 95% credible intervals."	Thank you for highlighting this. The results have now been marked as academic in confidence, however the data from the random effects model have not been updated – please see response to Issue 2 above.
Section 4.5.7.2, Pages 47 and 48	Unpublished NMA results are interpretable from the current confidentiality highlighting approach.	Page 47: "…and to [redacted]; CS Addendum Figure 4)." Page 48: "and [redacted] CS Addendum Figure 5)."	Thank you for bringing this to our attention. We have extended the text marked as academic in confidence, to align with the company's marking shown here.
Section 4.5.7.2.2, Page 48	The results of the maintenance phase NMA for clinical remission are currently unpublished and should therefore be marked as academic in confidence.	"There was however [redacted] (Table 5; CS Addendum Figure 10)."	Thank you for bringing this to our attention. We have marked the relevant text as academic in confidence.
Section 5.2.1, Page 52	The baseline characteristics of the modelled cohort are derived from unpublished LUCENT trial data and should therefore be marked as academic in confidence.	"The company's cost analyses modelled two patient cohorts with mean age of [redacted] years for biologic-naïve and [redacted] years for biologic-failed patients respectively (CS Table 39)."	Thank you. We have now marked the mean ages of the two patient cohorts as academic in confidence.
Section 8, Page 64	The statistically significant results of the Company's NMAs are unpublished and thus should be marked as academic in confidence.	"Based on the statistical significance of the NMA findings, mirikizumab appears to have [redacted], treatment effects (i.e. clinical response and remission in the induction and maintenance treatment phases) than, and a	Thank you. We have now amended the confidentiality marking to align with that specified by the company here.

		[redacted] safety profile to, vedolizumab and ustekinumab.”	