NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Guselkumab for treating moderately to severely active ulcerative colitis [ID6327]

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 Johnson & Johnson Innovative Medicine
2. **Summary of Information for Patients (SIP)**
3. **Clarification questions and company responses**
4. **NICE medicines optimisation team (MOT) report**
5. **Patient group, professional group, and NHS organisation submission** from:
   a. Crohn's & Colitis UK
6. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRiG)
7. **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

Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]

Document B

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6237 Guselkumab UC NICE CC Doc B_CON _27022025_redacted	Final	Yes	27 February 2025

Contents

List of Tables

List of figures

Abbreviations

Abbreviation	Definition
A&E	Accident and Emergency
ADT	Advanced therapy
ADT-IR	Advanced therapy inadequate responder
AE	Adverse event
AUC	Area under the curve
BNF	British National Formulary
BSG	British Society of Gastroenterology
CI	Confidence interval
CrI	Credible interval
CRP	C-reactive protein
DSU	Decision Support Unit
EAG	External Assessment Group
ECCO	European Crohn's and Colitis Organisation
eMIT	Drugs and pharmaceutical electronic market information tool
ERG	Evidence Review Group
FDA	US Food and Drug Administration
HRQoL	Health-related quality of life
HTA	Health technology assessment
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	Interleukin
IV	Intravenous
JAK	Janus kinase
MIMS	Monthly Index of Medical Specialities
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NMA	Network meta-analysis
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PSSRU	Personal Social Services Research Unit
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of life
RCT	Randomised controlled trial
S1PR	Sphingosine-1-phosphate receptor
SAE	Serious adverse event
SC	Subcutaneous

SF-36	36-item Short Form Health Survey
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TSD	Technical Support Document
UC	Ulcerative colitis
VBA	Visual Basic for Applications

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

B.1.1. Decision problem

Guselkumab is being investigated as a treatment option for inflammatory bowel disease (IBD) and is anticipated to receive a marketing authorisation for [redacted].(1)

The final scope for guselkumab for ulcerative colitis (UC) was issued by the National Institute for Health and Care Excellence (NICE) in January 2025, and guselkumab was selected to be appraised via a cost-comparison route.(2) Guselkumab is concurrently being appraised for previously treated moderately to severely active Crohn's disease.(3)

B.1.1.1. Population

In line with the anticipated use of guselkumab in UK clinical practice, the population relevant to this submission is narrower than the full anticipated marketing authorisation and includes adult patients with moderately or severely active UC who have had an inadequate response, lost response or were intolerant to a biologic or another advanced therapy (ADT), hereafter referred to as 'ADT-failure'. In line with the NICE recommendation for the selected comparators, this also includes a proportion of patients for whom tumour necrosis factor (TNF) inhibitors are deemed unsuitable.(4, 5)

B.1.1.2. Intervention

The evidence will be presented for guselkumab as induction therapy via two alternative administration routes (either 200 mg intravenous [IV] or 400 mg subcutaneous [SC] at Weeks 0, 4 and 8 following initiation) and as maintenance therapy via two alternative injectable dosing regimens (100 mg from Week 16

following initiation, once every 8 weeks [Q8W] SC; or 200 mg from Week 12 following initiation, once every 4 weeks [Q4W] SC) as per the anticipated marketing authorisation.

B.1.1.3. Comparators

The case for clinical effectiveness and cost-comparability will be made versus mirikizumab and vedolizumab, which are recommended by NICE.(4, 5) The published NICE guidance for these comparators recommends mirikizumab and vedolizumab for the subpopulations within their marketing authorisation, which are aligned to the population described in Section B.1.1.1, including patients unsuitable for TNF-inhibitors.

B.1.1.4. Comparative effectiveness analysis

The clinical effectiveness data for guselkumab-treated populations will be based on the results of one registrational Phase IIb study and three registrational Phase III studies: QUASAR IIb induction, QUASAR induction, QUASAR maintenance, and ASTRO.(6-9) In the absence of head-to-head randomised controlled trials (RCTs) of guselkumab versus the comparators, comparative effectiveness will be assessed via network meta-analyses (NMAs) for clinical remission and response in the population that is most informative to the decision problem (defined in Section B.1.1.1). Details of these analyses are presented in Section 0.

B.1.1.5. Cost-comparison analysis

To demonstrate the cost-comparability of guselkumab against vedolizumab and mirikizumab in the proposed population, a de novo cost-comparison model has been developed in Microsoft Excel® that accounts for any differences in the dosing schedules, acquisition costs and administration costs of these treatments. This is in line with recent cost-comparison appraisals in IBD (TA888, TA905, TA925, TA956, TA998) and another currently in progress (ID6244).(4, 10-14) Details of these analyses are presented in Section B.4.

The decision problem addressed in the submission 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 UC that have had an inadequate response, lost response to, or were intolerant to conventional therapy and/or a biological treatment or a JAK inhibitor	Adults with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to an advanced therapy, including patients for whom TNFis are deemed unsuitable.	Similar to the populations addressed in the comparator submissions (mirikizumab and vedolizumab) and the evidence base for guselkumab
Intervention	Guselkumab	Guselkumab	Not applicable
Comparator(s)	• TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • JAK inhibitors (such as tofacitinib, filgotinib or upadacitinib) • Vedolizumab • Ustekinumab • Ozanimod • Mirikizumab • Etrasimod • Risankizumab • Conventional therapies, without biological treatments	• Mirikizumab • Vedolizumab	Conventional therapy with aminosalicylates, oral corticosteroids and/or immunomodulators should not be considered as a comparator in the evaluation, as these are unlikely to be appropriate alternative options for the proposed population. This is also consistent with the mirikizumab appraisal (TA925). Guselkumab is positioned as an alternative to mirikizumab 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 advanced therapy.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			The anticipated use of guselkumab in UK clinical practice is similar to the patient populations in which mirikizumab and vedolizumab are recommended by NICE. Mirikizumab and vedolizumab are considered relevant comparators in this appraisal for the following reasons: • Both guselkumab and mirikizumab are IL-23 inhibitors and share a similar mechanism of action • In the NICE appraisal of mirikizumab (TA925), vedolizumab was identified as a relevant comparator to mirikizumab. Therefore, by extension, vedolizumab is also considered a relevant comparator to guselkumab • In UK clinical practice, vedolizumab has a significant market share in the proposed population as discussed in recent UC NICE submissions (4, 13) and a UK real-world evidence study on patients with IBD.(15) • The outcomes of NMAs demonstrate that guselkumab has similar efficacy to mirikizumab and vedolizumab in the intended treatment population

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• It is anticipated that guselkumab would be considered by UK clinicians as an alternative treatment to mirikizumab and vedolizumab in the proposed treatment population
Outcomes	• Rates of and duration of response, relapse and remission • Endoscopic healing • Endoscopic remission combined with histological improvement • Mortality • Measures of disease activity • Rates of hospitalisation (including readmission) • Rates of surgical intervention • Corticosteroid-free remission • Medicine adherence • Adverse effects of treatment • HRQoL	• Clinical remission and response • Endoscopic healing • Mucosal healing (histologic-endoscopic mucosal healing) • Measures of disease activity (symptomatic remission) • Rates of hospitalisation • Rates of surgical intervention • Corticosteroid-free remission • Maintenance of clinical remission • Fatigue response • Endoscopic normalisation • Adverse effects • HRQoL	Data for mortality as an efficacy outcome were not collected during QUASAR (similar to other trials conducted in this disease). However, it was reported as an adverse event. It is anticipated that mortality would not be a key driver within the cost-comparison analysis. Relapse was not an efficacy outcome in QUASAR and ASTRO; however, clinical remission was the primary efficacy endpoint. Since relapse is defined as a loss of remission, clinical remission is indicative of relapse rates. Data on medicine adherence was not collected during the QUASAR and ASTRO trials.

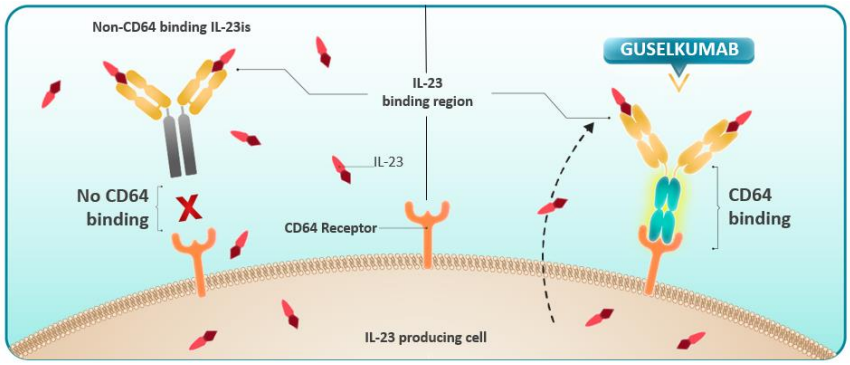
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	• The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • 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 PSS perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	• A cost-comparison analysis has been conducted to estimate the incremental costs of guselkumab versus mirikizumab 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 PSS perspective • An existing PAS for guselkumab has been included as part of the analysis	Johnson & Johnson asserts that guselkumab is most appropriately assessed through the NICE cost-comparison process due to similarities with mirikizumab and vedolizumab, in terms of both effectiveness and resource use. Therefore, a cost-comparison has been submitted. The cost-comparison compares the drug acquisition and administration costs for guselkumab versus mirikizumab and vedolizumab. A 10-year time horizon was adopted to sufficiently reflect all important differences in costs between the technologies being compared, as per the NICE health technology evaluations manual (PMG36).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• The availability and cost of biosimilar and generic products should be taken into account.		
Key: HRQoL, health-related quality of life; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus kinase; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PAS, patient access scheme; PSS, Personal Social Services; TNFi, tumour necrosis factor inhibitor; UC, ulcerative colitis.			

B.1.2. Description of the technology being evaluated

A description of guselkumab is presented in Table 2. The draft Summary of Product Characteristics (SmPC) is presented in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Guselkumab (Tremfya®)
Mechanism of action	Guselkumab is a fully human IgG1λ monoclonal antibody that binds selectively to the p19 protein subunit of IL-23 with high specificity and affinity through the antigen binding site. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines. Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in UC. Guselkumab has demonstrated in vitro blocking of IL-23 and binding to CD64. These results indicate that guselkumab is able to neutralise IL-23 at the cellular source of its production (Figure 1). **Figure 1: Inhibition of IL-23 and CD64 by guselkumab** 
Marketing authorisation/CE mark status	[redacted]
Indications and any restriction(s) as described in the Summary of Product	The anticipated indication is '[redacted]'

Characteristics (SmPC)	Guselkumab is contraindicated in patients with serious hypersensitivity to the active substance or to any of the following excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose, water for injections. Guselkumab may increase the risk of infection and is contraindicated in patients with clinically important active infections (e.g. active tuberculosis).
Method of administration and dosage	Guselkumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of UC. <u>Induction therapy</u>: The recommended induction dose is: • 200 mg administered by IV infusion at Week 0, Week 4, and Week 8; or • 400 mg administered by SC injection at Week 0, Week 4, and Week 8 <u>Maintenance therapy:</u> The recommended maintenance dose is 100 mg administered by SC injection at Week 16 and Q8W thereafter after completion of induction dosing. A dose of 200 mg administered by SC injection at Week 12 and Q4W thereafter may be considered for patients who do not show adequate therapeutic benefit, according to clinical judgement, after completion of induction dosing. Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	The list price of guselkumab is: • 200 mg solution for infusion = [redacted] • 100 mg pre-filled pen (solution for SC injection) = £2,250 • 200 mg pre-filled pen (solution for SC injection) = [redacted] **Induction:** The cost of induction treatment with guselkumab for one patient at list price is [redacted] for IV administration and [redacted] for SC administration **Maintenance:** The annual cost of maintenance treatment with guselkumab per patient with UC at list price is [redacted] for the 100 mg Q8W SC regimen and [redacted] for the 200 mg Q4W SC regimen.
Patient access scheme/commercial arrangement (if applicable)	A patient access scheme representing a simple discount of [redacted]% is currently in place for guselkumab resulting in the following net prices:

	• 200 mg solution for infusion = [redacted] • 100 mg pre-filled pen (solution for SC injection) = [redacted] • 200 mg pre-filled pen (solution for SC injection) = [redacted] **Induction:** The cost of induction treatment with guselkumab via per patient at net price is [redacted] for IV administration and [redacted] for SC administration **Maintenance:** The annual cost of maintenance treatment with guselkumab per patient with UC at net price is [redacted] for the 100 mg Q8W SC regimen and [redacted] for the 200 mg Q4W SC regimen.
Key: IL, interleukin; IV, intravenous; JAK, Janus kinase; MHRA, Medicines and Healthcare products Regulatory Agency; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SmPC, Summary of Product Characteristics; UC, ulcerative colitis. **Source:** Draft SmPC.(1)	

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

B.1.3.1. Disease overview

B.1.3.1.1. Background

UC is a chronic inflammatory condition of the gastrointestinal tract and is the most common form of IBD.(16) UC is characterised by continuous superficial inflammation of the mucosal surface in the colon and rectum, usually beginning distally from the rectum and moving upwards through the colon proximally as the disease progresses, typically following a relapsing–remitting course.(17-20) Patients with UC experience a range of debilitating symptoms.(21) The most common symptoms are rectal bleeding, bloody stools and diarrhoea; however, patients may also experience bowel urgency, increased stool frequency, faecal incontinence, mucus discharge, fatigue, abdominal pain and tenesmus.(21, 22) It is reported that 15% of patients experience an acute exacerbation requiring hospitalisation at some time during their illness.(23) Within 10 years of diagnosis, approximately 10% of adults with UC are reported to have undergone colectomy.(24) There has been only a modest reduction in colectomy rates (approximately 29% reduction 5-years post diagnosis) following the introduction of biologic therapies in 2004.(24)

Although UC primarily manifests in the colon, it is a systemic condition that can negatively impact the skin, joints, eyes and other organs.(17, 22, 25) Inflammatory pathologies that occur outside of the gastrointestinal tract are typically referred to as extraintestinal manifestations(26) and can occur in up to 20–35% of patients with UC.(21)

The pathogenesis of UC is multifactorial and involves a combination of genetic predisposition, dysbiosis, a disrupted defective intestinal epithelium, environmental factors, and dysregulated innate and adaptive immunity.(27-30)

B.1.3.1.2. Diagnosis and disease severity

While UC can develop at any age, peak incidence is between the ages of 15 and 25 years, with a second smaller peak occurring between 55 and 65 years.(31) The incidence between males and females is relatively similar; however, there is some evidence to suggest that females have a lower likelihood of being diagnosed later in their life than males.(32) Diagnosis of UC involves a combination of clinical, biochemical, stool, endoscopic, and histological investigations.(33) Endoscopy with biopsies is the most sensitive and specific tool to establish a diagnosis of UC.(21) In terms of biochemical analysis, the level of C-reactive protein (CRP) can be elevated, but has a low sensitivity.(21) Faecal calprotectin, a neutrophil-derived protein, appears to be the most sensitive marker of intestinal inflammation in IBD, and is widely used in clinical practice for both diagnosis and management.(33)

Since UC can present at various stages of disease severity, the assessment of its severity is important to guide optimal delivery of care.(34) A widely used scoring system for disease severity in UC – and one recommended by the British Society of Gastroenterology (BSG)(35) – is the Mayo score, which considers stool frequency, rectal bleeding, endoscopy subscores and physician global assessment.(36, 37) The score ranges from 0 to 12, with higher scores indicating more severe disease (mild: 3–5; moderate: 6–10; severe: 11–12).(35) Moderate UC is characterised by a complete loss of vascular pattern, blood adherent to the surface of the mucosa, erosions, and mucosal friability, while severe disease is defined by spontaneous bleeding and ulceration.(21) The modified Mayo score omits the physician global

assessment.(37) An overview of the Mayo scoring system is presented in Appendix G.

B.1.3.1.3. Epidemiology

In 2020, the prevalence of UC in the UK was estimated as 0.4%(38); accounting for population adjustments, this leads to an estimated 232,246 people living in England with UC in 2024.(39) Using estimates for the proportion of adults with UC (90%) and the proportion of patients with moderately to severely active UC (52%)(12), approximately 108,691 people over 18 years of age had moderately to severely active UC in 2024. Between 2000 and 2018, the incidence of UC was estimated as 23.2 (95% confidence interval [CI]: 22.8, 23.6) per 100,000 person years.(40)

B.1.3.2. Disease burden

UC is a lifelong disease to manage. Although disease activity improves in approximately 50–70% of patients within the first few years(41), 80% of patients relapse within 5 years(42) and approximately 30–50% of patients progress within 10 years of diagnosis.(43)

In addition, patients with UC are more likely to have multimorbidity (i.e. ≥ 2 comorbidities) compared with patients with Crohn's disease – another common IBD condition.(44) These comorbidities include cancer, cardiovascular diseases (including ischaemic heart disease and stroke), chronic pulmonary diseases, rheumatic diseases (including psoriasis and psoriatic arthritis), diabetes, liver disease, renal disease, neurological disorders and psychological disorders (including anxiety and depression).(45-49)

B.1.3.2.1. Impact on quality of life and psychosocial burden

UC can substantially affect a patient's life, leading to long-term burdensome complications, structural and functional changes, and disability.(21) Patients with UC have impaired physical and mental wellbeing as a result of debilitating symptoms, incontinence, social stigma and sexual challenges.(50-52) Their quality of life (QoL) worsens during periods of flare or active disease and as the disease severity increases, but in remission their QoL may be similar to that of the general

population.(50, 53-56) Patients with moderate or severe symptoms of UC were reported to have significantly lower QoL compared with patients with mild symptoms, as assessed by the 36-item Short Form Health Survey (SF-36), EQ-5D-5L® questionnaire, and the disease-specific Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores.(54, 55) In a systematic literature review (SLR) conducted in 2017, most studies (60–80%) reported that SF-36 scores for the mental and physical component summaries in patients with active UC were meaningfully impaired relative to those of the general population.(50) Fear of disease progression also reduces the patient's QoL, as assessed by the SIBDQ instrument.(57) Non-responders to the treatment are reported to have worse QoL versus responders, regardless of their advanced treatment status (i.e. whether they were ADT-naïve or experienced).(58)

UC has a direct negative impact on patients, their families and caregivers.(59) Symptoms of UC, particularly bowel incontinence and urgency, disrupt the daily life of patients reducing their ability to participate in caregiving, parenting and family planning, and placing unequal burden on the family unit.(60, 61) Moderate to extreme fatigue is associated with a higher likelihood of experiencing extreme difficulties conducting domestic activities.(61) A patient survey investigated the impact of UC on patients' lives compared with other chronic conditions such as rheumatoid arthritis, asthma and migraines.(62) Significantly more patients with UC (53%) felt their condition was controlling their lives compared with patients with other chronic conditions.(62) Patients with UC also reported significantly more worry about disease complications (84%), depression (62%) and embarrassment (70%) compared with patients with the other chronic conditions.(62)

B.1.3.2.2. Economic burden

As well as the physical symptoms of UC, patients often require medical attention or treatment which can contribute to the economic burden on healthcare systems. Healthcare resource use often includes – but is not limited to – outpatient visits for treatment administration, inpatient hospitalisation due to uncontrolled disease, and surgery. As the severity of disease worsens, patients utilise more healthcare

resources and the associated costs increase considerably, compared with patients with mild disease severity.(55)

In addition to this, given its chronic and unpredictable nature, the societal impact of UC is considerable. An SLR on real-world data reported that up to a quarter of patients with UC experience sick leave, up to 17% experience short-term disability, and 7% experience long-term disability.(63) Patients with moderately or severely active UC experience greater work productivity loss, health resource utilisation and associated costs, compared with patients with mild symptoms.(55) Those with surgical interventions also experience substantial productivity loss.(56)

B.1.3.3. Current pathway of care and the anticipated positioning of guselkumab

Treatment options for UC are guided by the severity and the extent of the disease, and the goal of therapy is to relieve symptoms during flare-ups and maintain remission thereafter.(21, 31) The BSG recommends that the primary treatment goal for UC should be symptomatic remission combined with mucosal healing (absence of macroscopic mucosal inflammation or ulceration).(35) Mucosal healing is an important therapeutic goal in clinical practice as there is growing evidence that the presence of endoscopic and histological inflammation is predictive of future flares, lack of sustained remission, and the need for corticosteroids and colectomy.(35)

Guidelines from NICE and the BSG recommend conventional therapy, such as 5-ASA (aminosalicylate), as first-line therapy to induce remission, or corticosteroids and immunomodulator for when 5-ASA is intolerable.(31, 35) Although these therapies are often effective for mild to moderate disease, moderate to severe disease is more challenging to treat. When conventional treatments fail, are not tolerated or are contraindicated, ADTs are recommended for moderately to severely active UC as the standard of care.(31, 35) Advanced therapies recommended by NICE (presented in Figure 2) include biologics: TNF-alpha inhibitors (infliximab, adalimumab, golimumab), anti-integrin (vedolizumab), interleukin (IL)-12/-23 inhibitors (ustekinumab) and IL-23 inhibitors (mirikizumab, risankizumab), and small molecules including: Janus kinase (JAK) inhibitors (tofacitinib, filgotinib and

upadacitinib) and sphingosine-1-phosphate receptor (S1PR) modulators (ozanimod and etrasimod).

TNF-alpha inhibitors are the most commonly used treatments for first-line ADT, given the vast experience of use in UK clinical practice(31). Treatments such as JAK inhibitors, ustekinumab, vedolizumab and etrasimod may be used as first-line ADT in some circumstances – for example, if TNF-alpha inhibitors cannot be tolerated or are unsuitable.(5, 12, 64-66) When first-line ADT has not been effective, clinical guidelines recommend JAK inhibitors (e.g. tofacitinib), anti-integrin (vedolizumab), an IL-12/23 inhibitor (ustekinumab), an IL-23 inhibitor (mirikizumab or risankizumab) or an S1PR modulator (ozanimod or etrasimod).(4, 5, 13, 64, 66) A summary of treatment guidelines from NICE, BSG and the European Crohn's and Colitis Organisation (ECCO) is presented in Appendix G.

Patients are treated until remission and then usually stay on treatment to maintain remission. Importantly, even when receiving ADTs, patients may still lose response to treatment and require switching to a more effective treatment and cycling through different ADTs to achieve and maintain remission, highlighting the importance of treatment options for patients with this life-long chronic condition.(35, 67)

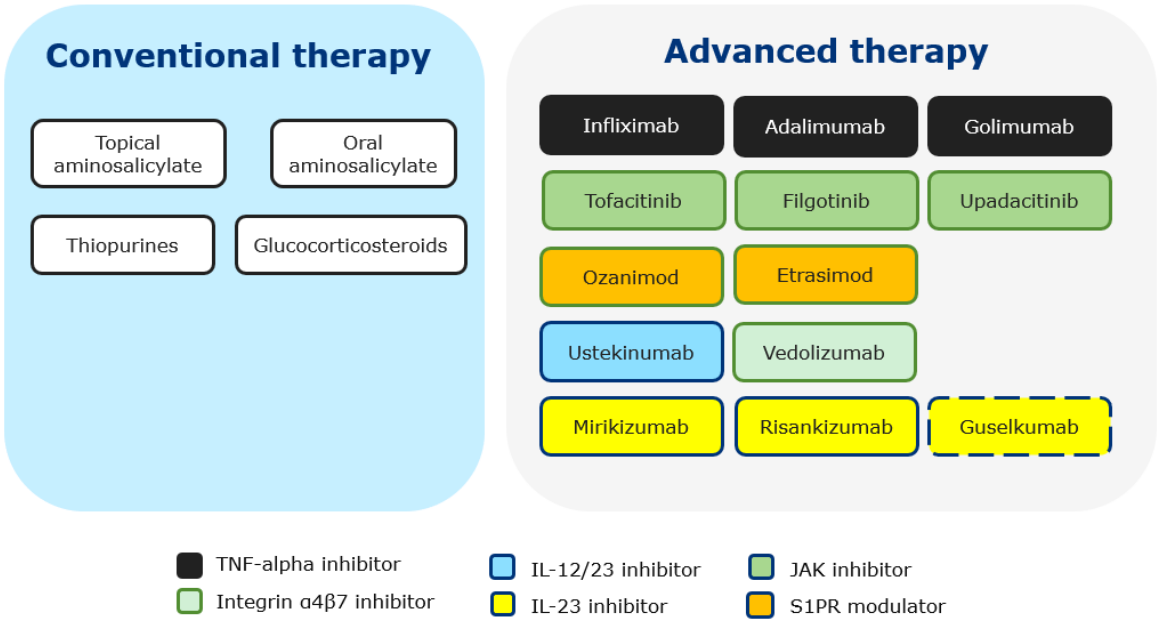
In some patients, surgery such as colectomy (removal of the large bowel) may be an option. Surgery can lead to long-term complications including small bowel obstruction, pouchitis and faecal incontinence.(68) For patients who want to avoid or delay surgery, the need for additional therapeutic treatments in the current treatment landscape is amplified, this is supported by clinical expert opinion.(64)

B.1.3.3.1. Anticipated positioning of guselkumab

Guselkumab is positioned for use in patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to an ADT, including biologics and small molecules such as JAK inhibitors. In line with the recommendations for the selected comparators, it is also anticipated that guselkumab may be used in a small proportion of patients for whom TNF inhibitors are not suitable, similar to the comparators.(4, 5) Figure 2 presents the current

clinical pathway of care for UC in the UK including the proposed positioning of guselkumab.

Figure 2: Clinical pathway of care for patients with ulcerative colitis and anticipated positioning of guselkumab



Key: IL, interleukin; JAK, Janus kinase; S1PR, sphingosine-1-phosphate receptor; TNF, tumour necrosis factor.
Source: Based on NG130(31) and NICE technology appraisals (TA329(69), TA547(66), TA792(65), TA856(70), TA828(64), TA956(12), TA633(71), TA342(5), TA925(4) and TA998(13)).

B.1.3.3.2. Limitations of current treatments

Although multiple treatment options are available to patients with UC in the current pathway of care, including ADTs with different mechanisms of action, there are several challenges remaining.

Corticosteroids are effective for short periods for inducing remission in UC.(72) However, they have no role in the maintenance of remission due to lack of efficacy. Despite this, steroid dependency and excess are common in patients with IBD. Long-term steroid use has substantial side effects including increased rates of infection, adrenal suppression, osteoporosis, diabetes, cardiovascular events, mood disorders and all-cause mortality.

Each class of ADT has limitations and may not be appropriate for all patients:

- TNF inhibitors are not suitable for patients with heart disease, high risk of infections, recurrent infections, malignancies and the elderly(73)
- JAK inhibitors should be used at the lowest dose possible and, due to safety concerns, avoided in people with risk factors if alternatives are available.(74, 75) These risk factors include: age 65 years and older; cigarette smokers or significant smoking history; risk factors for cancer; or risk factors for major adverse cardiovascular events
- S1PR modulators are not suitable for patients with heart disease, heart block, severe infections, active malignancies and severe hepatic impairment; or for people of childbearing potential not using effective contraception(76, 77)

It is estimated that up to 40% of patients with UC will not respond to initial TNF therapy (primary non-response) and up to 46% will lose response over time (secondary loss of response).(78-80) These primary and secondary therapy failure rates remain high despite available treatment options, resulting in suboptimal disease control and frequent treatment switching, leading to considerable patient and economic burden.(81, 82)

A real-world evidence study demonstrated that within 1 year after treatment initiation, 60% or more of patients with UC or Crohn's disease had an inadequate response to their first ADTs (TNF inhibitors or other biologics).(83) Adherence and persistence with therapy was low, which is likely the result of inadequate response to treatment and/or adverse events (AEs) as patients are unlikely to persist taking a medication that is ineffective or causes intolerance or AEs.(83) Furthermore, a 2023 analysis of real-world data regarding patients with UC demonstrated that physicians cited safety concerns in choosing not to prescribe JAK inhibitors to patients otherwise eligible for them.(58)

Following first-line TNF therapy failure, real-world outcomes among patients with UC are less favourable when cycling to another TNF therapy compared with switching to a non-TNF therapy.(84) Therefore, when patients fail or are intolerant to TNF-alpha

inhibitors, treatments that have different mechanisms of action are typically recommended.(35, 37) Even on these treatments, there are challenges such as loss of response and continued uncontrolled UC.(85, 86) Given the challenges with treatment cycling and suboptimal disease control, there is a need for additional treatments in the pathway that are effective, durable and safe.

B.1.3.4. Unmet need

The discussions presented above highlight that there remains a substantial unmet need for effective and well-tolerated therapies that can help patients to achieve and sustain remission.

There is also a need for flexible treatment administration methods. For the population relevant to this submission, i.e. adult patients with moderately or severely active UC who have had an inadequate response, lost response or were intolerant to a biologic or another ADT, the majority of biologic treatment options available are administered via IV infusion in the induction period. This can be difficult for patients whose circumstances mean that attending hospital to receive their treatment is challenging, as well as for those who prefer SC administration. A SLR was conducted that looked at the preference of patients with chronic immune diseases that received IV- or SC-administered treatments. Out of 49 studies reviewed, 36 reported patients favouring SC administration, with a preference to have treatment at home to avoid attending hospital as well as having the convenience and comfort of being at home.(87) Another preference study, specific to IBD, found that the route of administration was one of the most important attributes when choosing a treatment for people with UC; patients preferred oral tablets and SC injections over IV infusion.(88)

In addition to providing more treatment options for this patient population, there is a clear unmet need to broaden treatment administration options to accommodate patient preferences and not further add to the burden of the disease.

B.1.3.5. Relevance of current appraisal to NHS England

As well as increasing options for patients, flexible treatment administration can also contribute to relieving current National Health Service (NHS) pressures in key areas such as reducing waiting times. Many treatment options for UC have a lengthy hospital-administered induction phase due to their IV mode of administration which has considerable patient, carer and healthcare provider burden. Treatments that reduce outpatient visits – such as SC injections, which can be administered at home – are a much-needed addition to the treatment options for moderately to severely active UC.

B.1.4. Equality considerations

Living with IBD is not classed as a disability under the Equality Act. However, it may be considered a disability depending on the effect it has on a patient's daily life.(89) People living with IBD often require specialist medications and surgery, hospital admissions, investigations, and outpatient appointments. Relapses are unpredictable in nature, and around 50% of people with Crohn's disease or UC experience at least one flare-up per year.(90) More than a quarter of people with Crohn's disease or UC had to wait over 1 year for diagnosis, with almost half ending up in Accident and Emergency (A&E) departments during this time.(91) Availability of an additional treatment option that can be safely administered at home may reduce inequalities between people with IBD with varying degrees of disability, and reduce reliance on an overburdened healthcare system.

UC as a type of IBD is often called an invisible disability because it is not easy to see how it affects someone. People with UC can struggle to manage work, education or social activities, and they may not want others to know they have the condition. Many patients feel embarrassed about their symptoms and worry about having accidents, which can lead them to avoid work and social events. An effective treatment can help them feel better and can allow them to live a more normal life, giving them the same chances at work or education and helping them maintain their relationships (emotional and physical), just like anyone without IBD.

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

B.2.1. Clinical outcomes and measures

As discussed in Section B.1.1.3, the two comparators considered in this appraisal are vedolizumab and mirikizumab. Both comparators have received a positive recommendation from NICE that includes the proposed population for this submission. This section provides an overview of the clinical outcomes and measures considered in TA342 (vedolizumab) and TA925 (mirikizumab).(4, 5)

For both appraisals, the economic model structures typically consisted of two phases: a short-term induction phase and a longer-term maintenance phase, which reflected the design of the respective clinical trials. To allow for the varying lengths of induction phase for the different treatments (as per their respective SmPCs), 2-week tunnel states were modelled. Clinical remission and response were the outcomes used to determine whether patients moved on to the maintenance phase.

Across the appraisals, clinical remission and response were defined by the Mayo scoring system (see Section B.1.3.2) and were used to assess patients' disease activity at the end of the induction phase and during the maintenance phase. The maintenance phase in the vedolizumab appraisal (TA342) included surgery and post-surgery health states, the latter of which being dependent on whether or not patients experienced complications.(5) Health states in the maintenance phase were not considered in the mirikizumab submission (TA925) given that it was appraised as a cost-comparison. Instead, the maintenance phase consisted of patients either on treatment or off treatment. This was accepted by the Committee, and the External Assessment Group (EAG) commented that the exclusion of other health states and model simplification was reasonable due to similar downstream costs across treatments driven by the assumption of similar efficacy between mirikizumab and its comparators.(4)

Health-related quality of life (HRQoL) data were captured in the vedolizumab submission via utility values. In TA342, utility data captured in the relevant clinical trial were assigned to health states that used the Mayo score to determine response and remission, whereas literature values (Arseneau et al., 2006(92)) were used for the surgery and post-surgery health states. As TA925 presented a cost-comparison analysis, utilities were not considered.

Management of loss of response or inadequate disease control in the maintenance phase was included in the mirikizumab appraisal. This was modelled as dose escalation for vedolizumab and ustekinumab in TA925.(4) The proportion of patients assumed to receive dose escalation in the maintenance phase was assumed to be 30% for both treatments, with the corresponding higher drug acquisition costs being applied. Dose escalation is not approved for mirikizumab in its SmPC; however, patients receiving mirikizumab maintenance therapy that lose response may receive induction treatment again, known as re-induction. The proportion of patients receiving mirikizumab who received re-induction treatment was based on the observed proportion from the LUCENT-2 trial in the base case (30%) and explored in scenario analyses.(4) A constant risk of discontinuation during the maintenance phase was considered in both appraisals, TA925 used loss of response and TA342 used loss of response as well as AEs.(4, 5)

Finally, AEs were considered in the vedolizumab cost-effectiveness evaluation.(5) These included serious infections and consisted of a weighted average of different infections included in the national schedule of NHS costs. AEs were not modelled in TA925 as comparable safety was demonstrated between mirikizumab and its comparators. This was deemed reasonable by the EAG.(4)

Further details on the clinical outcomes and measures in each of these appraisals are discussed in Table 3. It should be noted that some of these outcomes are relevant to a cost-effectiveness analysis only and therefore not relevant or considered in this appraisal.

Table 3: 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
TA342 (vedolizumab)(5)					
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 lack of available data for infliximab and golimumab in this patient population	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 a random-effects model to be used given the heterogeneity in the studies included 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

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
					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 1 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 1 year if they were responding or in remission. This increased the ICER.	The Committee agreed with the Company that implementing a 1 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	N/A	The Committee did not discuss the approach	N/A

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
		could enter at the end of the induction phase, response dependent. Health states for 'post-surgical remission' and 'post-surgical complications' were also included.		taken to modelling surgery.	
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	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.

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
		states to be derived from the same source.			
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.
TA925 (mirikizumab)(4)					
Response (including remission) after standard induction	Definitions of clinical response were based on the Mayo scoring system as per the LUCENT-1 trial	Response rates in the model were informed by the NMA, synthesised with data for all treatments of interest. Response rates were assumed equal for all treatments in the model.	N/A	N/A	N/A

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
Response after extended induction (scenario)	It was not feasible to perform an NMA on delayed response, as delayed response assessment was not placebo-controlled in any trial. Response after extended induction was therefore assumed equal to ustekinumab overall response rate from TA633, Table 41.		N/A	N/A	N/A
Loss of response in maintenance phase	Discontinuation of maintenance treatment was based on the notion that patients who lose response to treatment also discontinue treatment. This was based on 1-response observed in maintenance RCTs	Loss of response rates were derived from the company's maintenance NMA. The odds ratio for response at the end of the maintenance period for mirikizumab relative to placebo was transformed to an absolute probability. The inverse of this probability (i.e. 1-response) when then used to model the probability of discontinuation. The model assumes that all treatments have the same risk of treatment	N/A	N/A	N/A

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
		discontinuation as mirikizumab. with a constant loss of response within and beyond the trial duration of 1 year.			
Dose escalation / re-induction	The proportion of patients who receive dose escalation or re-induction due to loss of response	The model included dose escalation for vedolizumab and ustekinumab, and re-induction for mirikizumab, as per their SmPCs. For vedolizumab and ustekinumab, 30% of patients were assumed to receive an escalated dose in the maintenance period at any one time, in line with the Committee-preferred approach in TA633 and clinical opinion. For mirikizumab, re-induction was modelled based on the proportion of patients who were re-inducted	The Company performed scenario analyses in which no dose escalation or re-induction was modelled, and in which mirikizumab re-induction was modelled for 30% of patients, similar to all comparators, instead of using the re-induction rates from the trial (results redacted).	N/A	N/A

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
		in the LUCENT-2 trial (redacted).			
Surgery	Surgery and post-surgery health states were not modelled as downstream costs were assumed to be similar across all treatments, in alignment with the assumption of similar efficacy between the intervention and comparators.		N/A	N/A	N/A
HSUVs	Health state utility values were not included given that the submission was appraised via a cost comparison.		N/A	N/A	N/A
Adverse events	Adverse events were not included, as comparable safety was demonstrated across all treatments, therefore it was assumed that costs related to safety would be similar.		N/A	N/A	N/A

Key: ERG, Evidence Review Group; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; N/A, not applicable; RCT, randomised controlled trial; SmPC, Summary of Product Characteristics; TNFi, tumour necrosis factor inhibitor.

B.2.2. Resource use assumptions

The inclusion of resource use and cost elements differed between TA342 and TA925. Drug acquisition and administration costs were common in all appraisals, whilst health state costs, costs of surgery, and costs associated with the management of AEs were only considered in the cost-effectiveness appraisal of vedolizumab (TA342)(5). These costs will not be considered in this cost-comparison submission as it assumed that, with efficacy being similar between guselkumab and its comparators, the downstream health state, surgery and AE costs associated with each treatment would also be similar. This is in line with the cost-comparison appraisal for mirikizumab in UC.(4) Although these costs are not considered in this appraisal, they have been described below for completeness, and a summary is presented in Table 4.

Drug acquisition costs

For both appraisals, drug acquisition unit costs were derived from the British National Formulary (BNF), the drugs and pharmaceutical electronic market information tool (eMIT), the Monthly Index of Medical Specialities (MIMS), previous NICE submissions, and published literature.(93-95) These costs were modelled separately for the induction and maintenance phases; a similar approach is adopted in this submission for consistency.(4, 5)

Dose escalation

TA925 included scenarios with dose escalation for vedolizumab and re-induction for mirikizumab. The Evidence Review Group (ERG) / EAG generally considered the modelling of a 30% dose escalation in the maintenance phase a reasonable assumption. This is supported by a multinational chart review conducted in Europe and Canada of patients with IBD who received treatment with TNF inhibitor, which found that 25.8% of patients with UC required dose escalation.(96)

Administration costs

Administration costs are dependent upon the route of administration. Injectable treatments that are self-administered are assumed to have no additional cost to the NHS after the initial cost associated with self-administering training with a nurse (consistent with administration costs applied to mirikizumab maintenance therapy in TA925).(4) Where IV administration is required, associated costs were informed by the cost of an outpatient visit, based on a weighted average of the NHS reference costs for consultant-led and non-consultant-led non-admitted, face-to-face follow-up appointments (gastroenterology).(4, 97)

Health state and adverse event costs

As described in Section B.2.1, TA342 modelled health state costs such as active UC, response without remission, remission, surgery, and post-surgery.(5) In TA342, healthcare resource use and costs for all non-surgery health states were informed by the publication Tsai et al., 2008.(98) AE costs were modelled in TA342, and costs for serious infections were based on a weighted average of different infections sourced from NHS reference costs.(97)

Table 4: Comparator resource use assumptions in past TAs

Cost category	TA342	TA925
Drug acquisition costs	• Derived from BNF(93), eMIT(94) and MIMS(95) • No dose escalation • Included a stopping rule after 1 year	• Derived from BNF(93), eMIT(94) and MIMS(95) • Included dose escalation/re-induction for 30% of patients • No stopping rule
Drug administration costs	• IV costs were based on NHS tariff FZ37F(99) • No SC costs	• IV costs were based on NHS reference costs CL and NCL WF01A(97) • The first SC dose was assumed to be nurse led; therefore a one-off cost was applied. Subsequent administrations had no cost assigned.

Cost category	TA342	TA925
Healthcare resource use costs	Included as health state specific costs	Not included, due to cost-comparison approach
Costs of surgery	Included	Not included, due to cost-comparison approach
AE costs	Included	Not included, due to cost-comparison approach
Key: AE, adverse event; BNF, British National Formulary; CL, consultant led; eMIT, electronic market information tool; IV, intravenous; MIMS, Monthly Index of Medical Specialities; NCL, non-consultant led; NHS, National Health Service; SC, subcutaneous.		

B.3. Clinical effectiveness

QUASAR and ASTRO trials

- The efficacy and safety data for guselkumab versus placebo are derived from the QUASAR Phase IIb/III and ASTRO Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre trials:
  - QUASAR evaluated the safety and efficacy of guselkumab as IV induction therapy (200 mg at Weeks 0, 4 and 8) and SC maintenance therapy (100 mg Q8W and 200 mg Q4W)
  - ASTRO evaluated the efficacy and safety of guselkumab SC induction therapy (400 mg at Weeks 0, 4 and 8) followed by SC maintenance therapy (100 mg Q8W and 200 mg Q4W)
- The population relevant to the decision problem in this submission is aligned with the pre-specified ADT-failure and ADT-Inadequate Responder (ADT-IR) subgroups in QUASAR and ASTRO, respectively. Although these populations are of interest for this appraisal, efficacy and safety data for the Full Analysis Set for both trial programmes are also presented for completeness

Efficacy data from QUASAR

Induction phase

- A significantly greater proportion of patients in the guselkumab 200 mg IV group achieved clinical remission, symptomatic remission, endoscopic healing, clinical response, histologic-endoscopic mucosal healing and Inflammatory Bowel Disease Questionnaire (IBDQ) remission at Week 12 compared with the placebo group in both the Full Analysis Set and ADT-failure populations

Maintenance phase

- Both guselkumab maintenance dose regimens (200 mg SC and 100 mg SC) demonstrated robust efficacy and improved outcomes compared with placebo across primary and secondary endpoints

Safety data from QUASAR

- Overall, the frequency of serious adverse events (SAEs), AEs leading to discontinuation, and serious infections through Week 44 were low for both placebo and guselkumab
- The guselkumab safety results were consistent with the well-characterised and favourable safety profile of guselkumab in its approved indications of plaque psoriasis and psoriatic arthritis

Efficacy and safety data from ASTRO

- A greater proportion of patients in the guselkumab groups achieved the primary and secondary endpoints compared with placebo, for both the Full Analysis Set and the ADT-IR populations
- Efficacy and safety data for guselkumab SC induction in ASTRO were consistent with results for the IV induction in QUASAR

Efficacy data from the NMA

- In the absence of direct head-to-head data for the efficacy of guselkumab versus the comparators, an NMA was performed to compare the efficacy of guselkumab with that of mirikizumab and vedolizumab
- Guselkumab is a numerically better treatment than vedolizumab and is comparable to mirikizumab for the outcomes of clinical response and remission at the induction stage and at 1 year of maintenance treatment.

Conclusion

- The introduction of guselkumab into UK clinical practice for the treatment of patients with moderately to severely active UC would provide patients with an additional efficacious treatment option with a tolerable and well-characterised safety profile
- The option for an at-home SC induction or hospital-administered IV induction provides additional choice to patients, which can help to reduce the patient, carer and healthcare provider burden. The two maintenance doses also offer flexibility in patients' treatment

B.3.1. Identification and selection of relevant studies

Appendix D describes the details of the SLR process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

A SLR was conducted to identify and select evidence on the efficacy of treatments for patients with moderately to severely active UC. (100) This SLR included treatments and dosages approved globally for UC, including some that are not approved for use in the UK. The results of the SLR were then filtered, and only studies relevant to the decision problem presented in this submission were considered. The SLR identified 188 records reporting on 45 unique RCTs. Of these, five studies were relevant to the NICE decision problem.

QUASAR (Phase IIb induction, Phase III induction and maintenance) and ASTRO are the only trials to provide direct evidence for guselkumab in the treatment of moderately to severely active UC. These studies form the basis of the clinical effectiveness evidence provided in this submission. The methodology and results of these trials are presented in the following sections. The results of the remaining trials (GEMINI-1, LUCENT-1, LUCENT-2 and VISIBLE-1) were utilised for indirect treatment comparisons, and are presented in Section 0.

B.3.2. List of relevant clinical effectiveness evidence

Table 5 summarises the clinical effectiveness evidence supporting guselkumab for the treatment of patients with moderately to severely active UC.

The two pivotal trial programmes for guselkumab in patients with moderately to severely active UC are QUASAR and ASTRO. These studies were designed to support the marketing authorisation of guselkumab in UC and are the largest and most robust Phase IIb/III RCTs analysing the efficacy and safety of the relevant dose of guselkumab in the population of interest for this submission. Full details of the pivotal Phase III trials are provided in Sections B.3.3–B.3.5.4. Supportive data from the QUASAR Phase IIb induction study are presented in Appendix I.

Table 5: Clinical effectiveness evidence

Study	QUASAR (NCT04033445)	ASTRO (NCT05528510)
Study design	A Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study	A Phase III, randomised, double-blind, placebo-controlled, parallel-group multicentre study
Population	Adults ≥ 18 years of age with moderately to severely active ulcerative colitis who had demonstrated an inadequate response or failure to tolerate conventional therapy (6-mercaptopurine, azathioprine or corticosteroids) or advanced therapy (TNF-alpha antagonists, vedolizumab or tofacitinib)	Adults ≥ 18 years of age with moderately to severely active ulcerative colitis who had demonstrated an inadequate response to or intolerance of conventional therapy (6-mercaptopurine, azathioprine or corticosteroids) or advanced therapy (TNF-alpha antagonists, vedolizumab, ozanimod or approved JAK inhibitors)
Intervention(s)	Guselkumab: • 200 mg IV induction at Weeks 0, 4 and 8 followed by guselkumab 200 mg SC maintenance every 4 weeks • 200 mg IV induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg SC maintenance every 8 weeks	Guselkumab: • 400 mg SC induction at Weeks 0, 4 and 8 followed by guselkumab 200 mg SC maintenance every 4 weeks • 400 mg SC induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg SC maintenance every 8 weeks
Comparator(s)	Placebo	Placebo
Indicate if study supports application for marketing authorisation (yes/no)	Yes	Yes
Reported outcomes specified in the decision problem	• Symptomatic remission • Clinical response • Clinical remission • UC-related hospitalisations • UC-related surgeries	• Symptomatic remission • Clinical response • Clinical remission • Endoscopic improvement • Histologic-endoscopic mucosal improvement

Study	QUASAR (NCT04033445)	ASTRO (NCT05528510)
	• Endoscopic healing • Histologic-endoscopic mucosal healing • Corticosteroid-free clinical remission • Adverse events • HRQoL	• Adverse events
All other reported outcomes	• Maintenance of clinical remission • Fatigue response • Endoscopic normalisation	
Key: HRQoL, health-related quality of life; IV, intravenous; JAK, Janus kinase; SC, subcutaneous; TNF, tumour necrosis factor; UC, ulcerative colitis. **Sources:** Johnson & Johnson. Data on file (2025) (101, 102)		

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

B.3.3.1. QUASAR

B.3.3.1.1. Study design

The clinical development programme for guselkumab in UC included three studies conducted under a single protocol: Phase IIb induction dose-ranging study (IS1), Phase III induction study (IS2) and Phase III maintenance study (CNTO1959UCO3001; QUASAR). The three studies were randomised, double-blind, placebo-controlled, parallel-group, multicentre studies that evaluated the safety and efficacy of guselkumab in adults with moderately to severely active UC with a history of an inadequate response or failure to tolerate conventional therapies (i.e. 6-mercaptopurine, azathioprine or corticosteroids) or ADTs (i.e. TNF-alpha antagonists; vedolizumab; tofacitinib).(101)

The study scheme for QUASAR is presented in Figure 3. The maintenance study was a randomised withdrawal study; the randomised population were clinical responders to IV guselkumab from IS1 or IS2 who were randomised to receive guselkumab 200 mg SC Q4W, guselkumab 100 mg SC Q8W, or placebo SC. These included guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24.

Phase IIb induction study

A Phase IIb dose-ranging study was conducted to inform the induction dose for the Phase III induction study. Patients were randomised in a 1:1:1 ratio to receive guselkumab 200 mg IV, guselkumab 400 mg IV or placebo IV administered at Weeks 0, 4 and 8.(8) An interim analysis of the first 150 randomised participants who completed the Week 12 visit or had terminated study participation before Week 12 was performed. The results showed no apparent incremental benefit with the higher guselkumab induction dose across key efficacy measures, and thus guselkumab

200 mg IV was selected as the induction dose for confirmatory evaluation in the Phase III induction study. Further details of this trial are presented in Appendix I.

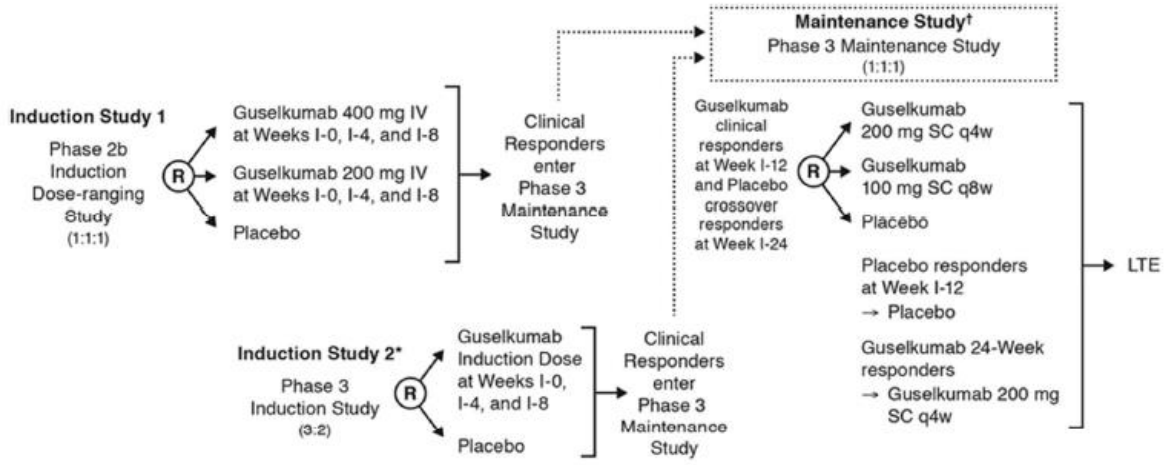
Pivotal Phase III induction study

A Phase III study was conducted to evaluate the efficacy and safety of guselkumab as induction therapy. Patients were randomised in a 3:2 ratio to receive guselkumab 200 mg IV or placebo IV administered at Weeks 0, 4 and 8.(101) All patients were evaluated for clinical response at Week 12. Patients initially randomised to placebo who were not in clinical response at Week 12 crossed over to guselkumab, received three doses of guselkumab 200 mg IV at Weeks 12, 16 and 20, and were re-evaluated for clinical response at Week 24. Patients who were initially randomised to guselkumab and who did not achieve clinical response at Week 12 received three doses of guselkumab 200 mg SC at Weeks 12, 16 and 20 and were re-evaluated for clinical response at Week 24.

Pivotal Phase III maintenance study

A Phase III study was conducted to evaluate the efficacy and safety of guselkumab as maintenance therapy. Guselkumab clinical responders at Week 12 and placebo crossover responders at Week 24 were randomised in a 1:1:1 ratio to guselkumab 200 mg SC every 4 weeks, guselkumab 100 mg SC every 8 weeks, or placebo SC.(101) Patients who responded on placebo at Week 12 entered the Phase III maintenance study on placebo, and patients who responded on guselkumab at Week 24 entered the Phase III maintenance study on guselkumab 200 mg SC every 4 weeks, but were not re-randomised.

Figure 3: Study scheme for QUASAR



Key: IV, intravenous; LTE, long-term extension; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous.
Notes: * Induction Study 2 will not begin until the Phase III guselkumab induction dose is selected based on an interim analysis of Induction Study 1. † Placebo responders at Week I-12 and guselkumab 24-Week responders will enter the maintenance study but will not undergo re-randomisation.
Source: Johnson & Johnson, Data on File (2025).(101)

B.3.3.1.1.1 Eligibility criteria

Key inclusion criteria were adults ≥ 18 years, documented diagnosis (histological and either endoscopic or radiographic) of UC at least 3 months prior to screening.(101) At baseline, patients must have had moderately to severely active UC with a baseline modified Mayo score of 4–9, inclusive. Patients must have also had a Mayo rectal bleeding subscore ≥ 1 and a screening endoscopy with ≥ 2 on the endoscopy subscore of the Mayo score. Patients who had demonstrated inadequate response to or failed either conventional therapy or ADT were included. Main exclusion criteria included patients who had severe extensive colitis. Further details regarding the inclusion and exclusion criteria can be found in Appendix I.

B.3.3.1.1.2 Study endpoints

In the QUASAR studies, the primary endpoint was clinical remission. Key secondary endpoints included symptomatic remission, endoscopic healing, clinical response and histologic-endoscopic mucosal healing.(101) An overview of the clinical

effectiveness outcomes are presented in Table 6 and the definitions are presented in Table 7.

Table 6: Overview of the endpoints presented for QUASAR induction and maintenance studies

Type of endpoint	QUASAR Phase III induction study	QUASAR phase III maintenance study
Primary	Clinical remission at week 12	Clinical remission at week 44
Secondary	Symptomatic remission at week 12	Symptomatic remission at week 44
	Endoscopic healing at week 12	Endoscopic healing at week 44
	Clinical response at week 12	Corticosteroid-free clinical remission at week 44
	Symptomatic remission at week 4	Maintenance of clinical response at week 44
	Histologic-endoscopic mucosal healing at week 12	Histologic-endoscopic mucosal healing at week 44
	IBDQ remission at week 12	IBDQ remission at week 44
	Fatigue response at week 12	Fatigue response at week 44
	Symptomatic remission at week 2	Maintenance of clinical remission
	Endoscopic normalisation at week 12	Endoscopic normalisation at week 44

Key: IBDQ, Inflammatory Bowel Disease Questionnaire.
Source: Johnson & Johnson. Data on file (2025) (101)

Table 7: Definitions of clinical outcomes in QUASAR

Outcome	Definition
Clinical remission	A Mayo stool frequency subscore of 0 or 1 which has not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy,
Symptomatic remission	A stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore has not increased from induction baseline
Endoscopic healing	An endoscopy subscore of 0 or 1 with no friability present on the endoscopy
Corticosteroid-free clinical remission	Clinical remission without any use of corticosteroids for ≥ 8 weeks prior to assessment and also meeting the criteria for clinical remission at assessment

Outcome	Definition
Clinical response	A decrease from baseline in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a ≥ 1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
Histologic-endoscopic mucosal healing	Achieving a combination of histologic healing and endoscopic healing: • Histological healing defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system(103) (i.e. Geboes score ≤ 3.1) • Endoscopic healing defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy
IBDQ remission	Total IBDQ score ≥ 170(104, 105)
Fatigue response	A ≥ 7-point improvement from induction baseline in PROMIS-Fatigue short form 7a
Endoscopic normalisation	An endoscopy subscore of 0 (which requires that no friability is present)
Maintenance of clinical remission	Clinical remission at Week 44 among participants in clinical remission at maintenance baseline

Key: IBDQ, Inflammatory Bowel Disease Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System.
Source: Johnson & Johnson, Data on File (2025).(101)

B.3.3.1.2. Summary of statistical analysis

B.3.3.1.2.1 Analysis sets in QUASAR

The data sets analysed and number of patients in each analysis population for the QUASAR Phase III induction and Phase III maintenance studies relevant to this submission are presented in Table 8.

Analysis was performed on the predefined ADT-failure subpopulation. The ADT-failure subpopulation in the trial comprised patients who had inadequate response or failure to tolerate TNF-alpha antagonists, vedolizumab, or tofacitinib.

Table 8: Analysis sets used to analyse outcomes in QUASAR Phase III induction and maintenance study

Analysis set	Description
Induction study	
Randomised Analysis Set (n = 736)	All participants who were randomised in the study.
Full Analysis Set (primary analysis population) (n = 701)	All randomised participants with a baseline modified Mayo score of 5 to 9 who received at least 1 (partial or complete) dose of study intervention. Participants were analysed according to their randomised or assigned study intervention regardless of the study intervention they actually received.
Safety Analysis Set (primary safety population) (n = 701)	All randomised participants with a baseline modified Mayo score of 5 to 9 who received at least 1 (partial or complete) dose of study intervention. Participants were analysed according to the study intervention they actually received.
Maintenance study	
Randomised Analysis Set (n = 599)	All participants who were randomised in the maintenance study (regardless of a modified Mayo score).
Randomised Full Analysis Set (primary analysis population) (n = 568)	Participants with a modified Mayo score of 5 to 9 who were randomised and treated in the maintenance study. Participants were analysed according to their randomised or assigned study intervention regardless of the study intervention they actually received.
Randomised Safety Analysis Set (primary safety population) (n = 568)	Participants with a modified Mayo score of 5 to 9 who were randomised and treated in the maintenance study. Participants were analysed according to the study intervention they actually received.
Source: QUASAR induction study, clinical study report (6) and QUASAR maintenance study, clinical study report.(7)	

B.3.3.1.2.2 Statistical analysis

The sections below summarise the statistical analysis conducted in the QUASAR Phase III induction and maintenance studies. The consistency of the efficacy of guselkumab induction and guselkumab maintenance dose regimens was evaluated across clinically relevant subgroups of participants with UC in the induction studies and in the primary population of participants who were clinical responders to guselkumab IV induction and randomised in the maintenance study, respectively.

B.3.3.1.2.2.1 QUASAR Phase III induction study

A global hierarchical testing procedure was employed to control the overall Type 1 error rate over the primary and the major secondary efficacy analyses at the (2-sided) 0.05 significance level. A major secondary endpoint was considered significant only if all the previous endpoints in the hierarchy and the current endpoint tested positive at the 2-sided 0.05 level of significance. If an endpoint was not deemed to be statistically significant, all subsequent tests in the hierarchy were considered not to be significant. The global testing procedure for primary and major secondary endpoints is presented in Appendix I.

No interim analyses were completed for the QUASAR Phase III induction study. The date of the last observation recorded as part of the database lock was 12 January 2023. A summary of the analysis performed during the QUASAR Phase III induction trial is shown in Table 9.

Table 9: Summary of statistical analyses for QUASAR Phase III induction study

Hypothesis objective	The primary hypothesis was that guselkumab is superior to placebo in inducing clinical remission at Week 12
Statistical analysis	The analysis of the primary endpoint was based on the Full Analysis Set. For patients experiencing ICE category 4, their observed clinical remission status (if available) at Week 12 was used. In the primary analysis, data were analysed according to the randomised study intervention regardless of the study intervention actually received. The treatment difference between groups was tested using a CMH test (2-sided) stratified by ADT-failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No). Summaries of the proportion of patients in clinical remission at Week 12 by treatment group, the adjusted treatment difference (with CMH weight) between the guselkumab treatment group and the placebo group, as well as the associated 95% CIs, were presented. The comparison between guselkumab and placebo was controlled at the 2-sided 0.05 significance level. The study was considered positive if the guselkumab group was significantly different from the placebo group for the primary endpoint. The major secondary endpoints were analysed based on the Full Analysis Set. The statistical methodology for testing of the major secondary endpoints was the same as the methodology for the primary endpoint analysis.

Sample size, power calculation	The sample size in the induction study is based on statistical power considerations for clinical remission at Week 12, and the objective of providing a sufficient number of patients, in conjunction with Induction Study 1, for the primary population of the maintenance study. Assuming an 8% clinical remission in the placebo group and 20% in the guselkumab, 148 patients in the placebo group and 222 patients in the 200 mg IV guselkumab group (370 patients in total 2:3 randomisation ratio for placebo: guselkumab) provided statistical power of 90% to detect a treatment difference in the primary efficacy evaluation of clinical remission at Week 12 between the guselkumab group and placebo using a 2-sided Chi-squared test at a 0.05 significance level. To provide a sufficient number of patients for the primary analysis population in the Maintenance Study, it was estimated that a total sample size of approximately 1,000 patients across Induction Study 1 and Induction Study 2 was required and that the sample size for Induction Study 2 would be at least 560 patients in the primary analysis population. A sample size of 560 patients in the primary analysis population of Induction Study 2 provided approximately 90% power or above for all the primary and major secondary endpoints except for the endpoints of symptomatic remission at Week 2 and endoscopic normalisation at Week 12.
Data management, patient withdrawals	After accounting for the ICE strategies, patients who were missing any or all of the Mayo subscores that comprised the primary endpoint at Week 12 were considered not to be in clinical remission at Week 12 (i.e. non-responder imputation). After accounting for the ICE strategies, any missing data for the major secondary endpoints were handled with non-responder imputation.
Key: ADT, advanced therapy; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ICE, intercurrent event; IV, intravenous. **Source:** QUASAR induction study, clinical study report.(6)	

B.3.3.1.2.2.2 QUASAR Phase III maintenance study

A hierarchical testing procedure was used to control the overall Type 1 error rate over the primary and major secondary efficacy analyses at the 2-sided 0.05 significance level within a guselkumab dose group. The primary endpoint was tested using a fixed sequence testing procedure, beginning with the high maintenance dose group (guselkumab 200 mg SC every 4 weeks [Q4W]). Each dose that tested positive for the primary endpoint was then tested in hierarchical order. A major secondary endpoint for a dose group was considered significant only if the previous endpoints in the hierarchy and the current endpoint tested positive at the 2-sided

0.05 level of significance. If an endpoint was not deemed to be statistically significant, all subsequent tests in the hierarchy for that dose were considered not to be significant. The global testing procedure for primary and major secondary endpoints is presented in Appendix I.

No interim analyses were completed for the QUASAR Phase III maintenance study. The date of the last observation recorded as part of the database lock was 19 September 2023. A summary of the analysis performed during the QUASAR Phase III maintenance trial is shown in Table 10.

Table 10: Summary of statistical analyses for QUASAR Phase III maintenance study

Hypothesis objective	The primary hypothesis was that guselkumab is superior to placebo in achieving clinical remission at Week 44.
Statistical analysis	In the primary analysis, data from all patients in the Randomised Full Analysis Set were analysed according to the randomised study intervention regardless of the study intervention they actually received. Summaries of the proportion of patients in clinical remission at Week 44 (as well as the associated 95% CI) by treatment group, the adjusted treatment difference (with CMH weight) between each guselkumab treatment group and the placebo group, as well as the associated 95% CI were presented. For testing of the primary endpoint, the efficacy of each guselkumab group versus placebo was compared. For all statistical comparisons of the primary endpoint, a CMH test (2-sided) stratified by clinical remission status at maintenance baseline based on the final endoscopy score (Yes/No), and induction dose treatment (guselkumab 400 mg IV, guselkumab 200 mg IV, placebo IV → guselkumab 200 mg IV) was used. A fixed sequence multiplicity-controlled testing procedure, starting with the high guselkumab dose group (200 mg SC Q4W) for clinical remission at Week 44 was used to control the overall Type 1 error rate at the 0.05 level (2-sided) over the primary and major secondary endpoints. The study was considered positive if the test involving the high maintenance dose group shows a statistically significant difference versus placebo for the primary endpoint of clinical remission at Week 44. The major secondary endpoints were analysed based on the Randomised Full Analysis Set. The attributes and strategies for the ICEs that were used for the primary estimand for the primary endpoint analysis were also used for each of the major secondary endpoints (except for clinical remission at Week 44 among the

	patients who had achieved clinical remission at maintenance baseline). For clinical remission at Week 44 among the patients who had achieved clinical remission at maintenance baseline, a CMH test (2-sided) stratified by induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo IV→ guselkumab 200 mg) was used.
Sample size, power calculation	Assuming a 25% clinical remission rate at Week 44 for placebo and 45% for each of the guselkumab treatment groups), 118 patients in each randomised group (354 patients in total) provided a statistical power of 90% at a significance level of 0.05 (2-sided) for the primary endpoint. However, the targeted number in the primary analysis population was increased to 484 patients due to the need to power at least 90% for the major secondary endpoints except for the endpoints of maintenance of clinical remission at Week 44 (among the patients who had achieved clinical remission at maintenance baseline) and endoscopic normalisation at Week 44 (the statistical power for these two endpoints was < 75%). The actual number of patients in the primary analysis population of this study depended on the number of guselkumab clinical responders at Week 12 and placebo IV → guselkumab clinical responders at Week 24 from induction study 1 and 2.
Data management, patient withdrawals	For all binary endpoints, including the primary endpoint, patients who were missing one or more component scores pertaining to a binary endpoint at the designated timepoint, after accounting for ICE strategies, were considered not to have achieved the endpoint at that timepoint, unless stated otherwise.
Key: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; ICE, intercurrent event; IV, intravenous; Q4W, every 4 weeks; SC, subcutaneous. **Source:** QUASAR maintenance study, clinical study report.(7)	

B.3.3.1.3. Patient disposition and baseline characteristics

B.3.3.1.3.1 QUASAR Phase III induction study

In the QUASAR Phase III induction study, 736 patients were randomised, of whom 702 had a baseline modified Mayo score of 5–9.(6) Following discontinuation of one patient, the Full Analysis Set comprised 701 treated patients, including 421 in the guselkumab arm and 280 in the placebo arm. The patient flow diagram for the QUASAR Phase III induction study is presented in Appendix D.

The baseline characteristics for the Full Analysis Set in the QUASAR Phase III induction study are presented in Table 11 and indicate that the treatment arms were

generally well balanced.(6) The proportion of patients with a history of ADT-failure was 49.4% in the guselkumab arm and 48.6% in the placebo arm.

Baseline characteristics for the ADT-failure population are presented in Appendix I.

Table 11: Baseline characteristics of patients in QUASAR Phase III induction study, Full Analysis Set

Characteristic	Placebo (N = 280)	Guselkumab 200 mg (N = 421)	Total (N = 701)
Age, years			
Mean (SD)	39.8 (13.4)	41.0 (13.9)	40.5 (13.7)
Median (range)	38.0 (18–75)	39.0 (18–79)	39.0 (18–79)
Sex, n (%)			
Female	119 (42.5)	183 (43.5)	302 (43.1)
Male	161 (57.5)	238 (56.5)	399 (56.9)
Weight (kg)			
Mean (SD)	71.83 (17.032)	72.87 (16.713)	72.45 (16.837)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.2)	1 (0.1)
Asian	66 (22.1)	88 (20.9)	150 (21.4)
Black or African American	3 (1.1)	4 (1.0)	7 (1.0)
Native Hawaiian or Other Pacific Islander	0	2 (0.5)	2 (0.3)
White	205 (73.2)	303 (72.0)	508 (72.5)
Multiple	0	1 (0.2)	1 (0.1)
Not reported	10 (3.6)	22 (5.2)	32 (4.6)
UC disease duration, years			
Mean (SD)	7.09 (6.545)	7.80 (7.728)	7.52 (7.282)
Median (IQR)	5.21 (2.40–9.47)	5.52 (2.61–10.61)	5.31 (2.54–10.03)
Extent of disease, n (%)			
Limited to left side of colon	133 (47.5)	233 (55.3)	366 (52.2)
Extensive	147 (52.5)	188 (44.7)	335 (47.8)
Mayo score			
Mean (SD)	9.2 (1.34)	9.1 (1.36)	9.1 (1.35)
Median (IQR)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)

Characteristic	Placebo (N = 280)	Guselkumab 200 mg (N = 421)	Total (N = 701)
Modified Mayo score			
Mean (SD)	6.9 (1.07)	6.9 (1.13)	6.9 (1.10)
Median (IQR)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)
Partial Mayo score			
Mean (SD)	6.5 (1.21)	6.4 (1.22)	6.5 (1.22)
Median (IQR)	6.0 (6.0–7.0)	6.0 (6.0–7.0)	6.0 (6.0–7.0)
Severity of UC disease, n (%)			
Moderate (6 ≤ Mayo score≤ 10)	229 (81.8)	346 (82.2)	575 (82.0)
Severe (Mayo score > 10)	51 (18.2)	75 (17.8)	126 (18.0)
Severity of endoscopy subscore, n (%)			
Moderate (endoscopy subscore = 2)	100 (35.7)	125 (29.7)	225 (32.1)
Severe (endoscopy subscore = 3)	180 (64.3)	296 (70.3)	476 (67.9)
Extraintestinal manifestations, n (%)			
Present	30 (10.7)	60 (14.3)	90 (12.8)
Absent	250 (89.3)	361 (85.7)	611 (87.2)
CRP (mg/L)			
Mean (SD)	8.3 (11.66)	9.0 (12.40)	8.7 (12.11)
Median (IQR)	3.8 (1.6–9.1)	4.3 (1.5–11.2)	4.2 (1.5–10.1)
Abnormal CRP (> 3 mg/L), n (%)	160 (57.6)	248 (59.6)	408 (58.8)
Faecal calprotectin (mg/kg)			
Mean (SD)	2,709.2 (4,018.92)	3,422.5 (5,174.90)	3,132.8 (4,749.07)
Median (IQR)	1,606.0 (654.0–3,077.0)	1,651.0 (647.0–3,479.0)	1,641.0 (647.0–3,304.0)
Abnormal faecal calprotectin (> 250 mg/kg), n (%)	225 (88.9)	333 (90.0)	558 (89.6)
Albumin (g/L)			
Mean (SD)	43.0 (4.07)	42.9 (4.08)	43.0 (4.07)
Median (IQR)	43.0 (41.0–46.0)	43.0 (41.0–46.0)	43.0 (41.0–46.0)

Characteristic	Placebo (N = 280)	Guselkumab 200 mg (N = 421)	Total (N = 701)
UC-related ADT medication history			
Patients without a history of ADT-failure, N (%)	144 (51.4)	213 (50.6)	357 (50.9)
ADT-naïve, n (%)	137 (48.9)	202 (48.0)	339 (48.4)
ADT-experienced, without documented failure, n (%)	7 (2.5)	11 (2.6)	18 (2.6)
Patients with a history of ADT-failure, N (%)	136 (48.6)	208 (49.4)	344 (49.1)
Key: ADT, advanced therapy; CRP, C-reactive protein; IQR, interquartile range; SD, standard deviation; UC, ulcerative colitis. **Notes**: Includes only patients with modified Mayo score 5–9 at induction baseline. **Source**: QUASAR induction study, clinical study report.(6)			

B.3.3.1.3.2 QUASAR Phase III maintenance study

A total of 846 patients who completed the Phase IIb induction study (n = 267) or the Phase III (n = 579) induction study, and who were in clinical response, were enrolled in the maintenance study.(7) Of these patients, 599 were randomised and 568 had a modified Mayo score of 5–9 at induction baseline. Therefore, the Randomised Full Analysis Set comprised 568 treated patients, including 188 in the guselkumab 100 mg SC Q8W) arm, 190 in the guselkumab 200 mg SC Q4W arm, and 190 in the placebo arm. The patient flow diagram for the QUASAR Phase III maintenance study is presented in Appendix D.

The baseline characteristics for Randomised Full Analysis Set in QUASAR Phase III maintenance study are listed in Table 12. In line with the induction study, treatment arms were well balanced.(7) The proportion of patients with a history of ADT-failure was 43.7% in the guselkumab arm and 39.5% in the placebo arm.

Table 12: Baseline characteristics of patients in QUASAR Phase III maintenance study, Randomised Full Analysis Set

Characteristic	Placebo[a] (N = 190)	Guselkumab combined (N = 378)	Total (N = 568)
Age, years			
Mean (SD)	41.2 (13.58)	40.4 (13.84)	40.7 (13.75)
Median (range)	39.5 (18–76)	39.0 (18–79)	39.0 (18–79)
Sex, n (%)			
Female	81 (42.6)	176 (46.6)	257 (45.2)
Male	109 (57.4)	202 (53.4)	311 (54.8)
Weight, kg			
Mean (SD)	73.56 (16.997)	70.81 (16.669)	71.73 (16.815)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	34 (17.9%)	82 (21.7%)	116 (20.4%)
Black or African American	2 (1.1%)	4 (1.1%)	6 (1.1%)
Native Hawaiian or Other Pacific Islander	1 (0.5%)	0	1 (0.2%)
White	142 (74.7%)	274 (72.5%)	416 (73.2%)
Multiple	1 (0.5%)	0	1 (0.2%)
Not Reported	10 (5.3%)	18 (4.8%)	28 (4.9%)
Mayo score			
Mean (SD)	3.3 (2.01)	3.2 (1.88)	3.2 (1.92)
Median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)
Modified Mayo score			
Mean (SD)	2.5 (1.57)	2.5 (1.51)	2.5 (1.53)
Median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Partial Mayo score			
Mean (SD)	1.7 (1.34)	1.6 (1.18)	1.6 (1.24)
Median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)
Endoscopic healing[b], n (%)			
Yes	68 (35.8)	154 (40.7)	222 (39.1)
No	122 (64.2)	224 (59.3)	346 (60.9)
Endoscopic normalisation[c], n (%)			
Yes	39 (20.5)	88 (23.3)	127 (22.4)
No	151 (79.5)	290 (76.7)	441 (77.6)

Characteristic	Placebo[a] (N = 190)	Guselkumab combined (N = 378)	Total (N = 568)
Clinical remission[d], n (%)			
Yes	59 (31.1)	135 (35.7)	194 (34.2)
No	131 (68.9)	243 (64.3)	374 (65.8)
IBDQ remission[e], n (%)			
Yes	142 (75.5)	262 (69.5)	404 (71.5)
No	46 (24.5)	115 (30.5)	161 (28.5)
CRP, mg/L			
Mean (SD)	3.5 (5.13)	4.0 (9.18)	3.8 (8.05)
Abnormal CRP (> 3 mg/L), n (%)	63 (33.2)	119 (31.5)	182 (32.0)
Faecal calprotectin, mg/kg			
Mean (SD)	1143.2 (2,683.43)	1116.4 (2,367.19)	1125.4 (2,475.49)
Abnormal faecal calprotectin (> 250 mg/kg), n (%)	102 (54.3)	198 (53.2)	300 (53.6)
Albumin (g/L), mean (SD)	45.9 (3.08)	45.6 (3.40)	45.7 (3.30)
UC-related ADT medication history, n (%)			
Patients without a history of ADT-failure	115 (60.5)	213 (56.3)	328 (57.7)
ADT-naïve	108 (56.8)	201 (53.2)	309 (54.4)
ADT-experienced, without documented failure	7 (3.7)	12 (3.2)	19 (3.3)
Patients with a history of ADT-failure	75 (39.5)	165 (43.7)	240 (42.3)

Key: ADT, advanced therapy; CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis; IQR, interquartile range; SC, subcutaneous; SD, standard deviation.
Notes: Includes only participants with modified Mayo score 5-9 at induction baseline. [a] Participants who were in clinical response to guselkumab IV induction dosing and were randomised to placebo SC on entry into the maintenance study. [b] Defined as an endoscopy subscore of 0 or 1 with no friability present on the endoscopy. [c] Defined as an endoscopy subscore of 0. [d] Defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline. [e] Defined as a total IBDQ score ≥ 170.
Source: QUASAR maintenance study, clinical study report.(7)

B.3.3.2. ASTRO

B.3.3.2.1. Study design

ASTRO is a Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of guselkumab SC induction therapy in adult participants with moderately to severely active UC who had demonstrated an inadequate response to or intolerance of conventional therapy (i.e. 6-mercaptopurine, azathioprine, or corticosteroids) or ADT (i.e. TNF antagonists; vedolizumab; ozanimod; JAK inhibitors).(102)

Week 12 analyses in QUASAR Phase IIb induction study demonstrated similar efficacy with guselkumab induction doses of 200 mg IV and 400 mg IV.(102) With an estimated bioavailability of approximately 50% for guselkumab SC, a 400 mg SC dose of guselkumab is expected to result in comparable overall guselkumab exposure (area under the curve [AUC]) to the 200 mg IV dose. As a result, a single SC induction guselkumab dose regimen (400 mg SC at Weeks 0, 4, and 8) was selected in the ASTRO study.

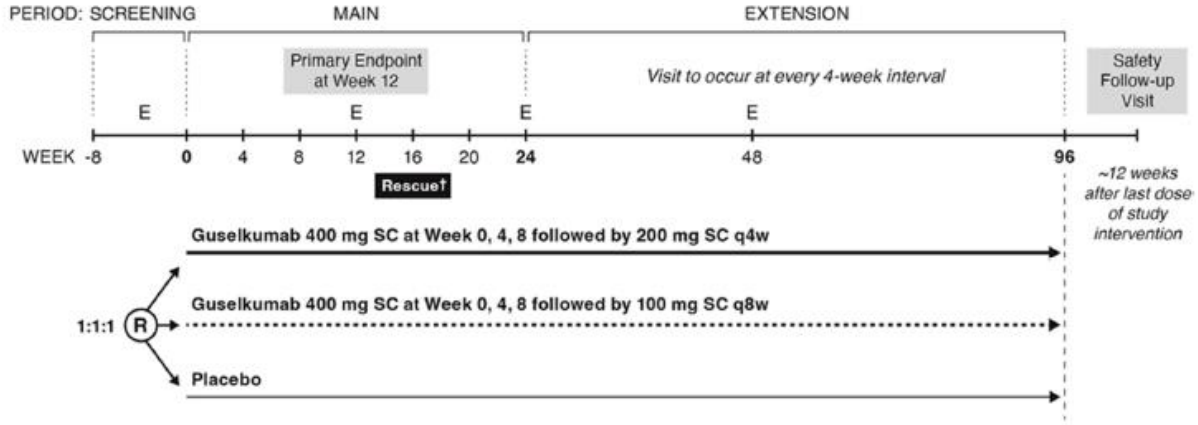
To determine the efficacy of guselkumab SC versus placebo, eligible patients were randomised in a 1:1:1 ratio to the following intervention groups(102):

- Guselkumab 400 mg SC at Weeks 0, 4 and 8 followed by guselkumab 200 mg SC every 4 weeks (starting at week 12) through Week 24
- Guselkumab 400 mg SC at Weeks 0, 4 and 8 followed by guselkumab 100 mg SC every 8 weeks (starting at week 16) through Week 24
- Placebo SC every 4 weeks from Week 0 through Week 24

All patients in the placebo group who met rescue criteria at Week 16 (defined as no improvement in Mayo endoscopy subscore at Week 12 and a < 2-point improvement in partial Mayo score at Weeks 12 and 16, when compared with baseline) received rescue treatment (i.e. guselkumab 400 mg SC at Weeks 16, 20 and 24 followed by guselkumab 100 mg SC every 8 weeks).(102) Patients randomised to guselkumab who met rescue criteria at Week 16 continued their assigned treatment regimen and

received blinded sham rescue with matching placebo SC injections at Weeks 16, 20 and 24. All patients who reached the Week 24 visit and benefited from the study intervention, in the opinion of the investigator, were eligible for the 72-week study extension. At Week 24, patients who entered the 72-week extension period continued the same treatment regimen they received before Week 24 (either the treatment regimen assigned at randomisation, or the rescue regimen as described). This is presented in Figure 4.

Figure 4: Schematic overview of ASTRO



Key: E, endoscopy; q4w, every 4 weeks; q8w, every 8 weeks; R, randomisation; SC, subcutaneous.
Notes: †, rescue initiation at Week 16 upon meeting rescue criteria.
Source: Johnson & Johnson, Data on File (2025).(102)

B.3.3.2.1.1 Eligibility criteria

Key inclusion criteria were adults ≥ 18 years with documented diagnosis (histological and either endoscopic or radiographic) of UC at least 12 weeks before screening. At baseline, patients must have had a modified Mayo score of 5–9, inclusive. Patients must have also had a Mayo rectal bleeding subscore ≥ 1 at baseline and a screening endoscopy with ≥ 2 on the endoscopy subscore of the Mayo score. The study included patients who had demonstrated an inadequate response to or intolerance of conventional therapy (i.e. 6-mercaptopurine, azathioprine or corticosteroids) or ADT (i.e. TNF-alpha antagonists; vedolizumab; ozanimod; or approved JAK inhibitors). Further details regarding the inclusion and exclusion criteria can be found in Appendix I.

B.3.3.2.1.2 Study endpoints

The primary outcome was clinical remission at Week 12, in line with the QUASAR Phase III induction trial. Key secondary outcomes included were:(102)

- Symptomatic remission at Weeks 12 and 24
- Endoscopic improvement at Weeks 12 and 24
- Clinical response at Weeks 12 and 24
- Clinical remission at Week 24
- Histologic-endoscopic mucosal improvement at Week 12

Table 13 provides an overview of the definition of clinical outcomes included in ASTRO.

Table 13: Definitions of clinical outcomes in ASTRO

Outcome	Definition
Clinical remission	A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy
Symptomatic remission	A stool frequency subscore of 0 or 1 and not increased from baseline, and a rectal bleeding subscore of 0
Endoscopic improvement	An endoscopy subscore of 0 (regardless of friability) or 1 with no friability present on the endoscopy
Clinical response	A decrease from induction baseline in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a ≥ 1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
Histologic-endoscopic mucosal improvement	A combination of histologic improvement [neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system] and endoscopic improvement as defined above
Source: Johnson & Johnson, Data on File (2025).(102)	

B.3.3.2.2. Summary of statistical analysis

B.3.3.2.2.1 Analysis sets in ASTRO

The data sets analysed and number of patients in each analysis population in ASTRO are presented in Table 14.

Analysis was performed on the predefined ADT-IR (Inadequate Responder) subpopulation. The ADT-IR subpopulation in the trial comprised patients who had inadequate response or failure to tolerate TNF-alpha antagonists, vedolizumab, ozanimod, or JAK inhibitors.

Table 14: Analysis sets used for the analysis of outcomes in ASTRO

Analysis set	Description
Randomised Analysis Set (n = 418)	All participants who were randomised in the study
Full Analysis Set (primary analysis population) (n = 418)	All randomised participants who received at least 1 (partial or complete) dose of study intervention.
Safety Analysis Set (n = 418)	All randomised participants who received at least 1 (partial or complete) dose of study intervention.
Source: Johnson & Johnson, Data on file.(2025) (9)	

B.3.3.2.2.2 Statistical analysis

A multiplicity-controlled testing procedure was used to control the overall Type 1 error rate in the study at the 2-sided 0.05 significance level. The testing procedure followed a fixed-sequence approach where the primary endpoint and Week 12 secondary endpoints (with the exception of histologic-endoscopic mucosal improvement) for the combined guselkumab groups versus placebo were tested before the secondary endpoints at Week 24. The testing procedure for the primary and secondary endpoints is presented in Appendix I.

No interim analyses were planned or completed for the ASTRO Phase III study. The date of the last observation recorded as part of the database lock was April 2024. A summary of the analysis performed during the ASTRO trial is shown in Table 15.

Table 15: Summary of statistical analyses for ASTRO

Hypothesis objective	The primary hypothesis was that guselkumab SC induction is superior to placebo SC as measured by clinical remission at Week 12 among patients with moderately to severely active UC
Statistical analysis	The analysis of the primary endpoint was based on the Full Analysis Set. Patients were analysed according to the treatment group to which they were randomised regardless of the treatment they received. Summaries of the proportion of patients in clinical remission at Week 12 are presented by treatment group. The common risk difference and the associated 95% CI between the combined guselkumab SC induction group and the placebo group has been computed by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The primary endpoint was tested by a two-sided Mantel-Haenszel test for the common risk difference. Stratification by the ADT-IR status (Yes/No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]) as obtained during central review of the video endoscopy was conducted. The study was considered successful if the test for the primary endpoint was positive. While a multiplicity-controlled testing procedure was implemented to control for the Type 1 error rate at the 0.05 significance level (two-sided) across the primary and secondary endpoints, the primary endpoint was tested at full significance level. Only if this test was significant, secondary endpoints were tested in a confirmatory manner. A multiple testing procedure was conducted to control the overall Type 1 error rate in the study at the 2-sided 0.05 significance level. It followed a fixed sequence approach, where the primary endpoint and the Week 12 secondary endpoints (with the exception of histologic-endoscopic mucosal improvement) for the combined guselkumab groups versus placebo were tested prior to the secondary endpoints at Week 24. For the Week 24 endpoints, the testing sequence continued with testing all four endpoints in the guselkumab 400 mg SC Q4W [Weeks 0, 4, and 8] followed by guselkumab 200 mg SC Q4W group against placebo and then testing all four endpoints in the guselkumab 400 mg SC Q4W [Weeks 0, 4, and 8] followed by guselkumab 100 mg SC Q8W group against placebo. Histologic-endoscopic mucosal improvement at Week 12 was the last element of the testing sequence and was tested for the combined guselkumab groups against placebo.
Sample size, power calculation	Sample size was determined by the power to detect significant differences in the primary endpoint of clinical remission at Week 12, and by the objective of maintaining at least 85% power across secondary endpoints at Week 12 between the combined guselkumab SC induction groups and the placebo SC group as well as for secondary endpoints at Week 24 between each guselkumab group and the placebo group, using 2-sided chi-square tests with significance level 0.05. Combination of

	guselkumab SC induction groups for the primary endpoint and other Week 12 endpoints is warranted by the fact their treatment is identical through the induction period, and only differs after assessment of the primary endpoint at Week 12. With assumed clinical remission rates of 8% for placebo and 22% for the combined guselkumab groups, a total of 399 patients (randomised 1:1:1 for guselkumab 400 mg SC Q4W (Weeks 0, 4, and 8) followed by guselkumab 200 mg SC Q4W: guselkumab 400 mg SC Q4W (Weeks 0, 4, and 8) followed by guselkumab 100 mg SC Q8W: Placebo, yielding a 2:1 guselkumab: placebo randomisation ratio for Week 12 comparisons) will ensure > 95% power for the primary endpoint. This sample size also protects against a slightly lower remission rate of 20% for the combined guselkumab groups or a slightly higher remission rate of 9.5% in the placebo group, yielding a power of 90% in both cases.
Data management, patient withdrawals	After accounting for the ICE strategies, any patients who are missing any or all of the three subscores that comprise the primary endpoint at Week 12 were considered not to be in clinical remission at Week 12 (i.e. non-responder imputation).
Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; ICE, intercurrent event; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; UC, ulcerative colitis. **Source:** Johnson & Johnson, Data on File (2025).(102)	

B.3.3.2.3. Patient disposition and baseline characteristics

In ASTRO, the Full Analysis Set comprised 418 treated patients, including 139 in the guselkumab 400 mg SC to guselkumab 100 mg SC arm; 140 in the guselkumab 400 mg SC to guselkumab 200 mg SC arm; and 139 in the placebo arm. A summary of the treatment disposition before Week 12 is provided in Appendix D.

The baseline characteristics for the Full Analysis Set in ASTRO are presented in Table 16 and indicate that the treatment arms were generally well balanced. The proportion of patients who were ADT-IR was 40.3% in the placebo arm, 41.0% in the guselkumab 400 mg SC to guselkumab 100 mg SC arm, and 39.3% in the guselkumab 400 mg SC to guselkumab 200 mg SC arm.

Table 16: Baseline characteristics of patients in ASTRO, Full Analysis Set

Characteristic, n (%)	Placebo SC (N = 139)	Guselkumab combined (N = 279)	Total (N = 418)
Age, years			
Mean (SD)	39.5 (13.6)	42.9 (14.4)	41.7 (14.2)
Median (range)	37.0 (18–73)	40.0 (18–80)	40.0 (18–80)
Sex, n (%)			
Female	49 (35.3)	113 (40.5)	162 (38.8)
Male	90 (64.7)	166 (59.5)	256 (61.2)
Weight (kg)			
Mean (SD)	71.51 (15.915)	71.35 (16.733)	71.40 (16.447)
Race, n (%)			
American Indian or Alaska Native	0	4 (1.4)	4 (1.0)
Asian	40 (28.8)	81 (29.0)	121 (28.9)
Black or African American	1 (0.7)	12 (4.3)	13 (3.1)
Native Hawaiian or Other Pacific Islander	0	0	0
White	94 (67.6)	176 (63.1)	270 (64.6)
Multiple	1 (0.7)	2 (0.7)	3 (0.7)
Not reported	3 (2.2)	4 (1.4)	7 (1.7)
UC disease duration, years			
Mean (SD)	6.61 (6.228)	8.04 (6.847)	7.56 (6.674)
Median (IQR)	5.20 (2.23–9.16)	6.45 (2.71–11.42)	5.84 (2.48–10.62)
Extent of disease, n (%)			
Extensive	73 (52.5)	151 (54.1)	224 (53.6)
Limited to left side of colon	66 (47.5)	128 (45.9)	194 (46.4)
Mayo score			
Mean (SD)	9.1 (1.28)	8.9 (1.33)	9.0 (1.32)
Median (IQR)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
Modified Mayo score			
Mean (SD)	6.8 (1.09)	6.7 (1.18)	6.7 (1.15)
Median (IQR)	7.0 (6.0–8.0)	7.0 (6.0–7.0)	7.0 (6.0–7.0)
Severity of UC disease, n (%)			
Moderate (Modified Mayo score 5–6)	49 (35.5)	98 (35.1)	147 (35.3)
Severe (Modified Mayo score 7–9)	87 (63.0)	172 (61.6)	259 (62.1)
Severity of endoscopy subscore, n (%)			

Characteristic, n (%)	Placebo SC (N = 139)	Guselkumab combined (N = 279)	Total (N = 418)
Moderate (endoscopy subscore = 2)	61 (43.9)	123 (44.1)	184 (44.0)
Severe (endoscopy subscore = 3)	78 (56.1)	156 (55.9)	234 (56.0)
CRP (mg/L)			
Mean (SD)	9.7 (15.94)	7.6 (12.30)	8.3 (13.64)
Median (IQR)	3.8 (1.2–10.9)	4.1 (1.5–8.2)	4.1 (1.4–8.9)
Abnormal CRP (> 3 mg/L), n (%)	77 (55.8)	161 (58.3)	238 (57.5)
Faecal calprotectin (mg/kg)			
Mean (SD)	3,005.0 (3,799.00)	3,190.0 (5,307.37)	3,127.1 (4,842.77)
Median (IQR)	1,749.0 (617.0–3,202.0)	1,494.5 (678.0–2,963.0)	1,566.0 (641.0; 2,964.0)
Abnormal faecal calprotectin (> 250 mg/kg), n (%)	119 (90.8)	226 (89.0)	345 (89.6)
UC-related ADT medication history			
Patients who were non-ADT-IR, N (%)	83 (59.7)	167 (59.9)	250 (59.8)
ADT-naïve, n (%)	79 (95.2)	164 (98.2)	243 (97.2)
ADT-experienced, without documented inadequate response, n (%)	4 (4.8)	3 (1.8)	7 (2.8)
Patients who were ADT-IR, N (%)	56 (40.3)	112 (40.1)	168 (40.2)

Key: ADT, advanced therapy; ADT-IR, inadequate response to or intolerance of advanced therapy; CRP, C-reactive protein; IQR, interquartile range; SC, subcutaneous; SD, standard deviation; UC, ulcerative colitis.
Source: Johnson & Johnson. Data on file (2025).(9)

B.3.4. Critical appraisal of the relevant clinical effectiveness evidence

QUASAR and ASTRO were conducted in accordance with the ethical principles of Good Clinical Practice and are both considered to be good-quality studies. A

complete quality assessment in accordance with the NICE quality assessment checklist is presented in Appendix D.

B.3.5. Clinical effectiveness results of the relevant studies

In the QUASAR and ASTRO trials, the primary endpoint and all key secondary endpoints were met.(6, 7, 9) These trials were powered to detect differences in treatment effect between patients receiving guselkumab versus those receiving placebo based on the Primary Analysis Set. However, the population relevant to the decision problem in this submission is more closely aligned with the pre-specified ADT-failure subgroup of the Randomised Full Analysis Set (QUASAR) and with the ADT-IR population (ASTRO). The clinical efficacy of guselkumab in these subgroups was found to be consistent with the Primary Analysis Set for all relevant endpoints, and these data are also described within this section.

B.3.5.1. QUASAR Phase III induction study

The following section summarises the data for the Full Analysis Set and the ADT-failure subgroup. Results for other secondary endpoints not reported below (fatigue response and endoscopic normalisation) are presented in Appendix I.

B.3.5.1.1. Primary endpoint: clinical remission at Week 12

A substantially greater proportion of patients in the guselkumab group achieved clinical remission at Week 12 compared with patients in the placebo group in the Full Analysis Set (22.6% versus 7.9%), as well as in the ADT-failure population (12.5% versus 3.7%), with statistically significant differences between treatment groups (Table 17). (106)

Table 17: Number of patients in clinical remission at Week 12

	Induction (Week 12)	
	Placebo	**GUS 200 mg IV**
FAS		
Number of patients in clinical remission, n/N (%)	22/280 (7.9)	95/421 (22.6)
Adjusted treatment difference, % (95% CI)	–	14.9 (9.9, 19.9)
P-value	–	$p < 0.001$

	Induction (Week 12)	
	Placebo	**GUS 200 mg IV**
ADT-failure		
Number of patients in clinical remission, n/N (%)	5/136 (3.7)	26/208 (12.5)
Adjusted treatment difference, % (95% CI)	–	8.8 (3.4, 14.3)
P-value	–	p < 0.01
Key: ADT, advanced therapy, CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; IV, intravenous. **Source:** Rubin et al 2025. (106)		

B.3.5.1.2. Secondary endpoint: symptomatic remission at Week 12

A greater proportion of patients in the guselkumab group achieved symptomatic remission at Week 12 compared with patients in the placebo group in the Full Analysis Set (49.9% versus 20.7%), as well as in the ADT-failure population (38.5% versus 14.0%), with statistically significant differences between treatment groups (Table 18). (106)

Table 18: Number of patients in symptomatic remission at Week 12

	Induction (Week 12)	
	Placebo	**GUS 200 mg IV**
FAS		
Number of patients in symptomatic remission, n/N (%)	58/280 (20.7)	210/421 (49.9)
Adjusted treatment difference, % (95% CI)	–	29.4 (22.8, 36.0)
P-value	–	p < 0.0001
ADT-failure		
Number of patients in symptomatic remission, n/N (%)	19/136 (14.0)	80/208 (38.5)
Adjusted treatment difference, % (95% CI)	–	24.5 (15.2, 33.3)
P-value	–	p < 0.001
Key: ADT, advanced therapy, CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; IV, intravenous. **Source:** Rubin et al 2025. (106)		

B.3.5.1.3. Secondary endpoint: endoscopic healing at Week 12

A greater proportion of patients in the guselkumab group achieved endoscopic healing at Week 12 compared with patients in the placebo group in the Full Analysis

Set (26.8% versus 11.1%), as well as in the ADT-failure population (14.9% versus 5.1%), with statistically significant differences between treatment groups (Table 19). (106)

Table 19: Number of patients with endoscopic healing at Week 12

	Induction (Week 12)	
	Placebo	**GUS 200 mg IV**
FAS		
Number of patients with endoscopic healing, n/N (%)	31/280 (11.1)	113/421 (26.8)
Adjusted treatment difference, % (95% CI)	–	16.0 (10.5, 21.4)
P-value	–	p < 0.001
ADT-failure		
Number of patients with endoscopic healing, n/N (%)	7/136 (5.1)	31/208 (14.9)
Adjusted treatment difference, % (95% CI)	–	9.8 (3.7, 15.8)
P-value	–	p < 0.01

Key: ADT, advanced therapy, CI, confidence interval; FAS, Full Analysis Set; IV, intravenous; GUS, guselkumab.
Source: Rubin et al 2025. (106)

B.3.5.1.4. Secondary endpoint: clinical response at Week 12

A greater proportion of patients in the guselkumab group achieved clinical response at Week 12 compared with patients in the placebo group in the Full Analysis Set (61.5% versus 27.9%), as well as in the ADT-failure population (51.4% versus 19.9%), with statistically significant differences between treatment groups (Table 20). (106)

Table 20: Number of patients in clinical response at Week 12

	Induction (Week 12)	
	Placebo	**GUS 200 mg IV**
FAS		
Number of patients in clinical response, n/N (%)	78/280 (27.9)	259/421 (61.5)
Adjusted treatment difference, % (95% CI)	–	33.8 (26.9, 40.7)
P-value	–	p < 0.001
ADT-failure		
Number of patients in clinical response, n/N (%)	27/136 (19.9)	107/208 (51.4)

Adjusted treatment difference, % (95% CI)	–	31.6 (22.0, 41.1)
P-value	–	p < 0.001
Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; IV, intravenous. **Source:** Rubin et al 2025. (106)		

B.3.5.1.5. Secondary endpoint: Inflammatory Bowel Disease Questionnaire remission at Week 12

A greater proportion of patients in the guselkumab group achieved IBDQ remission at Week 12 compared with patients in the placebo group in the Full Analysis Set (51.3% versus 29.6%), as well as in the ADT-failure population (39.4% versus 24.3%), with statistically significant differences between treatment groups (Table 21).(6)

Table 21: Number of patients in IBDQ remission at Week 12

	Induction (Week 12)	
	Placebo	**GUS 200 mg IV**
FAS		
Number of patients in IBDQ remission, n/N (%)	83/280 (29.6)	216/421 (51.3)
Adjusted treatment difference, % (95% CI)	–	21.9 (14.9, 29.0)
P-value	–	p < 0.001
ADT-failure		
Number of patients in IBDQ remission, n/N (%)	33/136 (24.3)	82/208 (39.4)
Adjusted treatment difference, % (95% CI)	–	15.2 (5.4, 24.9)
P-value	–	p < 0.01
Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous. **Source:** Rubin et al 2025. (106)		

B.3.5.1.6. Secondary endpoint: histologic-endoscopic mucosal healing at Week 12

A greater proportion of patients in the guselkumab group achieved histologic-endoscopic mucosal healing at Week 12 compared with patients in the placebo group in the Full Analysis Set (23.5% versus 7.5%), as well as in the ADT-failure

population (13.5% versus 4.4%), with statistically significant differences between treatment groups (Table 22).(6)

Table 22: Number of patients with histologic-endoscopic mucosal healing at Week 12

	Induction (Week 12)	
	Placebo	**GUS 200 mg IV**
FAS		
Number of patients with histologic-endoscopic mucosal healing, n/N (%)	21/280 (7.5)	99/421 (23.5)
Adjusted treatment difference, % (95% CI)	–	16.2 (11.1, 21.2)
P-value	–	p < 0.001
ADT-failure		
Number of patients with histologic-endoscopic mucosal healing, n/N (%)	6/136 (4.4)	28/208 (13.5)
Adjusted treatment difference, % (95% CI)	–	9.1 (3.3, 14.8)
P-value	–	p < 0.01
Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; IV, intravenous. **Source:** Rubin et al 2025. (106)		

B.3.5.1.7. Guselkumab clinical non-responders at Week 12

As discussed in Section B.3.3, in the induction study, patients who did not achieve clinical response at Week 12 received additional study intervention administration as follows:

- Patients initially randomised to placebo who were not in clinical response at Week 12 crossed over to guselkumab and received three doses of guselkumab 200 mg IV at Weeks 12, 16 and 20
- Patients initially randomised to guselkumab 200 mg IV who were not in clinical response at Week 12 received three doses of guselkumab 200 mg SC at Weeks 12, 16 and 20

Table 23 summarises key endpoints for the Week 12 Clinical Non-responder Analysis Set, which comprised patients with a baseline modified Mayo Score of 5 to

9 who were not in clinical response at Week 12 as determined by the interactive web response system (IWRS) and who received study intervention at or after Week 12.

The proportions of patients who achieved the clinical endpoints in the placebo IV to guselkumab 200 mg IV group at Week 24 (12 weeks following administration of guselkumab 200 mg IV) were generally similar to those observed at Week 12 in the guselkumab 200 mg IV group (also 12 weeks following administration of guselkumab 200 mg IV) based on the non-responder analysis set as well the ADT-failure population in the non-responder analysis set (Table 24)

Table 23: Clinical endpoints among Week 12 clinical non-responders, full analysis set

	GUS 200 mg IV to GUS 200 mg SC	Placebo IV to GUS 200 mg IV
Clinical remission		
Number of patients, n/N (%)	[redacted]	32/165 (19.4)
95% CI for treatment proportion	[redacted]	13.4, 25.4
Clinical response		
Number of patients, n/N (%)	[redacted]	115/165 (69.7)
95% CI for treatment proportion	[redacted]	62.7, 76.7
Symptomatic remission		
Number of patients, n/N (%)	[redacted]	94/165 (57.0)
95% CI for treatment proportion	[redacted]	49.4, 64.5
Endoscopic healing		
Number of patients, n/N (%)	[redacted]	38/165 (23.0)
95% CI for treatment proportion	[redacted]	16.6, 29.5
Endoscopic normalisation		
Number of patients, n/N (%)	[redacted]	21/165 (12.7)
95% CI for treatment proportion	[redacted]	7.6, 17.8
Histologic-endoscopic mucosal healing		
Number of patients, n/N (%)	[redacted]	31/165 (18.8)
95% CI for treatment proportion	[redacted]	12.8, 24.7

Key: CI, confidence interval; IV, intravenous; GUS, guselkumab; SC, subcutaneous.
Source: QUASAR induction study, clinical study report (6), Rubin et al 2025. (106).

Table 24: Clinical endpoints among Week 12 clinical non-responders, ADT-failure population

	GUS 200 mg IV to GUS 200 mg SC	Placebo IV to GUS 200 mg IV
Clinical remission		
Number of patients, n/N (%)	[redacted]	[redacted]
95% CI for treatment proportion	[redacted]	[redacted]
Clinical response		
Number of patients, n/N (%)	[redacted]	[redacted]
95% CI for treatment proportion	[redacted]	[redacted]
Symptomatic remission		
Number of patients, n/N (%)	[redacted]	[redacted]
95% CI for treatment proportion	[redacted]	[redacted]
Endoscopic healing		
Number of patients, n/N (%)	[redacted]	[redacted]
95% CI for treatment proportion	[redacted]	[redacted]
Endoscopic normalisation		
Number of patients, n/N (%)	[redacted]	[redacted]
95% CI for treatment proportion	[redacted]	[redacted]
Histologic-endoscopic mucosal healing		
Number of patients, n/N (%)	[redacted]	[redacted]
95% CI for treatment proportion	[redacted]	[redacted]

Key: CI, confidence interval; IV, intravenous; GUS, guselkumab; SC, subcutaneous.
Source: QUASAR induction study, clinical study report.(6)

B.3.5.2. QUASAR Phase III maintenance study

The following sections summarise data for the Randomised Full Analysis Set and ADT-failure subgroup. All p-values in the ADT-failure population at Week 44 are nominal.

B.3.5.2.1. Primary endpoint: clinical remission at Week 44

A greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved clinical remission at Week 44 compared with patients in the placebo group in the Randomised Full Analysis Set (50.0% and 45.2% versus 18.9%), as well as in the ADT-failure population (39.8% and 40.3% versus 8.0%), with statistically significant differences between treatment groups (Table 25).(7)

Table 25: Number of patients in clinical remission at Week 44

	Maintenance (Week 44)		
	Placebo	**Guselkumab 100 mg SC**	**Guselkumab 200 mg SC**
FAS [a]			
Number of patients in clinical remission, n/N (%)	36/190 (18.9)	85/188 (45.2)	95/190 (50.0)
Adjusted treatment difference, % (95% CI)	-	25.2 (16.4, 33.9)	29.5 (20.9, 38.1)
P value	-	p < 0.001	p < 0.001
ADT-failure			
Number of patients in clinical remission, n/N (%)	6/75 (8.0)	31/77 (40.3)	35/88 (39.8)
Adjusted treatment difference, % (95% CI)	-	30.4 (18.7, 42.1)	32.4 (21.1, 43.7)
P value	-	p < 0.001	p < 0.001

Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; SC, subcutaneous.
Notes: [a] For the maintenance phase, data for the randomised FAS is presented.
Source: Rubin et al 2025. (106)

B.3.5.2.2. Secondary endpoint: symptomatic remission Week 44

A greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved symptomatic remission at Week 44 compared with patients in the placebo group in the Randomised Full Analysis Set (68.9% and 70.2% versus 31.4%), as well as in the ADT-failure population (60.2% and 64.9% versus 24.0%), with statistically significant differences between treatment groups (Table 26).(7)

Table 26: Number of patients in symptomatic remission at Week 44

	Maintenance (Week 44)		
	Placebo	**Guselkumab 100 mg SC**	**Guselkumab 200 mg SC**
FAS [a]			
Number of patients in symptomatic remission, n/N (%)	71/190 (37.3)	132/188 (70.2)	131/190 (68.9)
Adjusted treatment difference, % (95% CI)	-	31.9 (22.5, 41.2)	30.5 (21.2, 39.9)
P value	-	p < 0.001	p < 0.001
ADT-failure			

	Maintenance (Week 44)		
	Placebo	**Guselkumab 100 mg SC**	**Guselkumab 200 mg SC**
Number of patients in symptomatic remission, n/N (%)	18/75 (24.0)	50/77 (64.9)	53/88 (60.2)
Adjusted treatment difference, % (95% CI)	-	39.1 (25.9, 52.2)	36.8 (23.4, 50.2)
P value	-	p < 0.001	p < 0.001

Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; SC, subcutaneous.
Notes: [a] For the maintenance phase, data for the randomised FAS is presented.
Source: Rubin et al 2025. (106)

B.3.5.2.3. Secondary endpoint: endoscopic healing at Week 44

A greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved endoscopic healing at Week 44 compared with patients in the placebo group in the Randomised Full Analysis Set (51.6% and 49.5% versus 18.9%), as well as in the ADT-failure population (42.0% and 45.5% versus 8.0%), with statistically significant differences between treatment groups (Table 27).(7)

Table 27: Number of patients with endoscopic healing at Week 44

	Maintenance (Week 44)		
	Placebo	**GUS 100 mg SC**	**GUS 200 mg SC**
FAS[a]			
Number of patients with endoscopic healing, n/N (%)	36/190 (18.9)	93/188 (49.5)	98/190 (51.6)
Adjusted treatment difference, % (95% CI)	–	29.5 (20.7, 38.3)	31.1 (22.5, 39.8)
P-value	–	p < 0.001	p < 0.001
ADT-failure			
Number of patients with endoscopic healing, n/N (%)	6/75 (8.0)	35/77 (45.5)	37/88 (42.0)
Adjusted treatment difference, % (95% CI)	–	35.8 (23.8, 47.8)	34.6 (23.1, 46.0)
P-value	–	p < 0.001	p < 0.001

Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Notes: [a] For the maintenance phase, data for the randomised FAS is presented.
Source: Rubin et al 2025. (106)

B.3.5.2.4. Secondary endpoint: corticosteroid-free clinical remission at Week 44

A greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved corticosteroid-free clinical remission at Week 44 compared with patients in the placebo group in the Randomised Full Analysis Set (48.9% and 45.2% versus 18.4%), as well as in the ADT-failure population (39.8% and 40.3% versus 6.7%), with statistically significant differences between treatment groups (Table 28).(7)

Table 28: Number of patients in corticosteroid-free clinical remission at Week 44

Population	Maintenance (Week 44)		
	Placebo	GUS 100 mg SC	GUS 200 mg SC
FAS[a]			
Number of patients in corticosteroid-free clinical remission, n/N (%)	35/190 (18.4)	85/188 (45.2)	93/190 (48.9)
Adjusted treatment difference, % (95% CI)	–	25.7 (17.0, 34.5)	29.0 (20.5, 37.6)
P-value	–	p < 0.001	p < 0.001
ADT-failure			
Number of patients in corticosteroid-free clinical remission, n/N (%)	5/75 (6.7)	31/77 (40.3)	35/88 (39.8)
Adjusted treatment difference, % (95% CI)	–	32.0 (20.6, 43.4)	33.8 (22.8, 44.9)
P-value	–	p < 0.001	p < 0.001

Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Notes: [a] For the maintenance phase, data for the randomised FAS is presented.
Source: Rubin et al 2025. (106)

B.3.5.2.5. Secondary endpoint: maintenance of clinical response at Week 44

A greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved maintenance of clinical response at Week 44 compared with patients in the placebo group in the Randomised Full Analysis Set (74.7% and 77.7% versus

43.2%), as well as in the ADT-failure population (67.0% and 70.1% versus 28.0%), with statistically significant differences between treatment groups (Table 29).(7)

Table 29: Number of patients in maintenance of clinical response at Week 44

Population	Maintenance (Week 44)		
	Placebo	GUS 100 mg SC	GUS 200 mg SC
FAS[a]			
Number of patients in maintenance of clinical response, n/N (%)	82/190 (43.2)	146/188 (77.7)	142/190 (74.7)
Adjusted treatment difference, % (95% CI)	–	33.6 (24.5, 42.7)	30.7 (21.5, 40.0)
P-value	–	p < 0.001	p < 0.001
ADT-failure			
Number of patients in maintenance of clinical response, n/N (%)	21/75 (28.0)	54/77 (70.1)	59/88 (67.0)
Adjusted treatment difference, % (95% CI)	–	40.8 (27.4, 54.2)	39.4 (25.8, 53.0)
P-value	–	p < 0.001	p < 0.001

Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Notes: [a] For the maintenance phase, data for the randomised FAS is presented.
Source: Rubin et al 2025. (106)

B.3.5.2.6. Secondary endpoint: histologic-endoscopic mucosal healing at Week 44

A greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved histologic-endoscopic mucosal healing at Week 44 compared with patients in the placebo group in the Full Analysis Set (47.9% and 43.6% versus 16.8%), as well as in the ADT-failure population (38.6% and 37.7% versus 8.0%), with statistically significant differences between treatment groups (Table 30).(7)

Table 30: Number of patients with histologic-endoscopic mucosal healing at Week 44

	Maintenance (Week 44)		
	Placebo	**GUS 100 mg SC**	**GUS 200 mg SC**
FAS[a]			
Number of patients with histologic-endoscopic mucosal healing, n/N (%)	32/190 (16.8)	82/188 (43.6)	91/190 (47.9)
Adjusted treatment difference, % (95% CI)	–	25.7 (17.1, 34.3)	29.6 (21.1, 38.0)
P-value	–	p < 0.001	p < 0.001
ADT-failure			
Number of patients with histologic-endoscopic mucosal healing, n/N (%)	6/75 (8.0)	29/77 (37.7)	34/88 (38.6)
Adjusted treatment difference, % (95% CI)	–	27.7 (16.0, 39.5)	31.2 (19.8, 42.5)
P-value	–	p < 0.001	p < 0.001

Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Notes: [a] For the maintenance phase, data for the randomised FAS is presented.
Source: Rubin et al 2025. (106)

B.3.5.2.7. Secondary endpoint: Inflammatory Bowel Disease Questionnaire remission at Week 44

A greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved IBDQ remission at Week 44 compared with patients in the placebo group in the Randomised Full Analysis Set (64.2% and 64.4% versus 37.4%), as well as in the ADT-failure population (53.4% and 58.4% versus 18.7%), with statistically significant differences between treatment groups (Table 31).(7)

Table 31: Number of patients in IBDQ remission at Week 44

	Maintenance (Week 44)		
	Placebo	**GUS 100 mg SC**	**GUS 200 mg SC**
FAS[a]			
Number of patients in IBDQ remission, n/N (%)	71/190 (37.4)	121/188 (64.4)	122/190 (64.2)
Adjusted treatment difference, % (95% CI)	–	26.3 (16.8, 35.7)	25.9 (16.5, 35.4)

P-value	–	p < 0.001	p < 0.001
ADT-failure			
Number of patients in IBDQ remission, n/N (%)	14/75 (18.7)	45/77 (58.4)	47/88 (53.4)
Adjusted treatment difference, % (95% CI)	–	37.9 (25.7, 50.1)	35.4 (22.7, 48.0)
P-value	–	p < 0.001	p < 0.001
Key: ADT, advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; IBDQ, Inflammatory Bowel Disease Questionnaire; SC, subcutaneous. **Notes:** [a] For the maintenance phase, data for the randomised FAS is presented. **Source:** Rubin et al 2025. (106)			

B.3.5.2.8. Health-related quality of life

At Week 12 and Week 44, the guselkumab treatment groups had greater improvements in IBDQ total and domain scores when compared with the placebo group, including a clinically meaningful improvement and resolution of bowel urgency and abdominal pain as measured by the IBDQ. Details of IBDQ, EQ-5D and EQ-VAS (visual analogue scale) scores are provided in Appendix I.

B.3.5.3. ASTRO

B.3.5.3.1. Primary efficacy endpoint: clinical remission at Week 12

A greater proportion of patients in the guselkumab group achieved clinical remission at Week 12 compared with patients in the placebo group in the Full Analysis Set (27.6% versus 6.5%), as well as in the ADT-IR population (16.1% versus 3.6%), with statistically significant differences between treatment groups (Table 32).

Table 32: Number of patients in clinical remission at Week 12

	Induction (Week 12)	
	Placebo SC	**GUS 400 mg SC**
FAS		
Number of patients in clinical remission, n/N (%)	9/139 (6.5)	77/279 (27.6)
Absolute difference, % (95% CI)	–	21.1 (14.5, 27.6)
P-value	–	p < 0.001
ADT-IR		
Number of patients in clinical remission, n/N (%)	2/56 (3.6)	18/112 (16.1)

	Induction (Week 12)	
	Placebo SC	**GUS 400 mg SC**
Absolute difference, % (95% CI)	–	11.6 (3.5, 19.8)
P-value	–	p = 0.005

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Source: Peyrin-Biroulet et al 2025(107)

B.3.5.3.2. Secondary endpoint: symptomatic remission at Week 12

A greater proportion of patients in the guselkumab group achieved symptomatic remission at Week 12 compared with patients in the placebo group in the Full Analysis Set (51.3% versus 20.9%), as well as in the ADT-IR population (41.1% versus 14.3%), with statistically significant differences between treatment groups (Table 33).

Table 33: Number of patients in symptomatic remission at Week 12

	Induction (Week 12)	
	Placebo SC	**GUS 400 mg SC**
FAS		
Number of patients in symptomatic remission, n/N (%)	29/139 (20.9)	143/279 (51.3)
Absolute difference, % (95% CI)	–	30.4 (21.6, 39.2)
P-value	–	p < 0.001
ADT-IR		
Number of patients in symptomatic remission, n/N (%)	8/56 (14.3)	46/112 (41.1)
Absolute difference, % (95% CI)	–	26.0 (13.1, 38.8)
P-value	–	p < 0.001

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Source: Peyrin-Biroulet et al 2025(107)

B.3.5.3.3. Secondary endpoint: endoscopic improvement at Week 12

A greater proportion of patients in the guselkumab group achieved endoscopic improvement at Week 12 compared with patients in the placebo group in the Full Analysis Set (37.3% versus 12.9%), as well as in the ADT-IR population (24.1%

versus 7.1%), with statistically significant differences between treatment groups (Table 34).

Table 34: Number of patients with endoscopic improvement at Week 12

	Induction (Week 12)	
	Placebo SC	**GUS 400 mg SC**
FAS		
Number of patients with endoscopic improvement, n/N (%)	18/139 (12.9)	104/279 (37.3)
Absolute difference, % (95% CI)	–	24.3 (16.6, 31.9)
P-value	–	p < 0.001
ADT-IR		
Number of patients with endoscopic improvement, n/N (%)	4/56 (7.1)	27/112 (24.1)
Absolute difference, % (95% CI)	–	15.8 (5.9, 25.6)
P-value	–	p = 0.002

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Source: Peyrin-Biroulet et al 2025(107)

B.3.5.3.4. Secondary endpoint: clinical response at Week 12

A greater proportion of patients in the guselkumab group achieved clinical response at Week 12 compared with patients in the placebo group in the Full Analysis Set (65.5% versus 34.5%), as well as in the ADT-IR population (57.1% versus 25.0%), with statistically significant differences between treatment groups (Table 35).

Table 35: Number of patients in clinical response at Week 12

	Induction (Week 12)	
	Placebo SC	**GUS 400 mg SC**
FAS		
Number of patients in clinical response, n/N (%)	48/139 (34.5)	183/279 (65.6)
Absolute difference, % (95% CI)	–	31.0 (21.6, 40.5)
P-value	–	p < 0.001
ADT-IR		
Number of patients in clinical response, n/N (%)	14/56 (25.0)	64/112 (57.1)
Absolute difference, % (95% CI)	–	31.1 (16.8, 45.4)

P-value	–	p < 0.001
Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous. **Source:** Peyrin-Biroulet et al 2025(107)		

B.3.5.3.5. Secondary endpoint: clinical remission at Week 24

At Week 24 (secondary endpoint), a greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved clinical remission compared with patients in the placebo group in the Full Analysis Set ([redacted]), as well as in the ADT-IR population [redacted]), with statistically significant differences between guselkumab 200 mg versus placebo in the ADT-IR population (Table 36).

Table 36: Number of patients in clinical remission at Week 24

	Maintenance (Week 24)		
	Placebo SC	**GUS 100 mg SC**	**GUS 200 mg SC**
FAS			
Number of patients in clinical remission, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
ADT-IR			
Number of patients in clinical remission, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous. **Source:** Johnson & Johnson. Data on file (2025). (9)			

B.3.5.3.6. Secondary endpoint: symptomatic remission at Week 24

At Week 24, a greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved symptomatic remission compared with patients in the placebo group in the Full Analysis Set ([redacted]), as well as in the

ADT-IR population ([redacted]), with statistically significant differences between treatment groups (Table 37).

Table 37: Number of patients in symptomatic remission at Week 24

	Maintenance (Week 24)		
	Placebo SC	**GUS 100 mg SC**	**GUS 200 mg SC**
FAS			
Number of patients in symptomatic remission, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
ADT-IR			
Number of patients in symptomatic remission, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Source: Johnson & Johnson. Data on file (2025). (9)

B.3.5.3.7. Secondary endpoint: endoscopic improvement at Week 24

At Week 24, a greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved endoscopic improvement compared with patients in the placebo group in the Full Analysis Set ([redacted]), as well as in the ADT-IR population ([redacted]), with statistically significant differences between treatment groups (Table 38).

Table 38: Number of patients with endoscopic improvement at Week 24

	Maintenance (Week 24)		
	Placebo SC	**GUS 100 mg SC**	**GUS 200 mg SC**
FAS			
Number of patients with endoscopic improvement, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]

	Maintenance (Week 24)		
	Placebo SC	**GUS 100 mg SC**	**GUS 200 mg SC**
P-value	[redacted]	[redacted]	[redacted]
ADT-IR			
Number of patients with endoscopic improvement, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Source: Johnson & Johnson. Data on file (2025). (9)

B.3.5.3.8. Secondary endpoint: clinical response at Week 24

At Week 24, a greater proportion of patients in the guselkumab 200 mg and 100 mg groups achieved clinical response compared with patients in the placebo group in the Full Analysis Set ([redacted]), as well as in the ADT-IR population ([redacted]), with statistically significant differences between treatment groups (Table 39).

Table 39: Number of patients in clinical response at Week 24

	Maintenance (Week 24)		
	Placebo SC	**GUS 100 mg SC**	**GUS 200 mg SC**
FAS			
Number of patients in clinical response, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
ADT-IR			
Number of patients in clinical response, n/N (%)	[redacted]	[redacted]	[redacted]
Absolute difference, % (95% CI)	[redacted]	[redacted]	[redacted]

P-value	[redacted]	[redacted]	[redacted]

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Source: Johnson & Johnson. Data on file (2025). (9)

B.3.5.3.9. Secondary endpoint: histologic-endoscopic mucosal improvement at Week 12

A greater proportion of patients in the guselkumab group achieved histologic-endoscopic mucosal improvement at Week 12 compared with patients in the placebo group in the Full Analysis Set (30.5% versus 10.8%), as well as in the ADT-IR population (18.8% versus 7.1%), with statistically significant differences between treatment groups (Table 40).

Table 40: Number of patients with histologic-endoscopic mucosal improvement at Week 12

	Induction (Week 12)	
	Placebo SC	**GUS 400 mg SC**
FAS		
Number of patients in clinical response, n/N (%)	15/139 (10.8)	85/279 (30.5)
Absolute difference, % (95% CI)	–	19.6 (12.4, 26.9)
P-value	–	p < 0.001
ADT-IR		
Number of patients in clinical response, n/N (%)	4/56 (7.1)	21/112 (18.8)
Absolute difference, % (95% CI)	–	10.5 (1.1, 19.9)
P-value	–	p = 0.028

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CI, confidence interval; FAS, Full Analysis Set; GUS, guselkumab; SC, subcutaneous.
Source: Peyrin-Biroulet et al 2025(107)

B.3.5.4. Comparability of outcomes between QUASAR induction and ASTRO

A comparison of the key efficacy parameters in ASTRO and QUASAR shows consistent clinical, endoscopic, and histologic benefits of guselkumab induction,

regardless of route of induction administration, in participants with moderately to severely active UC. The efficacy of guselkumab SC and IV induction was comparable across key subgroups (e.g., ADT-IR status).

Additionally, both SC and IV routes demonstrated a similar rapid onset of efficacy. Among guselkumab induction responders, maintenance of efficacy with either 100 mg SC q8w or 200 mg SC q4w through 24 weeks of treatment was comparable, regardless of the route of administration of induction treatment.

B.3.6. Subgroup analysis

The pre-specified subgroup analyses relevant to the decision problem (ADT-failure and ADT-IR populations) are presented in Section B.3.5. No additional subgroup analyses are considered.

B.3.7. Meta-analysis

A meta-analysis was not conducted as there are no RCTs with head-to-head comparisons between guselkumab and the comparators within the scope of this submission. The comparative efficacy of guselkumab with that of mirikizumab and vedolizumab was explored by indirect treatment comparisons, which is presented in Section 0.

B.3.8. Indirect and mixed treatment comparisons

To date, guselkumab has not been compared in head-to-head studies with the comparators selected in the decision problem, for the treatment of moderately to severely active UC. In the absence of such comparisons, an NMA was performed to determine the relative treatment effect amongst guselkumab, vedolizumab and mirikizumab.(100) Indirect efficacy comparisons were performed for the induction and maintenance treatment phases separately for the population of interest (ADT-failure). The outcomes of the efficacy NMA are presented in Section B.3.8.5 and are considered further in the economic analysis discussed in Section B.4.

B.3.8.1. Identification and selection of relevant studies

Evidence for the efficacy of guselkumab, mirikizumab and vedolizumab were identified as part of a broader SLR conducted in July 2023, details of which are described in Appendix D.

Overall, five trials identified by the global SLR included the comparators relevant to this submission, with efficacy data available to inform the NMA (Table 41). (100) All studies included in the NMA were double-blind, comparative, randomised trials. A summary of the trials included and excluded in the NMA, including explanation of relevance to this submission, is presented in Appendix D.

Table 41: Summary of trials included in the NMA

Trial name	Relevant active treatment	Trial duration
QUASAR(6, 7, 108)	Guselkumab	• Induction: 12 weeks • Maintenance: 44 weeks
GEMINI-1(109, 110)	Vedolizumab	• Induction: 6 weeks • Maintenance: 46 weeks
VISIBLE-1(111)	Vedolizumab	• Induction: 6 weeks • Maintenance: 46 weeks
LUCENT-1 and LUCENT-2(112, 113)	Mirikizumab	• Induction: 12 weeks • Maintenance: 40 weeks
Key: NMA, network meta-analysis. **Source:** Johnson & Johnson Data on file (2025). (100)		

B.3.8.2. Feasibility assessment

A feasibility assessment was completed before conducting the NMA. (100) Heterogeneity with respect to population, study design and outcomes was assessed, and the potential implications of identified differences are summarised in the sections below.

B.3.8.2.1. Population

The patient population eligibility criteria for the SLR stated that patients must have moderately to severely active UC. (100) The inclusion criteria relevant to this submission was further refined to the ADT-failure subpopulation.

Overall, both age requirements and endoscopic and histological confirmation were relatively similar between comparator trials and QUASAR. There was little heterogeneity in baseline characteristics examined across the included trials. (100)

B.3.8.2.2. Study design

All included trials were double-blinded and were RCTs. With respect to inclusion criteria, age, endoscopic confirmation, and histological confirmation were relatively similar across trials in comparison to QUASAR. (100) Differences were noted between QUASAR and comparator trials with regards to disease duration, baseline Mayo Clinic score, prior failure, and extent of disease.

LUCENT-1/2 and QUASAR had similar exclusion criteria and excluded patients with any prior exposure to IL-12/23 or IL-23 inhibitors. (100) Otherwise, differences were noted between QUASAR and the comparator trials with regards to prior therapies received and prior therapies received within a specific time period.

B.3.8.2.3. Approved doses and regimens for treatments

Only treatments and dose regimens approved or pending approval by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) were included. (100) Different dosing arms of the same drug were treated as individual comparators within the NMA.

QUASAR assessed both outcomes at Week 12 for induction, and Week 44 for maintenance. However, timepoints used for outcome assessment varied across comparator trials and between outcomes. (100) Induction clinical response and clinical remission timepoints ranged from 6 weeks (GEMINI-1) to 12 weeks (LUCENT-1/2). The maintenance clinical response and clinical remission latest timepoints were 52 weeks for GEMINI, VISIBILE-1 and LUCENT-1/2.

B.3.8.2.4. Outcomes of interest

The feasibility assessment used the clinical response definition from QUASAR that was commonly used amongst comparator trials (i.e. the Total Mayo Clinic score). (100) The scoring criteria for clinical response including the scale used, the overall Mayo Clinic and rectal bleeding subscore requirements were similar across the majority of comparator trials. Differences between QUASAR and comparator trials emerged when trials used variants of the Mayo score, such as the Modified, Partial, and/or Adapted Mayo score.

As most trials used the Total Mayo Clinic score to define clinical remission, the alternative definition of clinical remission using Total Mayo score was used from the QUASAR trial. Across QUASAR and most comparator trials, the overall Mayo score and subscore requirements were similar. (100)

B.3.8.2.5. Feasibility assessment conclusion

Based on the initial assessment of patient and trial characteristics, including eligibility criteria and baseline data, an NMA was deemed feasible. (100) Evaluation of the availability of outcomes, outcome definitions, placebo response, and timepoints also supported the feasibility of performing NMAs for clinical remission and clinical response in both treatment phases (i.e. at induction and at approximately 1 year). However, a noted limitation is that the evidence base for each outcome varies due to data availability and/or inconsistent reporting of outcome definitions across trials. Based on the feasibility assessment, NMAs were recommended for clinical remission and clinical response, at induction and at approximately 1 year.

B.3.8.3. NMA methodology

Studies were included in the NMA if they were included in the SLR; had guselkumab, mirikizumab or vedolizumab as a comparator; and reported outcomes of interest for patients for whom ADT had failed. (100) NMA outcomes included clinical remission and clinical response, assessed at induction and approximately 1 year (i.e. during maintenance). For induction analyses, the trial's primary timepoint was used. For 1-year analyses, the timepoint closest to 52 weeks (and later than 24 weeks) was

used. Only studies with a minimum follow-up duration of 38 weeks were included in the 1-year analysis.

Bayesian NMAs were conducted using the R package JAGS. (100) All NMA models were based on code outlined in NICE Technical Support Document (TSD) 2 or modifications thereof. Clinical remission and clinical response were analysed together as an ordinal endpoint using an inverse logit multivariate regression model for ordered categorical data, with the final model selection driven by model fit. Estimated odds ratios were combined with model-estimated baselines from QUASAR to facilitate estimation of absolute outcomes to support economic model development. Ordinal variables were estimated using arm-based data entry but contrast-based estimation, whereby each study had a fixed-effect study intercept. Summary estimates included forest plots of all comparisons versus a common comparator; league tables of effect estimates comparing all therapies; and tables of direct and network estimates. All effect estimates were accompanied with 95% credible intervals (CrIs).

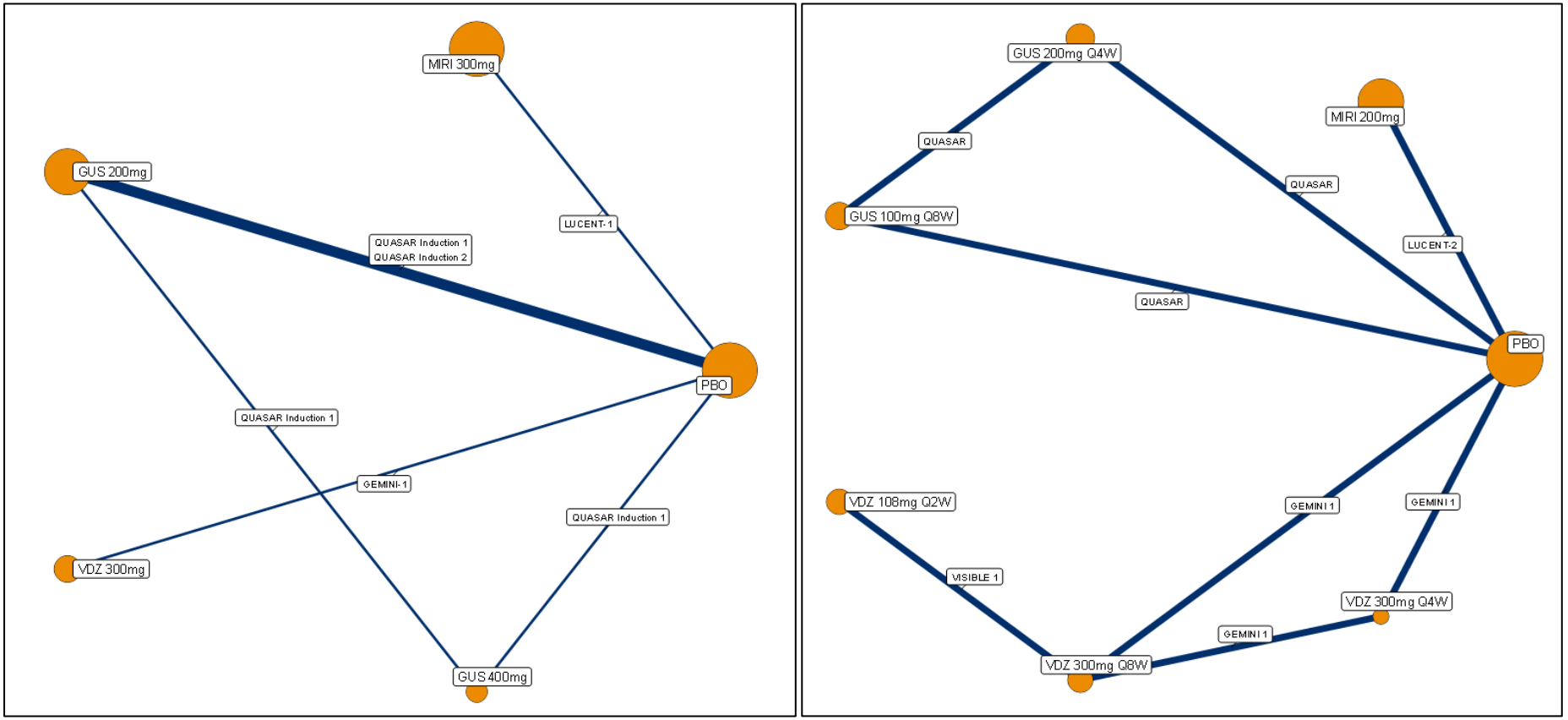
Random-effects NMAs were conducted and assume a shared estimate of the between-trial heterogeneity. (100) Informative prior distributions were assigned according to Turner et al.(114) in all analyses unless there was sufficient evidence for vague priors to converge to a reasonable posterior. Fixed-effects NMAs were also conducted for comparison, but random-effects models were preferred a priori given differences in trial designs. This is in alignment with recommendations of the NICE Decision Support Unit (DSU).(115)

For the 1-year NMAs, trial data were normalised to mimic a TYPE 1 treat-through trial design as best as possible. (100) This normalisation approach is termed the 1 year ‘with delayed responders’ analysis. However, sensitivity analyses applying imputation methods that do not account for delayed responders were also conducted.

B.3.8.4. NMA networks

A network diagram for studies reporting clinical response or clinical remission, during the induction phase and at approximately 1 year, in an ADT-failure population, is presented in Figure 5. (100) The induction phase network consisted of five treatment nodes informed by four RCTs, and all were placebo-controlled. Most connections between treatment nodes were informed by a single trial. The 1-year analysis network consisted of seven treatment nodes, and all connections between treatment nodes were informed by single trials (four trials in total). Only one trial, VISIBLE 1, was not placebo-controlled.

Figure 5: NMA networks for clinical response/remission in the induction (left) and 1-year analysis (right), ADT-failure population



Key: ADT, advanced therapy; GUS, guselkumab; MIRI, mirikizumab; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; VDZ, vedolizumab.
Source: Johnson & Johnson Data on file (2025). (100)

B.3.8.5. Results

Random-effects NMA results are presented below for the ADT-failure populations of the trials identified in the SLR. Endpoints are presented to align to the endpoints presented in the clinical efficacy results of the QUASAR trials (Sections B.3.5.1 andB.3.5.2). Pairwise comparisons are provided in Appendix J.

B.3.8.5.1. Induction: clinical response

In the NMAs of clinical response for the ADT-failure population (Figure 6), guselkumab 200 mg was numerically more efficacious than mirikizumab 300 mg and vedolizumab 300 mg; however, the effect was not deemed to be statistically significant (CrI includes 1). Guselkumab 200 mg was significantly more efficacious than placebo. Results of fixed-effects analyses were broadly aligned to the random-effects analyses.

Figure 6: Forest plot for random-effects NMA of clinical response in the induction phase, ADT-failure population

Key: ADT, advanced therapy; CrI, credible interval; GUS, guselkumab; MIRI, mirikizumab; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; VDZ, vedolizumab.
Source: Johnson & Johnson Data on file (2025). (100)

B.3.8.5.2. Induction: clinical remission

In the NMAs of clinical remission in the ADT-failure population (Figure 7), vedolizumab 300 mg was numerically more efficacious than guselkumab 200 mg; however, the effect was not deemed to be statistically significant and was associated with a large degree of uncertainty. Other comparators including placebo were

similarly or numerically less efficacious than guselkumab 200 mg. Results of fixed-effects analyses were broadly aligned to those of the random-effects analyses.

Figure 7: Forest plot for random-effects NMA of clinical remission in the induction phase, ADT-failure population

Key: ADT, advanced therapy; CrI, credible interval; GUS, guselkumab; MIRI, mirikizumab; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; VDZ, vedolizumab.
Source: Johnson & Johnson Data on file (2025). (100)

B.3.8.5.3. Maintenance: clinical response (1-year analysis)

Random-effects NMAs were conducted for clinical response at approximately 1 year in the ADT-failure population with delayed responders (Figure 8). Guselkumab 100 mg and 200 mg were numerically more efficacious than vedolizumab 300 mg and mirikizumab 200 mg; however, the effect was not deemed to be statistically significant. Guselkumab 100 mg and 200 mg were significantly more efficacious than placebo.

These results are aligned to those of similar NMAs conducted without delayed responders (presented in Appendix J). Results of fixed-effects analyses were broadly aligned to those of the random-effects analyses.

Figure 8: Forest plot for random-effects NMA of clinical response in the 1-year analysis, ADT-failure population

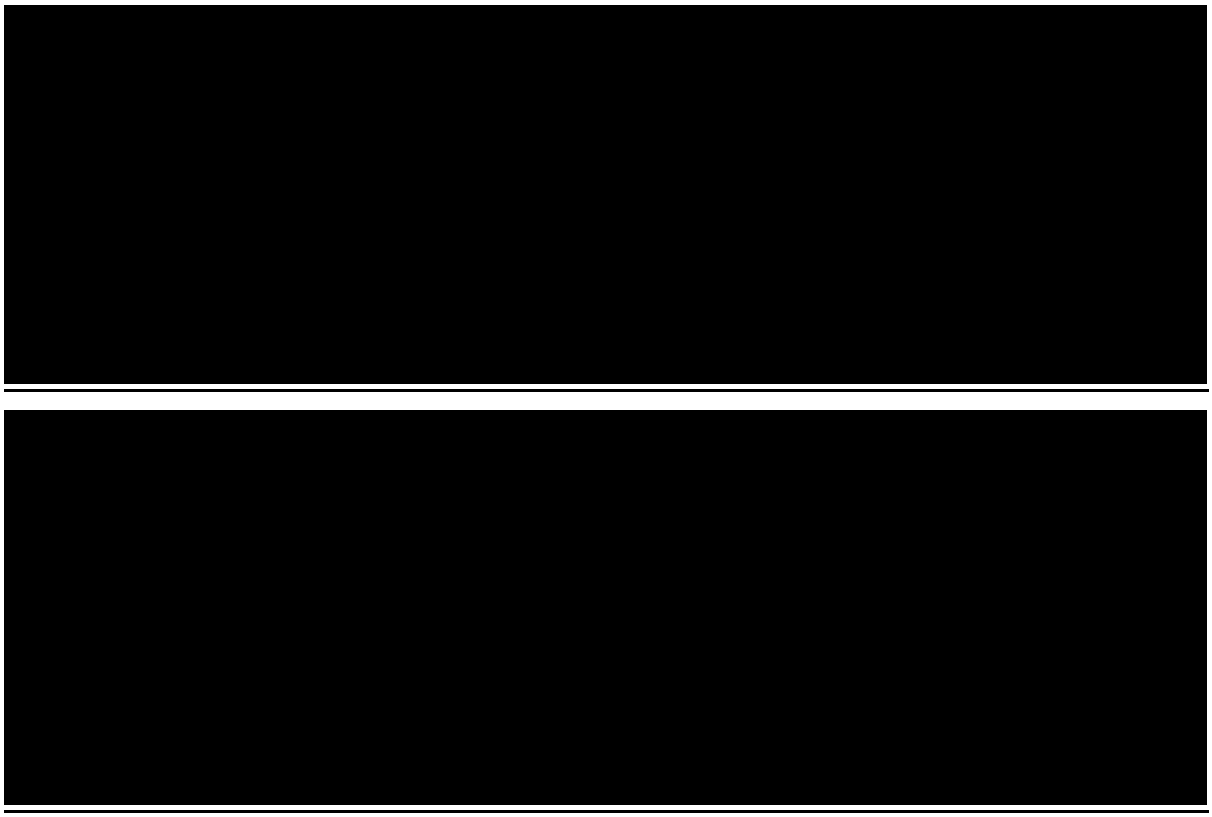
Key: ADT, advanced therapy; CrI, credible interval; GUS, guselkumab; MIRI, mirikizumab; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; VDZ, vedolizumab.
Source: Johnson & Johnson Data on file (2025). (100)

B.3.8.5.4. Maintenance: clinical remission (1-year analysis)

Random-effects NMAs were conducted for clinical remission at approximately 1 year in the ADT-failure population with delayed responders (Figure 9). Guselkumab 100 mg and 200 mg were similar or numerically more efficacious than comparators; however, the effect was not deemed to be statistically significant. Guselkumab 100 mg and 200 mg were significantly more efficacious than placebo.

These results are aligned to similar NMAs conducted without delayed responders (presented in Appendix J). Results of fixed-effects analyses were broadly aligned to the random-effects analyses.

Figure 9: Forest plot for random-effects NMA of clinical remission in the 1-year analysis, ADT-failure population



Key: ADT, advanced therapy; CrI, credible interval; GUS, guselkumab; MIRI, mirikizumab; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; VDZ, vedolizumab.
Source: Johnson & Johnson Data on file (2025). (100)

B.3.8.6. Uncertainties in the indirect and mixed treatment comparisons

NMA is a well-established approach to indirectly compare multiple interventions, especially when there is no direct evidence from head-to-head trials. Although multiple therapies for UC are available, there have been few head-to-head RCTs of comparator therapies. To simultaneously compare key therapies, an SLR was conducted to identify relevant RCTs, and NMAs were performed for clinical response and clinical remission outcomes, which are identified as primary outcomes of interest from a health technology assessment (HTA) perspective, assessed during induction and at approximately 1 year of treatment. These analyses were restricted to comparing guselkumab with the comparators considered in this appraisal:

mirikizumab and vedolizumab, in patients with UC for whom ADT has previously failed.

The analyses utilised robust methods for reliable estimation of the comparative efficacy of UC treatments. (100) To overcome the immense heterogeneity in trial design prevalent in UC, the conversion of studies to mimic a treat-through design in 1-year analyses ensured that late-onset responses after induction were accounted for, in alignment with the NICE appraisal and publication supporting ustekinumab in this indication.(71) Ignoring trial design differences would lead to biased comparisons, and splitting networks by trial design would have sacrificed a cohesive view of the comparability of treatments. Although NMAs have been published in UC, there is poor overlap in the included comparators between such analyses and our analyses, preventing an evaluation of alignment between studies. (100) Unlike previous NMAs, however, these analyses are strengthened by the implementation of imputation methods that allowed for delayed responders to be accounted for where re-randomised studies were included.

A limitation of the analyses presented is that the majority of connections within each evidence network were informed by a single study, and most trials were placebo-controlled, which resulted in a star-shaped network and limited the robustness of the analysis. (100) In addition, residual heterogeneity between studies may have reduced the validity of one or more analyses, despite best efforts to minimise bias by excluding insufficiently similar trials and/or trial data. In addition, there is a notable reduction in power resulting from re-randomisation of patients in some trials. These issues likely contributed to wide CrIs in the analyses and may have limited the identification of clinically relevant treatment differences.

Beyond the induction phase, it should be noted that although placebo is considered to be a common comparator across the majority of included trials, placebo arms across re-randomised trials may not be equivalent due to variation in treatments received during the preceding induction phase – an issue previously noted by Welty et al., 2020. (100) In particular, carry-over effects observed due to previous treatments are likely to vary based upon treatment mechanism, potentially

constituting a substantial source of cross-trial heterogeneity that is evidenced in part by variations in baseline risk across included trials.

Finally, a limitation specific to treat-through trials should be noted.(100) Dropout rates varied across trials, which may impact results. However, since drop-out rates and response rates were similar across these trials and non-responder imputation was implemented, the impact was judged to be minimal. Furthermore, although best measures were taken to impute data, the normalisation procedure could not perfectly replicate a true TYPE 1 treat-through design for all trials, since TYPE 2 treatment trials that condition on response by strict timepoint and TYPE 4 re-randomised trials with delayed response do not capture patients experiencing a response beyond this delay. The primary analysis therefore assumes that incorporation of delayed response beyond that time would not modify the effect estimate. The normalisation procedure further required the assumption that the probability of achieving final outcomes conditional on initial response/non-response was exchangeable across trials/doses for some treatments, particularly placebo. This is unlikely to be entirely true, since variations in placebo response across trials would be expected to induce differences in populations of patients evaluated for subsequent response. However, replication of results from included treat-through studies suggests that residual bias due to violations of this assumption is minimal. The largest remaining contributors to residual bias in the 1-year with delayed responder analysis are: potential measurement/reporting bias when data for non-responders / delayed-responders were available; and the requirement for the analysis to impute true placebo into re-randomised trials.

B.3.8.7. Conclusions from the indirect and mixed treatment comparisons

The current analysis represents a robust SLR and NMA for specific treatments in UC, relevant to the UK perspective.(100) The results of the NMA demonstrate that in the ADT-failure population, guselkumab is numerically more efficacious than vedolizumab in the outcomes of clinical response and remission at the induction stage and at 1 year, and is comparable to mirikizumab. Overall, guselkumab can be

considered clinically equivalent to vedolizumab and mirikizumab in clinical response and remission outcomes.

B.3.9. Adverse reactions

The overall summary of AEs for each trial (QUASAR Phase III induction, QUASAR Phase III maintenance and ASTRO) are presented in the sections below. Appendix E presents a breakdown of ≥ 3% treatment-emergent AEs (TEAEs) in any treatment group, SAEs, serious infections, and AEs leading to treatment discontinuation for each trial.

B.3.9.1. QUASAR Phase III induction study

Through Week 12, the proportions of patients who had one or more TEAE were comparable between treatment groups, with 49.4% in the guselkumab 200 mg group and 49.3% in the placebo group (Table 42). (106)Three deaths were reported, one (0.2%) in the guselkumab 200 mg group and two (0.7%) in the placebo group. The majority of TEAEs were mild to moderate for both treatment arms. The proportion of patients experiencing one or more SAE was broadly similar between the treatments, with 12 (2.9%) in the guselkumab group and 20 (7.1%) in the placebo group. The proportions of patients who had one or more infections (serious or non-serious infections) were 15.7% in the guselkumab 200 mg group and 15.4% in the placebo group, with three (0.7%) and one (0.4%) patients reporting serious infections in the guselkumab 200 mg group and the placebo group, respectively.

The most frequently reported AEs by preferred term (≥ 3% in any treatment group) were anaemia, COVID-19, headache, and UC.

Table 42: Overall summary of adverse events in QUASAR Phase III induction study through to Week 12, Safety Analysis Set

Characteristic, n (%)	Placebo (N = 280)	Guselkumab 200 mg IV (N = 421)
Deaths	2 (0.7)	1 (0.2)
Adverse events	138 (49.3)	208 (49.4)
Mild	72 (25.7)	133 (31.6)

Characteristic, n (%)	Placebo (N = 280)	Guselkumab 200 mg IV (N = 421)
Moderate	48 (17.1)	61 (14.5)
Severe	18 (6.4)	14 (3.3)
Serious adverse events	20 (7.1)	12 (2.9)
Adverse events leading to discontinuation	11 (3.9)	7 (1.7)
Infections[a]	43 (15.4)	66 (15.7)
Serious infections[a]	1 (0.4)	3 (0.7)

Key: IV, intravenous.
Notes: Includes only patients with modified Mayo score 5-9 at induction baseline. AE severity level of a subject was based on the worst severity event this subject experienced. [a] Infections were defined as any adverse event which was coded to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class 'Infections and infestations'.
Source: Rubin et al 2025. (106)

B.3.9.2. QUASAR Phase III maintenance study

Through Week 44 (up to the dose adjustment), the proportion of patients who had one or more AEs in the guselkumab 200 mg and 100 mg groups (70.0% and 64.5%, respectively) were comparable to the placebo group (68.2%) as presented in Table 43.(106) Overall, the proportions of patients who had one or more SAEs leading to discontinuation of the study agent were 6.3%, 2.7% and 0.5% for the guselkumab 200 mg group, guselkumab 100 mg group and placebo group, respectively. The proportion of patients that had serious infections was similar across the treatment arms and were low.

There was no clear pattern with respect to individual preferred terms or system organ class, and the majority of the SAEs were assessed as unrelated to study intervention by the investigator. No deaths occurred during the reporting period in any of the treatment groups.

The most frequently reported AEs by preferred term (≥ 3% in any treatment group) were COVID-19, UC and arthralgia.

Table 43: Overall summary of adverse events in QUASAR Phase III maintenance study through to Week 44, Randomised Safety Analysis Set

Characteristic, n (%)	Placebo[a,b] (N = 192)	Guselkumab 100 mg SC (N = 186)	Guselkumab 200 mg SC (N = 190)
Deaths	0	0	0
Adverse events	131 (68.2)	120 (64.5)	133 (70.0)
Mild[c]	57 (29.7)	61 (32.8)	73 (38.4)
Moderate[d]	69 (35.9)	49 (26.3)	54 (28.4)
Severe[e]	5 (2.6)	10 (5.4)	6 (3.2)
Serious adverse events	1 (0.5)	5 (2.7)	12 (6.3)
Adverse events leading to discontinuation	13 (6.8)	7 (3.8)	5 (2.6)
Infections[f]	63 (32.8)	59 (31.7)	59 (31.1)
Serious infections[f]	0	1 (0.5)	2 (1.1)

Key: IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; SC, subcutaneous.
Notes: Includes only patients with modified Mayo score 5-9 at induction baseline. [a] Participants who were in clinical response to guselkumab IV induction dosing and were randomised to placebo SC on entry into the maintenance study. [b] Includes data from Week M-0 up to the time of dose adjustment for participants who had a dose adjustment or through Week M-44 for those who did not. [c] Includes participants with at least one adverse event, where all adverse events are of mild intensity. [d] Includes participants with at least one adverse event of moderate intensity, and no adverse events of severe intensity. [e] Includes participants with at least one adverse event of severe intensity. [f] Infections were defined as any adverse event which was coded to the MedDRA system organ class 'Infections and infestations'.
Source: Rubin et al 2025. (106)

B.3.9.3. ASTRO

Through Week 12, the proportions of patients who had one or more TEAEs were comparable between treatment groups, with 39.4% in the guselkumab 400 mg combined group and 52.5% in the placebo group (Table 44). One death (0.7%) was reported in the placebo group and none in the guselkumab 400 mg combined group. Most AEs experienced were mild or moderate across the placebo group and combined guselkumab group. Seven (2.5%) patients experienced one or more SAEs in the guselkumab 400 mg combined group and 11 (7.9%) in the placebo group. The proportions of patients who had one or more infections (serious or nonserious infections) were 15.1% in the guselkumab 400 mg combined group and 20.1% in the placebo group. Two (0.7%) serious infections were reported in the guselkumab

400 mg combined group (pilonidal disease and gastroenteritis) and none in the placebo group. The most common AEs in the placebo and guselkumab combined groups were UC, arthralgia and headache.

Table 44: Overall summary of adverse events in ASTRO through to Week 12, Safety Analysis Set

Characteristic, n (%)	Placebo SC (N = 139)	Guselkumab 400 mg SC combined
Deaths	1 (0.7)	0
Adverse events	73 (52.5)	110 (39.4)
Mild[a]	42 (30.2)	62 (22.2)
Moderate[a]	24 (17.3)	43 (15.4)
Severe[a]	7 (5.0)	5 (1.8)
Serious adverse events	11 (7.9)	7 (2.5)
Adverse events leading to discontinuation	8 (5.8)	3 (1.1)
Infections[b]	28 (20.1)	42 (15.1)
Serious infections[b]	0	2 (0.7)

Key: MedDRA, Medical Dictionary for Regulatory Activities; SC, subcutaneous.
Notes: [a] The worst severity event experienced by the participant is used. [b] Infections were defined as any adverse event which was coded to the MedDRA system organ class 'Infections and infestations'.
Source: Johnson & Johnson Data on file (2025). (9)

Through Week 24, the proportions of patients who had one or more AEs in the guselkumab 200 mg and 100 mg groups ([redacted], respectively) were comparable to the placebo group ([redacted]) (Table 45). The proportions of patients in the guselkumab 200 mg and 100 mg treatment groups who had SAEs ([redacted]), AEs leading to discontinuation ([redacted]), and serious infections ([redacted]) were low. The most common AEs in the placebo and guselkumab combined groups were UC ([redacted]), arthralgia ([redacted]) and upper respiratory tract infection ([redacted]).

Table 45: Overall summary of adverse events in ASTRO through to Week 24, Safety Analysis Set

Characteristic, n (%)	Placebo SC[a] (N = 139)	Guselkumab 100 mg SC (N = 139)	Guselkumab 200 mg SC (N = 140)
Deaths	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Mild[b]	[redacted]	[redacted]	[redacted]
Moderate[b]	[redacted]	[redacted]	[redacted]
Severe[b]	[redacted]	[redacted]	[redacted]
Serious adverse events	[redacted]	[redacted]	[redacted]
Adverse events leading to discontinuation	[redacted]	[redacted]	[redacted]
Infections[c]	[redacted]	[redacted]	[redacted]
Serious infections[c]	[redacted]	[redacted]	[redacted]

Key: MedDRA, Medical Dictionary for Regulatory Activities; SC, subcutaneous.
Notes: [a] Includes all placebo participants excluding data after a participant is rescued with guselkumab. [b] The worst severity event experienced by the participant is used. [c] Infections were defined as any adverse event which was coded to the MedDRA system organ class 'Infections and infestations'.
Source: Johnson & Johnson Data on file (2025). (9)

B.3.10. Conclusions about comparable health benefits and safety

The anticipated positioning of guselkumab is for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to an ADT.

QUASAR comprised a Phase III induction and a Phase III maintenance study designed to evaluate the efficacy and safety of guselkumab as induction (200 mg IV) and maintenance regimens (100 mg SC and 200 mg SC) in patients with moderately to severely active UC.(6, 7) The trial was conducted globally and included two trial sites in the UK. Key inclusion criteria and previous treatments that patients with a history of ADT-failure received were reflective of NICE guidelines and representative of UK routine clinical practice.

In QUASAR, the efficacy of guselkumab IV induction and SC maintenance therapy was demonstrated and consistent across the Full Analysis Set and in patients with a history of ADT-failure.(6, 7) Guselkumab IV induction treatment demonstrated superior efficacy compared with placebo, as measured by the primary endpoint of clinical remission at Week 12.(6) A significantly greater proportion of patients in the guselkumab IV group achieved symptomatic remission, endoscopic healing, clinical response, histologic-endoscopic mucosal healing and IBDQ remission at Week 12 compared with the placebo group.(6) Both guselkumab maintenance dose regimens (200 mg SC and 100 mg SC) demonstrated robust efficacy across a range of endpoints, including those that encompass the signs and symptoms of UC (e.g. symptomatic remission, corticosteroid-free remission) and outcome measures of colonic inflammation (e.g. histologic-endoscopic mucosal healing).(7)

The guselkumab safety results through to Week 44 were consistent with the well-characterised and favourable safety profile of guselkumab in its approved indications of plaque psoriasis and psoriatic arthritis.(6, 7) Guselkumab IV and SC had a safety profile similar to placebo during the induction and maintenance periods, respectively.

ASTRO is an ongoing Phase III, randomised, placebo-controlled study investigating guselkumab as SC induction (400 mg) and maintenance (100 mg SC and 200 mg SC) therapy in patients with moderately to severely active UC.(9) Across the primary endpoint and all secondary endpoints, a greater proportion of patients in the guselkumab groups achieved each endpoint, compared with placebo, for both the Full Analysis Set and the ADT-IR subpopulation. Efficacy (primary and secondary endpoints) and safety data for guselkumab SC induction in ASTRO were consistent with results for the IV induction in QUASAR.

The findings of both QUASAR and ASTRO demonstrate the comparable efficacy benefits of guselkumab given as IV or SC induction and as either a 100 mg or 200 mg SC maintenance dose. The data support the use of guselkumab in a wide variety of patients with UC disease who have different induction needs and varying inflammatory burden throughout the maintenance phase. Furthermore, guselkumab offers two maintenance doses (100 mg and 200 mg), which provide dose flexibility

for patients who may achieve inadequate therapeutic benefit after completing induction dosing. A greater range of dosing options ensures patients receive the dose they need, prevents wastage and reduces the risk of over-treatment.

An NMA was performed to compare the efficacy of guselkumab in the ADT-failure population relative to that of comparators where head-to-head data are not available. To compare guselkumab with the mirikizumab and vedolizumab, five RCTs were utilised. The results of the NMA demonstrate that guselkumab induction and maintenance treatment offers similar efficacy to mirikizumab and vedolizumab in the ADT-failure population. (100)

B.3.11. Ongoing studies

The long-term extension to QUASAR is ongoing, with the next data cut expected [redacted]. ASTRO is ongoing with an expected completion in [redacted].

B.4. Cost-comparison analysis

Summary of cost-comparison analysis

- A cost-comparison analysis was conducted to demonstrate the cost-comparability of guselkumab against vedolizumab and mirikizumab in the proposed population
- The NMAs presented (Section B.3.9) provide evidence of comparable efficacy in terms of clinical response and remission between guselkumab and the comparators vedolizumab and mirikizumab. Therefore, a cost-comparison approach was deemed appropriate
- A de novo cost-comparison model was developed in Microsoft Excel® in line with the NICE reference case, and a 10-year time horizon was modelled. The model only considers drug acquisition and administration costs; due to the assumption of similar efficacy between treatments, subsequent downstream costs are assumed to be similar

Model results

- The model results are based on a 10-year time horizon and are inclusive of the existing PAS for guselkumab and list prices for vedolizumab and mirikizumab.
- Over the 10-year time horizon, the results show that guselkumab is cost saving versus vedolizumab and mirikizumab, resulting in an average cost saving of [redacted] and [redacted] per patient, respectively. The majority of the cost savings were achieved in the maintenance phase, where guselkumab saved [redacted] and [redacted] compared with vedolizumab and mirikizumab, respectively.
- These results were further explored in a one-way sensitivity analysis (OWSA) and a series of scenario analyses. These showed that the model was not sensitive to uncertainty around individual inputs, and guselkumab remained cost-saving across all scenarios, further illustrating the robustness of the model results.
- Overall, the cost-comparison analysis demonstrates that the introduction of guselkumab in the NHS will provide a cost-saving treatment to adults with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to a biologic or another ADT.

B.4.1. Changes in service provision and management

Nearly all injectable therapies currently available for previously treated UC in the NHS are approved as induction therapy via IV administration. The only biologic currently approved as a SC induction regimen is adalimumab, which is less likely to be offered to ADT-failure or TNF-unsuitable patients. Therefore, we conclude that most (if not all) patients included in the population relevant to this submission who do not select an oral therapy must begin their treatment journey with an IV infusion.

The administration of all IV doses takes place in an NHS secondary care setting, such as hospitals, outpatient clinics and specialist nursing facilities. It is expected that challenges with NHS capacity and resource would delay treatment initiation, due to delays in scheduling appointments for IV infusion suites.

Guselkumab has demonstrated positive results as induction therapy when delivered either IV or SC as discussed in Section B.3.5. It is anticipated that upon approval as a SC induction therapy, all guselkumab doses will be self-administered by the patient at home.

As a result, the introduction of guselkumab is expected to reduce resource use within the NHS, particularly during the induction phase. The flexibility of choosing between SC and IV induction provides physicians and patients with the option to personalise treatment according to individual preferences and NHS local service capabilities. This flexibility has the potential to alleviate the burden on the NHS by reducing the waiting times, as fewer IV administrations are required in comparison with the current standard of care.

B.4.2. Cost-comparison analysis inputs and assumptions

In line with the final scope agreed with NICE, a cost-comparison analysis was undertaken to evaluate the costs of guselkumab in NHS clinical practice versus those associated with vedolizumab and mirikizumab for the following reasons:

- Guselkumab is expected to provide similar or greater health benefits, at a similar or lower cost, compared with technologies that have been previously recommended in published NICE guidance for the same indication
- Guselkumab is likely to be similar in its clinical effectiveness and resource use to these comparators
- Guselkumab will be used in the same place in the treatment pathway as the comparators
- Guselkumab will be used to treat the same population as the comparators
- Overall, guselkumab is likely to offer similar or improved health benefits compared with the comparators

B.4.2.1. Features of the cost-comparison analysis

Population

The population in the cost-comparison model is reflective of ADT-failure patients from QUASAR and ADT-IR patients from ASTRO (Section B.3.2). These subpopulations are aligned with the population relevant to the NICE submission (B.1.1.1), and have comparable baseline characteristics, (Section B.3.3.1.3). To simplify the model, regardless of whether IV or SC induction is selected, baseline characteristics of the ADT-failure population from QUASAR were used to inform the model – i.e. mean age at model start, mean patient weight, and proportion of male and female patients.

Intervention and comparators

The intervention investigated within this model is guselkumab, corresponding to the intervention arm in QUASAR/ASTRO. Specifically, patients received guselkumab according to the anticipated marketing authorisation:

- As induction therapy via two alternative administration routes (200 mg IV or 400 mg SC)
- As maintenance therapy via two alternative injectable dosing regimens (100 mg Q8W SC or 200 mg Q4W SC)

The comparators evaluated in the cost-comparison analysis are mirikizumab and vedolizumab for the subpopulations within their marketing authorisation, as per their SmPCs, which are recommended by NICE.(4, 5)

B.4.2.1.1. Model structure

A de novo cost-comparison model was developed in Microsoft Excel in line with the NICE guidance to capture all differences in the expected costs of patients receiving these three interventions.(116) The model structure is aligned to the cost-comparison model accompanying a parallel submission for guselkumab for previously treated Crohn's disease (ID6238) and informed by previous cost-effectiveness and cost-comparison analyses in IBD as identified by the economic SLR (see Appendix F). The model is based on the UK NHS and Personal Social Services (PSS) perspective.

The state-transition (Markov) model structure consists of four health states: (1) Induction phase, (2) Maintenance phase, (3) No treatment, (4) Death.

The base case time horizon is 10 years to capture the relevant cost differences between the treatments and is in line with the base case or scenario analysis of prior cost-comparisons submitted to NICE in this disease area.(4, 13) A shorter time horizon of 5 years is explored in scenario analysis. The model uses a 2-week cycle length in both the induction and maintenance phase to allow for accurate modelling of dosing schedules and response assessment timepoints for each treatment according to their SmPCs. In the base case, discounting was not applied, according to the NICE guidance recommendation on cost-comparison appraisals; however, a discount of 3.5% on costs was explored in scenario analysis.(116)

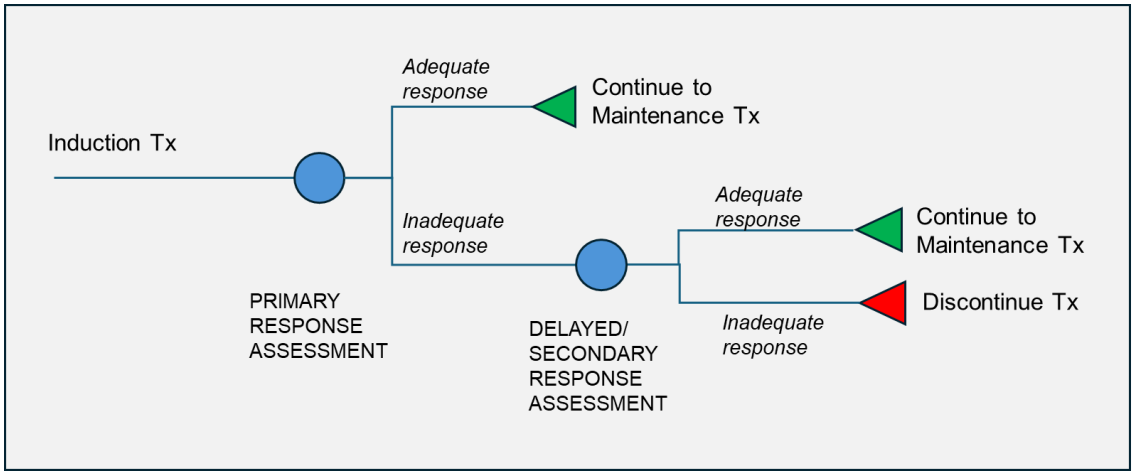
The analysis included treatment acquisition and administration costs. As the analysis assumes similar efficacy between guselkumab and its comparators, it is implied that downstream costs related to monitoring, subsequent treatments and surgery would be equal across all treatments. Therefore, these costs are not considered in the model and associated analyses. This is consistent with mirikizumab in TA925 and risankizumab in TA998 via cost-comparison approach submitted to NICE.(4, 13)

B.4.2.1.2. Induction phase model structure and efficacy

Induction phase

The decision tree for induction dosing within the economic model is based on the posologies of the comparators described in the respective SmPCs, and the draft SmPC for guselkumab.(1, 117, 118) A schematic overview of the induction phase is given in Figure 10.

Figure 10: Schematic for the induction phase



Key: Tx, treatment.

All patients entering the model commence treatment in the induction phase and transition through 2-week tunnel states, until the SmPC mandated timepoint for response assessment. (1, 117, 118) This timepoint varies depending on the treatment (Week 8 for patients receiving vedolizumab and Week 12 for those receiving guselkumab or mirikizumab). Patients who achieve adequate response (hereafter referred to as “primary responders”) then continue to maintenance phase in the model, where they receive treatment with a dosing frequency as per label.(1, 117, 118)

Patients who do not achieve an adequate response at the primary response assessment timepoint continue to receive additional doses as described within the label of the respective treatments.(1, 117, 118). Patients then undergo delayed or

secondary response assessment at a later timepoint. At this stage, patients that achieve an adequate response (hereafter referred to as “secondary or delayed responders”) will continue to the maintenance state and incur costs within the model. Patients who do not achieve an adequate response despite the additional doses will discontinue treatment and do not incur any further treatment costs.

It is assumed that all patients complete treatment induction (i.e. treat until secondary response assessment), unless the patient dies following general population mortality probabilities described in Section B.4.2.1.4. Table 46 outlines the details of dosing in the induction phase and duration of induction for the respective treatments. To note, extended induction for vedolizumab was modelled and is included in this submission in line with TA925 and adheres to the assumption of equivalence.

Table 46: Dosing schedule for primary and secondary response assessments

	Primary response assessment			**Secondary response assessment**		
Treatment	**Dosing regimen**	**Doses at Week:**	**Response assessment at Week:**	**Dosing regimen**	**Doses at Week:**	**Response assessment at Week:**
Guselkumab	200 mg IV/ 400 mg SC	0, 4, 8	12	200 mg SC	12, 16, 20	24
Vedolizumab	300 mg IV	0, 2, 6	10	300 mg IV	10	14
Mirikizumab	300 mg IV	0, 4, 8	12	300 mg IV	12, 16, 20	24
Key: IV, intravenous; SC, subcutaneous.						

In the model, the clinical response outcome determines whether patients achieve adequate response and move onto maintenance therapy. This is in line with feedback from UK clinical experts who were in agreement that clinical response would be a more appropriate endpoint to use than clinical remission given that the primary and secondary response assessment points are generally too short to determine remission status.(119)

Clinical response in the model was defined as a decrease from baseline in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a ≥ 1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1 (as

per the QUASAR and ASTRO trials).(101, 102) This definition was consistent with the NMA performed (Section 0) and as efficacy was demonstrated to be similar across all treatments, response rates were modelled to be the same for all treatments. These response rates are derived from the random-effects model response NMA and are presented in Table 47.

The probability of response after extended induction was assumed to be 46.5% and was informed by overall response data from ustekinumab NICE appraisal (TA633).(71) This probability of clinical response represented the proportion of biologic failure patients on ustekinumab with delayed response who did not respond during induction. This probability was modelled to be the same for all treatments. The use of data from the NMA to inform clinical response at the secondary response assessment was explored, however, the available data were considered to be insufficient given the variations in trial design and the fact that delayed response assessment period was not placebo-controlled in any trial. This approach was also adopted in TA925.(4)

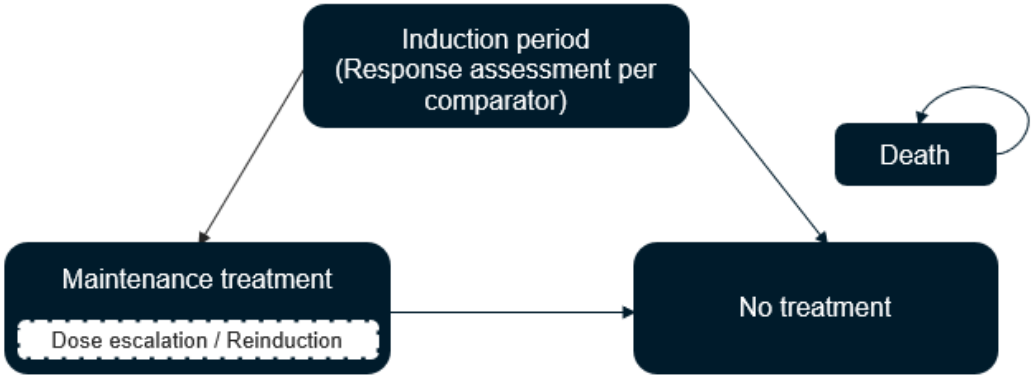
Table 47: Clinical response at the end of the primary response assessment

Treatment	**Response (including remission)**	
	OR (95% CI) relative to placebo	**Absolute probability**
Guselkumab		
Advanced therapy failure	[redacted]	[redacted]
Key: CI, confidence interval; OR, odds ratio.		

B.4.2.1.3. Maintenance phase (post-induction) model structure and efficacy

After the induction phase, patients who responded to treatment move to the maintenance treatment state. Patients who do not respond at the secondary response assessment move to the no-treatment state, as outlined in Section B.4.2.1.2

Figure 11: Markov model structure



Maintenance treatment

The maintenance phase of the model consists of three states: maintenance treatment, no treatment, and death (Figure 11). Patients can move from the maintenance treatment state to no treatment or death, but not vice versa. Patients are assumed to remain on maintenance treatment until they either discontinue treatment or die.

The proportion of responders are assumed to discontinue treatment at a constant rate during the maintenance phase. Treatment discontinuation in the model is informed by the all-cause treatment discontinuation observed in the QUASAR trial (Table 48). Given that the NMA presented in Section 0 demonstrated equivalent efficacy between treatments, the same discontinuation rate was applied to all treatments.

Table 48: Combined probability of discontinuation before completing maintenance dosing (W44)

Treatment	Probability of all-cause discontinuation	
	Absolute probability	Source
Guselkumab		
Full analysis set*	[redacted]	QUASAR W44 CSR Table 1. Combined % discontinuation prior to week M-44

Key: CI, confidence interval; CSR, clinical study report; OR, odds ratio.
Note: As per QUASAR protocol, all-cause discontinuation is defined as participants who discontinued study treatment prior to Week M-44, due to any reason. *All cause discontinuation was not available for the ADT-failure population

The observed probability of discontinuation at Week 44 is converted to a 2-weekly probability via geometric conversion through the steps below:

$$\gamma = -\ln(1 - P_{44\,weeks})$$

$$P_{2\,weeks} = 1 - e^{-\gamma/22}$$

$$44\,weeks\,probability = P_{44\,weeks}$$

$$Instantaneous\,rate = \gamma$$

$$2\,weeks\,probability = P_{2weeks}$$

As a result, the model uses a probability of treatment discontinuation of [redacted] per 2-week cycle.

Dose escalation / re-induction

In NHS clinical practice, patients that lose response to vedolizumab during the maintenance phase may be treated with increased doses or increased frequency of administration (i.e. dose escalation), as described in the SmPC.(117) In addition, patients who lose response to mirikizumab in the maintenance phase may also undergo re-induction. Dose escalation for vedolizumab and re-induction for mirikizumab are therefore included in the model to reflect UK clinical practice.(118) No such dose modifications are allowed for guselkumab within the maintenance phase and a patient is committed to a single dosing schedule (either 100 mg Q8W or 200 mg Q4W) until treatment discontinuation. (1)

To reflect clinical practice, the base case assumes that 30% of patients on vedolizumab require dose escalation. This is based on published literature on the frequency of TNF inhibitor dose escalation and is in line with the approach taken in TA925.(4, 96) The base case also assumes that 30% of patients on mirikizumab will undergo reinduction (as per scenario analysis conducted in TA925). Dose adjustments required by dose escalation/re-induction are outlined in Section B.4.2.2.

Patients are assumed to receive the escalated dosing schedule/re-induction from the first week of maintenance, to simplify the model. Given the assumption of equal efficacy for all treatments, dose escalation and re-induction are assumed to only affect costs, not efficacy. This assumption is consistent with the NMA results, which also showed comparable maintenance efficacy despite differences in dose-adjustment methods, and is in line with TA925 and TA998.(4, 13)

No treatment

Patients who transitioned to the no treatment state were assumed to stay in that state until death (Section B.4.2.1.4) or until the end of the model time horizon.

B.4.2.1.4. Mortality

Death is an absorbing health state that patients can transition to from all other health states at any time (induction period, maintenance treatment, and no treatment). In accordance with recent NICE TAs in IBD, UC is not associated with an increase in mortality.(4, 5, 13, 64, 66, 71) Mortality was therefore assumed to be equivalent across all health states and was modelled from the UK general population statistics based on the sex and age of the cohort in each cycle.(39)

B.4.2.2. Intervention and comparators' acquisition costs

Drug acquisition costs for the induction and maintenance phases of all included treatments are summarised in Table 49. Drug dosing schedules were derived from the SmPCs for each product with drug acquisition costs sourced from BNF. (117, 118, 120-122). Details of intervention and comparator costs per formulation used in the model can be found in Appendix H.

Table 49: Acquisition costs of the intervention and comparator technologies (UC)

	Guselkumab(1)	Mirikizumab(118)	Vedolizumab(117)
Pharmaceutical formulation	200 mg solution for injection in pre-filled syringe/pen (2 mL) 200 mg concentrate for solution for infusion vial (20 mL) 100 mg solution for injection in pre-filled pen (1 mL)	300 mg concentrate for solution for infusion vial (15 mL) 100 mg solution for injection in pre-filled syringe/pen (1 mL)	300 mg powder for concentrate for solution for infusion 108 mg solution for injection in pre-filled syringe/pen (0.68 mL)
(Anticipated) care setting	Secondary care		
Acquisition cost (excluding VAT) *	List prices: £2,250.00 per 100mg SC dose £[redacted] per 200 mg SC dose £[redacted] per 200 mg IV injection Net prices: applying simple discount of [redacted] [redacted] per 100 mg SC dose [redacted] per 200 mg SC dose [redacted] per 200 mg IV dose	List price: £2,056.56 per 300 mg injection List price: £2,056.56 for two 100 mg injections; £1,028.28 per 100 mg injection	List price: £2,050.00 per 300 mg infusion List price: £512.50 per 108 mg injection
Method of administration	• **Induction**: SC or IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC or IV
Doses	• **Induction**: 200 mg IV or 400 mg SC per administration	• **Induction**: 300 mg IV per administration	• **Induction**: 300 mg IV per administration • **Maintenance**: 300 mg IV or 108 mg SC

	Guselkumab(1)	Mirikizumab(118)	Vedolizumab(117)
	• **Maintenance**: 100 mg SC per administration or 200 mg SC per administration	• **Maintenance**: 200 mg SC per administration (two 100 mg injections)	
Dosing frequency	• **Induction**: Weeks 0, 4, 8 • **Maintenance**: The recommended maintenance dose of 100mg SC at Week 16 and then every 8 weeks thereafter. 200mg SC at Week 12 and then every 4 weeks thereafter may be considered for patients who do not show adequate therapeutic benefit.	• **Induction**: Weeks 0, 4 and 8 • **Maintenance**: Week 12 and then every 4 weeks	• **Induction**: Weeks 0, 2, and 6 • **Maintenance**: Week 10 and then every 8 weeks (IV) or every 2 weeks (SC)
Dose adjustments (i.e. re-induction, extended induction, dose escalation)	None	**Induction:** • For patients who do not achieve adequate therapeutic benefit at Week 12 of induction dosing, 300 mg by IV infusion may be continued at Weeks 12, 16 and 20 (extended induction therapy). **Maintenance:** • Patients with loss of therapeutic response during maintenance treatment may receive 300 mg mirikizumab by IV infusion every 4 weeks, for a total of three doses (re-induction)	**Induction:** • Patients who have not shown a response may benefit from a dose of intravenous vedolizumab at Week 10.** **Maintenance:** • 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

	Guselkumab(1)	Mirikizumab(118)	Vedolizumab(117)
			• There is no dose adjustment for patients receiving 108 mg SC 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)			
(Anticipated) average interval between courses of treatment			
(Anticipated) number of repeat courses of treatment			

Key: IV, intravenous; PAS, patient access scheme; SC, subcutaneous; UC, ulcerative colitis.
Note: * Indicate whether this acquisition cost is list price or includes an approved patient access scheme or other nationally available price reduction. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented. ** As disused in Section B.4.2.1, extended induction was considered for UC patients as per TA925.

Guselkumab has two dosing regimens that may be used during the induction phase: 200 mg IV and 400 mg SC (administered as 2 x 200 mg SC). A marketing authorisation will be sought for both formulations as induction therapy, as they have demonstrated similar efficacy based on trial results, (detailed in Section B.3.5), and are therefore included in the analysis.

All Week 12 primary responders on guselkumab induction therapy commence 100 mg SC maintenance therapy at week 16, and then every 8 weeks until treatment discontinuation. Inadequate responders at Week 12 will receive 200 mg SC at week 12 and then every 4 weeks until the secondary assessment point, and only delayed/secondary responders continue with 200 mg SC Q4W maintenance therapy. This is in line with the QUASAR trial design, posology described in the SmPC (Appendix C), and feedback from UK experts. (119)

Drug acquisition costs were estimated for the induction and maintenance phases of each comparator, with dosing regimens obtained from the respective SmPCs (as detailed in Table 49). The proportion of patients assumed to have escalated dosing for vedolizumab and re-induction for mirikizumab is 30%, Two administration forms are available for vedolizumab in the maintenance phase (SC and IV), as detailed in Table 49.

The total drug acquisition costs for the induction and maintenance phases are outlined in Table 50 and Table 51. These costs are inclusive of the current PAS discount in place for guselkumab and list prices for comparators.

Table 50: Drug acquisition costs for the induction phase

Treatment	No. of doses used during induction	Package size	Package price	Total induction costs
Guselkumab	3	IV 200 mg	[redacted]	[redacted]
	6	SC 200 mg	[redacted]	[redacted]
Vedolizumab	3	IV 300 mg	£2,050.00	£6,984.51
Mirikizumab	3	IV 300 mg	£2,056.56	£8,681.47
Key: IV, intravenous; SC, subcutaneous.				

Table 51: Drug acquisition costs for the maintenance phase

Treatment	Maintenance phase dosage	Package size	Package price	Year 1 maint. cost	Year 2+ maint. cost
Guselkumab	100 mg Q8W	SC 100 mg	[redacted]	[redacted]	[redacted]
	200 mg Q4W	SC 200 mg	[redacted]	[redacted]	[redacted]
Vedolizumab	Standard: 300 mg Q8W Escalated: 300 mg Q4W	IV 300 mg	£2,050.00	£8,604.94	£55,340.31
	108 mg Q2W	SC 108 mg	£512.50		
Mirikizumab	Standard: 200 mg Q4W	SC 200 mg	£2,056.56	£14,249.46	£96,923.01
	Re-induction: 300 mg Q4W (3 doses in total)	IV 300 mg	£2,056.56		

Key: IV, intravenous; Q2W, two-weekly; Q4W, four-weekly; Q8W, eight-weekly; Q12W, twelve-weekly. SC, subcutaneous.

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

B.4.2.3.1. Administration costs

As outlined in Section B.4.1, administration for guselkumab in the induction phase is flexible where patients can receive either IV infusion or SC injection. As presented in Table 49, administration for the comparator treatments in the induction phase is by IV infusion only. In the maintenance phase, all treatments aside from vedolizumab are administered via SC injection only, while patients receiving vedolizumab can have treatment administered as SC injection or IV infusion. The choice of IV or SC administration is subject to clinical judgement, patient preference, and resource availability.(123, 124)

Expert opinion from UK clinicians was elicited to understand the anticipated proportion of patients who would receive IV or SC administration for guselkumab and vedolizumab in the relevant treatment phases. Feedback from the clinicians ranged

regarding the use of guselkumab SC induction with three out of four clinicians favouring between 90% - 100% SC induction as base case, only one of the four clinicians suggesting allowing for greater use of IV induction as this may be preferred in some trusts/ certain patient types. All clinicians agreed on base assumption for guselkumab induction therapy, with a split of 80% patients receiving SC injection and 20% receiving IV infusion. A scenario is explored where 100% of patients receive IV induction since there may be a brief period after introduction in which only the IV induction formulation is available. For vedolizumab a 50%/50% assumption was validated from the expert feedback and is in line with the approach taken in TA888.(10, 119)

Table 52 outlines the proportion of patients receiving SC or IV formulations for guselkumab in the induction phase and vedolizumab in the maintenance phase.

Table 52: Proportion of patients on IV and SC in cost-comparison model

Intervention	Proportion IV	Proportion SC	Source
Guselkumab induction (IV/SC split)	20%	80%	Assumption validated with expert feedback (119)
Vedolizumab maintenance (IV/SC split)	50%	50%	Assumption validated with expert feedback and TA888(10, 119)
Key: IV, intravenous; SC, subcutaneous.			

In accordance with previous appraisals in IBD, including TA925, it was assumed that IV infusions are administered in an outpatient setting.(4) Unit costs for IV infusions were derived from 2022/2023 NHS Reference costs, and calculated as the weighted average of consultant led, and non-consultant-led, non-admitted face-to-face follow-up appointment in gastroenterology (code WF01A).(97) Consistent with recent appraisals, it was assumed that SC injections have an initial one-off cost attached that is associated with the time required for the patient to be trained in self-administration by a nurse. This cost was sourced from the Personal Social Services

Research Unit (PSSRU) 2023 under the cost per working hour of a Band 5 hospital-based nurse.(125) As patients self-inject subsequent doses, no additional costs were assigned in the model. Table 53 shows the administration costs for IV and SC therapies included in the cost-comparison model.

Table 53: Unit cost of treatment administration for IV and SC therapies

Administration type	Cost per administration	Source
IV	£181.09	2022/2023 NHS Reference Costs - weighted average of consultant led, and non-consultant led, WF01A (gastroenterology)(97)
SC (first dose)	£42.00	PSSRU 2023 - Cost per working hour of Band 5 hospital-based nurse(125)
SC (subsequent doses)	£0.00	Assumption (patients self-administer after first dose, in line with TA888 and TA925)
Key: IV, intravenous; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SC, subcutaneous.		

B.4.2.3.2. Disease management costs

Disease management costs are health-state-specific and are driven by efficacy. As efficacy has been demonstrated to be similar between guselkumab and its comparators by the NMA results presented in Section 0, the health state occupancy during the maintenance phase will be the same across all treatments. It is also expected for monitoring and testing in the induction phase to be similar across all treatments. Therefore, these costs are not modelled explicitly, in line with recent cost comparisons in UC.(4, 13)

B.4.2.4. Adverse reaction unit costs and resource use

The QUASAR and ASTRO trials had safety results consistent with the well-characterised safety profile of guselkumab in its approved indications of plaque psoriasis and psoriatic arthritis. No new safety concerns for guselkumab were identified in QUASAR and ASTRO. Overall, the safety data from the trials do not suggest a clinically meaningful difference between the safety profiles of the

guselkumab 200 mg SC Q4W and 100 mg SC Q8W. Additionally, the safety of guselkumab appears to be broadly similar to the comparators.

In line with previous cost-comparison appraisals in IBD, AEs were not included in the model analysis. This is discussed in TA925; where based on expert opinion elicitation, the EAG concluded it was reasonable to exclude AE costs from the analysis provided that the assumption of similar safety between all treatments held true.(4) In TA888 and TA998, AEs related to treatment were also excluded from the analysis.(10, 13) Therefore, to maintain consistency across the different appraisals, and applying the pragmatism of a cost-comparison approach, costs relating to SAEs have been excluded from the model analysis. The impact of SAEs will be indirectly considered in the inclusion of all-cause discontinuation.

B.4.2.5. Miscellaneous unit costs and resource use

No additional unit costs or resources were considered relevant for the cost-comparison model.

B.4.2.6. Expert validation

Clinical validation

Four UK clinicians were consulted individually to validate posology and health economic assumptions described in the dossier. (119) A summary of the assumptions validated are detailed below:

- The decision tree for guselkumab in UC to inform maintenance dosing choice
- Proportion of patients likely to receive IV and SC administration of guselkumab in the induction phase and IV and SC administration of vedolizumab in the maintenance phase
- Proportion of patients receiving escalated dosing on vedolizumab and re-induction on mirikizumab in the maintenance phase

Technical validation

The model went through independent quality control and technical validation processes from an independent health economist who was not previously involved in the model conceptualisation or programming. This included a thorough check of model calculations, including formulae and equations as well as the plausibility of inputs. Microsoft Excel® macros programmed in Visual Basic® for Applications (VBA) were also checked for coding errors and inconsistencies.(126) In addition, OWSAs and scenario analyses were reviewed. The model underwent technical and stress tests to verify output accuracy and stability under uncertainty.

B.4.2.7. Uncertainties in the inputs and assumptions

A summary of the inputs used in the cost-comparison analysis is provided in Table 54, and the key assumptions are presented in Table 55.

Table 54: Key inputs of the cost-comparison analysis

Input name	Base case value	Reference
Settings		
Perspective	UK NHS	Section B.4.2.1
Time horizon	10 years	Section B.4.2.1
Cost discount rate	0%	Section B.4.2.1
Model delayed response	Yes	Section B.4.2.1.2
Model dose escalation/re-induction	Yes	Section B.4.2.1.3
Patient characteristics		
Age in years, mean (SD)	42.6 (14.2)	Appendix I
Proportion male, mean	59.4%	Appendix I
Efficacy inputs		
Efficacy (%) response after induction period	[redacted]	Section B.3.8.5
All-cause discontinuation - probability per cycle (2 weeks) during maintenance (%)	[redacted]	Section B.4.2.1.2
Dosing inputs		
GUS SC/IV induction (%)	80%/20%	Section B.4.2.3.1
GUS 100 mg maintenance	100% for primary responders	Section B.4.2.1.2
GUS 200 mg maintenance	100% for delayed responders	Section B.4.2.1.2

Input name	Base case value	Reference
VDZ SC/IV maintenance (%)	50%/50%	Section B.4.2.3.1
VDZ and dose escalation and MIRI re-induction (%)	30%	Section B.4.2.1.3
Key: GUS, guselkumab; IV, intravenous; MIRI; mirikizumab; NHS, National Health Service; SC; subcutaneous; SD, standard deviation; VDZ, vedolizumab.		

Table 55: Key assumptions of the cost-comparison analysis

Assumption	Rationale for assumption
Non-responders discontinue treatment after the secondary response assessment	As described in the relevant SmPCs and consistent with previous appraisals.
Non-responding patients at the end of induction phase or patients that discontinue during maintenance treatment do not incur costs	This is a simplifying assumption. In clinical practice patients who do not respond may incur costs however, these would be similar across all treatments as similar efficacy has been demonstrated in the NMA between guselkumab and its comparators
No discontinuation during the induction phase	The length of the induction phase varies between treatments and in line with the assumption that all treatments have the same discontinuation probabilities, a simplifying assumption is made that patients do not discontinue treatment during the induction phase
All treatments in the model have the same efficacy	As shown by the NMA (Section 0) guselkumab is similar in efficacy to vedolizumab and mirikizumab
The different formulations of guselkumab have the same efficacy	As shown by the trial results (SectionB.3.5.4), guselkumab IV and SC induction achieved comparable response rates. It is therefore assumed that the IV/SC ratio in induction will only affect costs, with an assumed 80% of patients receiving SC induction, and 20% receiving IV induction.
Maintenance dose split of guselkumab 100 mg and 200 mg	As discussed in Section B.4.2.1.2, GUS maintenance is available in two different doses. It is assumed that all primary responders (week 12) receive the 100 mg dosing, and all delayed (secondary responders at week 24) receive the 200 mg dose. We assume the 100 mg /200 mg distribution will only impact the costs, since this flexible dosing is also reflected in the trials informing the NMA, which showed that GUS is equivalent to all included comparators.

Assumption	Rationale for assumption
Responders continue maintenance therapy with the same treatment until they lose response	Patients are unlikely to discontinue or switch treatments, given they remain effective in disease control. This is in line with the approach used in past UC TAs.(4, 5)
No costs for disease management, AEs, monitoring, or concomitant medication are included	No new safety concerns for guselkumab were identified in QUASAR and ASTRO. Additionally, the safety of guselkumab appears to be broadly similar to the comparators. The exclusion of AEs is in line with previous cost-comparison appraisals in IBD. Disease management costs are driven by efficacy and given that efficacy has been demonstrated to be similar between treatments, these costs are expected to be the same
Patients have the same mortality as the general population	Although UC is a debilitating disease, it is not known to impact patient survival, in line with the QUASAR and ASTRO trials. Survival is therefore modelled using UK general population mortality, consistent with past appraisals in IBD

Key: AE, adverse event; IBD, inflammatory bowel disease; IV, intravenous; NMA, network meta-analysis; SC, subcutaneous; SmPC, Summary of Product Characteristics; TA, technology appraisal; UC, ulcerative colitis.

B.4.3. Base case results

The results presented in Table 56 are inclusive of the existing PAS discount for guselkumab. As comparators have confidential PAS in place, comparisons are made against the list price of the comparators. The results show that guselkumab was cost saving versus vedolizumab and mirikizumab, resulting in an average cost saving of [redacted] and [redacted] per patient, respectively over a 10-year time horizon. The majority of these cost savings were achieved in the maintenance phase, where guselkumab saved [redacted] and [redacted] compared with vedolizumab and mirikizumab, respectively.

Table 56: Base case results (PAS price for guselkumab and list price for all comparators)

Treatment	Induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	Incremental costs relative to guselkumab
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Mirikizumab	[redacted]	[redacted]	[redacted]	[redacted]
Key: PAS, patient access scheme.				

B.4.4. Sensitivity and scenario analyses

B.4.4.1. One-way sensitivity analysis

OWSA was performed to assess the sensitivity of the model to uncertainty around the model inputs. This analysis assessed the impact on the total incremental costs versus each comparator, when changing a single parameter at a time to reflect the uncertainty/variability in the estimation of that parameter. When available, OWSA used the reported lower and upper bounds of the inputs, for example for patient characteristics from the trial or NMA estimates. If a reported range was not available, then the upper and lower values were calculated in the model, based on either the reported standard error if available, or an assumed standard error of 20%.

The top 10 most impactful parameters during the OWSA are shown per comparator in Table 57 and Table 58, with the respective tornado plots in Figure 12 and Figure 13. In all analyses, the guselkumab odds ratio of response after induction was the most influential parameter. This is expected, as the more patients achieve clinical response, the higher the incremental costs between guselkumab and its comparators. The placebo probability of response and discontinuation during maintenance was also among the most impactful parameters. However, overall, the incremental costs changed marginally for most parameters, suggesting that the model is not sensitive to uncertainty around individual parameter inputs. Guselkumab remained cost saving in each variation.

Table 57: Results of one-way sensitivity analyses versus vedolizumab

Top 10 most influential variables		Incremental costs	
Rank	**Name**	**Lower**	**Upper**
1	NMA GUS OR of response after induction (1.95 - 8.62)	[redacted]	[redacted]
2	Reported discontinuation rate (7.14% - 15.79%)	[redacted]	[redacted]
3	NMA PBO absolute probability of response after induction (0.17 - 0.37)	[redacted]	[redacted]
4	VDZ SC % maintenance (30.96% - 69.04%)	[redacted]	[redacted]
5	VDZ % dose escalation (19.05% - 42.25%)	[redacted]	[redacted]
6	Administration costs IV (£117.19 - £258.67)	[redacted]	[redacted]
7	Probability of response at the end of extended induction all therapies (28.95% - 64.51%)	[redacted]	[redacted]
8	Patient age at model start (32.00 - 54.00)	[redacted]	[redacted]
9	GUS SC % induction (44.01% - 98.85%)	[redacted]	[redacted]
10	Proportion male (0.38 - 0.85)	[redacted]	[redacted]

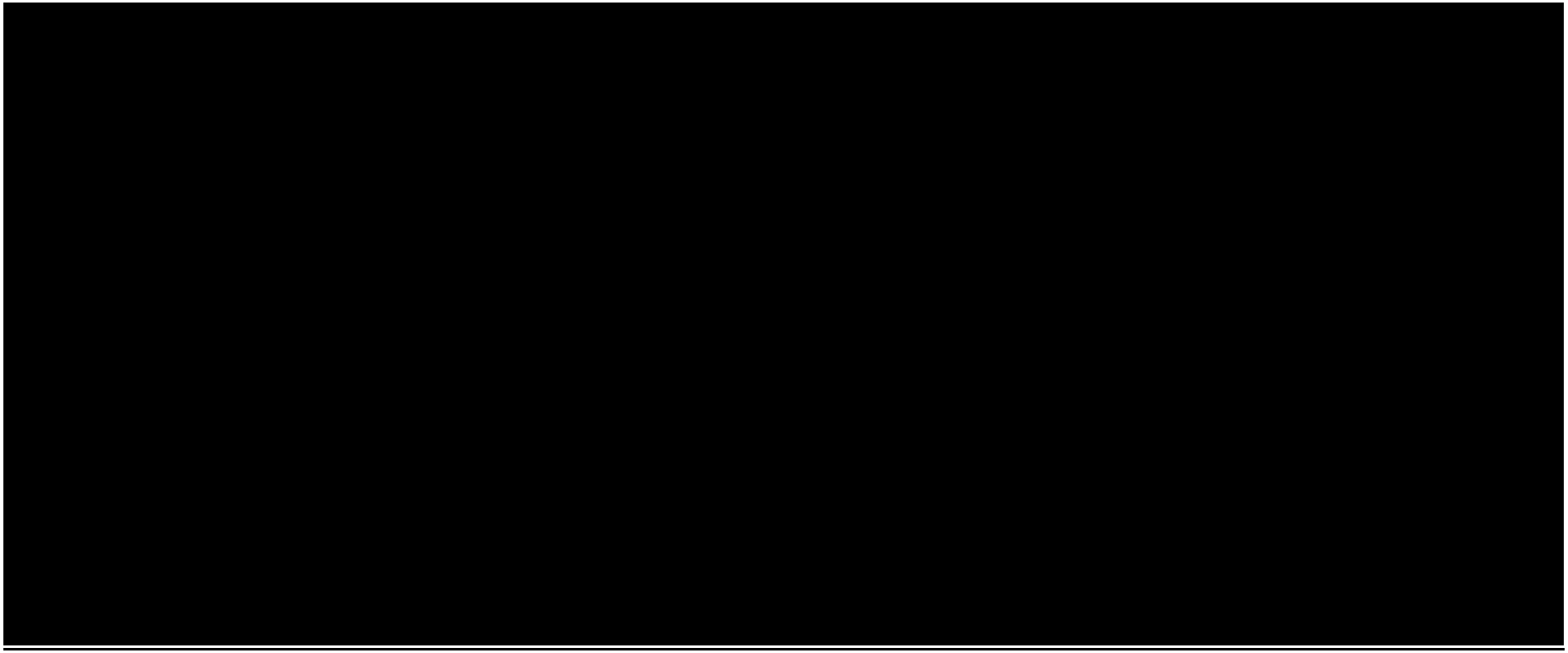
Key: GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; SC, subcutaneous; VDZ, vedolizumab.

Table 58: Results of one-way sensitivity analyses versus mirikizumab

Top 10 most influential variables		Incremental costs	
Rank	**Name**	**Lower**	**Upper**
1	Reported discontinuation rate (7.14% - 15.79%)	[redacted]	[redacted]
2	NMA GUS OR of response after induction (1.95 - 8.62)	[redacted]	[redacted]
3	NMA PBO absolute probability of response after induction (0.17 - 0.37)	[redacted]	[redacted]
4	Probability of response at the end of extended induction all therapies (28.95% - 64.51%)	[redacted]	[redacted]
5	Patient age at model start (32.00 - 54.00)	[redacted]	[redacted]
6	Administration costs IV (£117.19 - £258.67)	[redacted]	[redacted]
7	GUS SC % induction (44.01% - 98.85%)	[redacted]	[redacted]
8	Proportion male (0.38 - 0.85)	[redacted]	[redacted]
9	MIRI % re-induction (19.05% - 42.25%)	[redacted]	[redacted]
10	Administration costs SC first dose (£27.18 - £59.99)	[redacted]	[redacted]

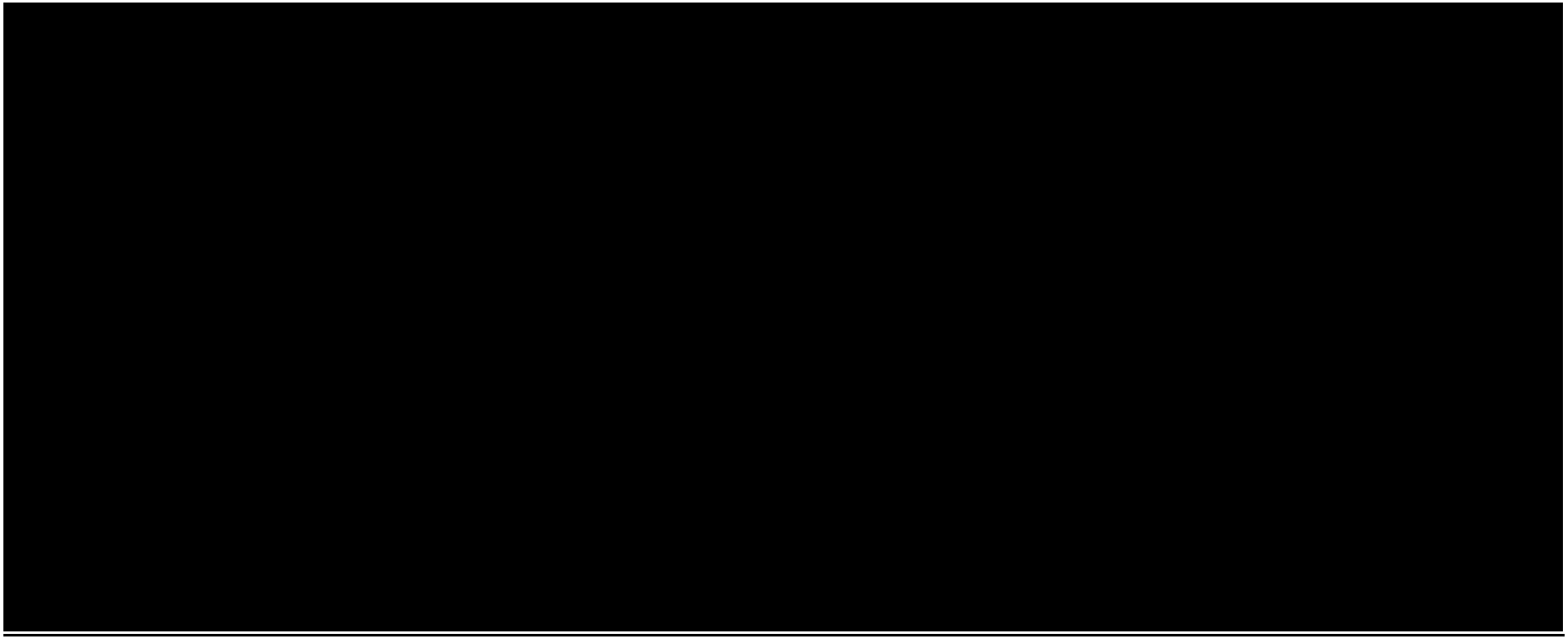
Key: GUS, guselkumab; IV, intravenous; MIRI, mirikizumab; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; SC, subcutaneous.

Figure 12: Tornado diagram of most influential parameters for guselkumab versus vedolizumab



Key: GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; OWSA, one-way sensitivity analysis; PBO, placebo; SC, subcutaneous; VDZ, vedolizumab.

Figure 13: Tornado diagram of most influential parameters for guselkumab versus mirikizumab



Key: GUS, guselkumab; IV, intravenous; MIRI, mirikizumab; NMA, network meta-analysis; OR, odds ratio; OWSA, one-way sensitivity analysis; PBO, placebo; SC, subcutaneous.

B.4.4.2. Scenario analysis

Scenario analyses were conducted to demonstrate the impact of varying individual input values and model assumptions. An overview of the scenario analyses considered is provided in Table 59.

Table 59: Summary of scenario analyses

Scenario analysis	Base case	Alternatives	Justification
Time horizon	10 years	5 years	Assess the impact of shorter time horizon
Discount for costs	0%	3.5%	Value testing to assess the impact of costs discounting
Proportion of patients receiving SC/IV induction for guselkumab	SC: 80% IV: 20%	SC: 0% IV: 100%	Assess the impact of including SC induction
Key: IV, intravenous; SC, subcutaneous; SmPC, summary of product characteristics. **Notes:** *Delayed responders receive 200 mg by default, in both the base case and scenarios, in line with the SmPC.			

Exploratory scenario results are shown per comparator in Table 60 and Table 61. Application of a 3.5% discounting rate and reducing the time horizon to 5 years resulted in a bigger decrease in incremental costs vs base case. An additional scenario that considers only IV induction for guselkumab in UC shows a minimal impact on overall costs to the system. Overall, guselkumab remains cost saving compared to vedolizumab and mirikizumab.

Table 60: Results of scenario analyses versus vedolizumab

Scenario name	Incremental costs	Difference to base case
Reduce time horizon to 5 years	[redacted]	[redacted]
Include a 3.5% discounting for costs	[redacted]	[redacted]
Assume 100% of GUS patients receive induction via IV	[redacted]	[redacted]
Key: GUS, guselkumab; SC, subcutaneous; IV, intravenous.		

Table 61: Results of scenario analyses versus mirikizumab

Scenario name	Incremental costs	Difference to base case
Reduce time horizon to 5 years	[redacted]	[redacted]
Include a 3.5% discounting for costs	[redacted]	[redacted]
Assume 100% of GUS patients receive induction via IV	[redacted]	[redacted]
Key: GUS, guselkumab; SC, subcutaneous; IV, intravenous.		

B.4.5. Subgroup analysis

In line with the decision problem, no subgroup analyses were considered as part of the cost-comparison.

B.4.6. Interpretation and conclusions of economic evidence

This analysis evaluated the costs associated with guselkumab, vedolizumab, and mirikizumab in the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to a biologic treatment, or JAK inhibitor, under the assumption of equivalent efficacy. The analysis showed that guselkumab was cost saving versus vedolizumab and mirikizumab, resulting in an average cost saving of [redacted] and [redacted] per patient, respectively over a 10-year time horizon. The outcomes from the OWSA and scenario analysis conducted showed that guselkumab remained cost-saving compared to vedolizumab and mirikizumab.

Overall, the results show that the implementation of guselkumab in the NHS would offer patients a valuable new treatment option, with comparable efficacy and tolerability to the current treatments, while providing more flexible treatment options for patients. The flexibility of choosing between subcutaneous and intravenous induction provides physicians and patients with the option to personalise treatment according to individual preferences and NHS local service capabilities. This flexibility has the potential to reduce the impact of treatment on patients' lives and alleviate the burden on the NHS by reducing waiting times, as fewer IV administrations would be required when compared with the current standard of care.

B.5. References

1. Janssen-Cilag Ltd (a Johnson & Johnson Company). Tremfya: Summary of Product Characteristics (draft). 2025.
2. National Institute for Health and Care Excellence. [ID6237] Guselkumab for moderately to severely active ulcerative colitis: final scope 2025 [Available from: https://www.nice.org.uk/guidance/gid-ta11247/documents/final-scope.
3. National Institute for Health and Care Excellence. [ID6238] Guselkumab for previously treated moderately to severely active Crohn's disease: Final Scope 2025 [Available from: https://www.nice.org.uk/guidance/gid-ta11245/documents/final-scope-2.
4. National Institute for Health and Care Excellence. [TA925] Mirikizumab for treating moderately to severely active ulcerative colitis. 2023 [Available from: https://www.nice.org.uk/guidance/ta925].
5. National Institute for Health and Care Excellence. [TA342] Vedolizumab for treating moderately to severely active ulcerative colitis. 2015 [Available from: https://www.nice.org.uk/guidance/ta342].
6. Janssen Research and Development. Clinical Study Report: QUASAR (Induction Study 2)- A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis. 2024.
7. Janssen Research and Development. Clinical Study Report: QUASAR (Maintenance Study) - A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis 2024.
8. Peyrin-Biroulet L, Allegretti JR, Rubin DT, Bressler B, Germinaro M, Huang K-H, et al. Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: QUASAR Phase 2b Induction Study. Gastroenterology. 2023;165(6):1443-57.
9. Johnson & Johnson. [Data on file] ASTRO clinical study report (Week 24). RF-4513332025.
10. National Institute for Health and Care Excellence. [TA888] Risankizumab for previously treated moderately to severely active Crohn's disease. 2023 [Available from: https://www.nice.org.uk/guidance/ta888].
11. National Institute for Health and Care Excellence. [TA905] Upadacitinib for previously treated moderately to severely active Crohn’s disease. 2023 [Available from: https://www.nice.org.uk/guidance/ta905].
12. National Institute for Health and Care Excellence. [TA956] Etrasimod for treating moderately to severely active ulcerative colitis in people aged 16 and over. 2024 [Available from: https://www.nice.org.uk/guidance/ta956].
13. National Institute for Health and Care Excellence. [TA998] Risankizumab for treating moderately to severely active ulcerative colitis. 2024 [Available from: https://www.nice.org.uk/guidance/ta998].

14. National Institute for Health and Care Excellence. [ID6244] Mirikizumab for treating moderately to severely active Crohn's disease. 2024 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11267].
15. Kapizioni C, Desoki R, Lam D, Balendran K, Al-Sulais E, Subramanian S, et al. Biologic Therapy for Inflammatory Bowel Disease: Real-World Comparative Effectiveness and Impact of Drug Sequencing in 13 222 Patients within the UK IBD BioResource. J Crohns Colitis. 2024;18(6):790-800.
16. National Institute for Health and Care Excellence. Clinical Knowledge Summary: Ulcerative colitis. 2024 [Available from: https://cks.nice.org.uk/topics/ulcerative-colitis/].
17. Feuerstein JD MA, Farraye FA. Ulcerative Colitis. Mayo Clin Proc. 2019;94(7):1357-73.
18. Qiu Y CB, Li Y, Xiong S, Zhang S, He Y, Zeng Z, Ben-Horin S, Chen M, Mao R. Risk factors and long-term outcome of disease extent progression in Asian patients with ulcerative colitis: a retrospective cohort study. BMC Gastroenterol. 2019;19(7):1-9.
19. Seyedian SS NF, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. J Med Life. 2019;12(2):113-22.
20. Yang AZ J-DL. Environmental variables and genome-environment interactions predicting IBD diagnosis in large UK cohort. Sci Rep. 2022;12(1):10890.
21. Le Berre C HS, Peyrin-Biroulet L. Ulcerative colitis. Lancet. 2023;402.
22. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389(10080):1756-70.
23. Willert RP, Lawrance IC. Use of infliximab in the prevention and delay of colectomy in severe steroid dependant and refractory ulcerative colitis. World J Gastroenterol. 2008;14(16):2544-9.
24. Dai N, Haidar O, Askari A, Segal JP. Colectomy rates in ulcerative colitis: A systematic review and meta-analysis. Dig Liver Dis. 2023;55(1):13-20.
25. Kilic Y, Kamal S, Jaffar F, Sriranganathan D, Quraishi MN, Segal JP. Prevalence of Extraintestinal Manifestations in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Inflammatory Bowel Diseases. 2023.
26. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. Gastroenterology. 2021;161(4):1118-32.
27. Kofla-Dłubacz A, Pytrus T, Akutko K, Sputa-Grzegrzółka P, Piotrowska A, Dzięgiel P. Etiology of IBD-Is It Still a Mystery? Int J Mol Sci. 2022;23(20).
28. Söderman J, Berglind L, Almer S. Inverse and Concordant Mucosal Pathway Gene Expressions in Inflamed and Non-Inflamed Ulcerative Colitis Patients: Potential Relevance to Aetiology and Pathogenesis. Int J Mol Sci. 2022;23(13).
29. Singh N, Bernstein CN. Environmental risk factors for inflammatory bowel disease. United European Gastroenterol J. 2022;10(10):1047-53.
30. Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. Gastroenterology. 2019;157(3):647-59.e4.
31. National Institute for Health and Care Excellence. [NG130] Ulcerative colitis: management. 2019 [Available from: https://www.nice.org.uk/guidance/ng130].

32. Lungaro L, Costanzini A, Manza F, Barbalinardo M, Gentili D, Guarino M, et al. Impact of Female Gender in Inflammatory Bowel Diseases: A Narrative Review. J Pers Med. 2023;13(2).
33. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019;13(2):144-64.
34. Pabla BS SD. Assessing Severity of Disease in Patients with Ulcerative Colitis. . Gastroenterol Clin North Am. 2020;49(4):671-88.
35. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1-s106.
36. Sturm A MC, Calabrese E, Annese V, Fiorino G. 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(3):273-84.
37. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114(3):384-413.
38. Crohn's and Colitis UK. Epidemiology Summary: Incidence and Prevalence of IBD in the United Kingdom. 2020 [Available from: https://crohnsandcolitis.org.uk/media/4e5ccomz/epidemiology-summary-final.pdf].
39. Office for National Statistics. National life tables: England and Wales [2020-2022]. 2024 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables].
40. King D RR, Thomas T, Chandan JS, Thayakaran R, Subramanian A, Gokhale K, Bhala N, Nirantharakumar K, Adderley NJ, Trudgill N. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. Aliment Pharmacol Ther 2020;51(10):922-34.
41. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(3):343-56.e3.
42. Zhao M, Gönczi L, Lakatos PL, Burisch J. The Burden of Inflammatory Bowel Disease in Europe in 2020. J Crohns Colitis. 2021;15(9):1573-87.
43. Verstockt B, Bressler B, Martinez-Lozano H, McGovern D, Silverberg MS. Time to Revisit Disease Classification in Inflammatory Bowel Disease: Is the Current Classification of Inflammatory Bowel Disease Good Enough for Optimal Clinical Management? Gastroenterology. 2022;162(5):1370-82.
44. Mosli MH, Alsahafi M, Alsanea MN, Alhasani F, Ahmed M, Saadah O. Multimorbidity among inflammatory bowel disease patients in a tertiary care center: a retrospective study. BMC Gastroenterol. 2022;22(1):487.
45. Bernstein CN, Nugent Z, Shaffer S, Singh H, Marrie RA. Comorbidity before and after a diagnosis of inflammatory bowel disease. Aliment Pharmacol Ther. 2021;54(5):637-51.
46. Chen B, Collen LV, Mowat C, Isaacs KL, Singh S, Kane SV, et al. Inflammatory Bowel Disease and Cardiovascular Diseases. Am J Med. 2022;135(12):1453-60.

47. Moon JM, Lee JY, Koh SJ, Park H, Kang S, Soh H, et al. Incidence of Psoriasis in Patients with Inflammatory Bowel Disease: A Nationwide Population-Based Matched Cohort Study. Dermatology. 2021;237(3):330-7.
48. Vadstrup K, Alulis S, Borsi A, Jørgensen TR, Nielsen A, Munkholm P, et al. Extraintestinal Manifestations and Other Comorbidities in Ulcerative Colitis and Crohn Disease: A Danish Nationwide Registry Study 2003–2016. Crohn's & Colitis 360. 2020;2(3).
49. Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(5):359-70.
50. Yarlas A, Rubin DT, Panés J, Lindsay JO, Vermeire S, Bayliss M, et al. Burden of Ulcerative Colitis on Functioning and Well-being: A Systematic Literature Review of the SF-36® Health Survey. J Crohns Colitis. 2018;12(5):600-9.
51. Armuzzi A, Liguori G. Quality of life in patients with moderate to severe ulcerative colitis and the impact of treatment: A narrative review. Dig Liver Dis. 2021;53(7):803-8.
52. Benchimol EI, Bernstein CN, Bitton A, Murthy SK, Nguyen GC, Lee K, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: A Scientific Report from the Canadian Gastro-Intestinal Epidemiology Consortium to Crohn's and Colitis Canada. J Can Assoc Gastroenterol. 2019;2(Suppl 1):S1-s5.
53. Mavroudis G, Simrén M, Öhman L, Strid H. Health-related quality of life in patients with long-standing ulcerative colitis in remission. Therap Adv Gastroenterol. 2022;15:17562848211062406.
54. Hagelund LM, Elkjær Stallknecht S, Jensen HH. Quality of life and patient preferences among Danish patients with ulcerative colitis - results from a survey study. Curr Med Res Opin. 2020;36(5):771-9.
55. Naegeli AN, Balkaran BL, Shan M, Hunter TM, Lee LK, Jairath V. The impact of symptom severity on the humanistic and economic burden of inflammatory bowel disease: a real-world data linkage study. Curr Med Res Opin. 2022;38(4):541-51.
56. Matsuoka K, Yamazaki H, Nagahori M, Kobayashi T, Omori T, Mikami Y, et al. Association of ulcerative colitis symptom severity and proctocolectomy with multidimensional patient-reported outcomes: a cross-sectional study. J Gastroenterol. 2023;58(8):751-65.
57. Keller R, Mazurak N, Fantasia L, Fusco S, Malek NP, Wehkamp J, et al. Quality of life in inflammatory bowel diseases: it is not all about the bowel. Intest Res. 2021;19(1):45-52.
58. Afzali A, Lukanova R, Hennessy F, Kakehi S, Knight H, Milligan G, et al. Unmet Needs in Real-World Advanced Therapy-Naïve and -Experienced Patients with Moderately to Severely Active Ulcerative Colitis in the United States. Advances in Therapy. 2023;40(10):4321-38.
59. Liu R, Tang A, Wang X, Shen S. Assessment of Quality of Life in Chinese Patients With Inflammatory Bowel Disease and their Caregivers. Inflamm Bowel Dis. 2018;24(9):2039-47.
60. Hibi T, Ishibashi T, Ikenoue Y, Yoshihara R, Nihei A, Kobayashi T. Ulcerative Colitis: Disease Burden, Impact on Daily Life, and Reluctance to Consult Medical

Professionals: Results from a Japanese Internet Survey. Inflamm Intest Dis. 2020;5(1):27-35.
61. Paulides E, Cornelissen D, Vries ACd, Woude CJvd. Inflammatory bowel disease negatively impacts household and family life. Frontline Gastroenterology. 2022;13(5):402-8.
62. Rubin DT, Dubinsky MC, Panaccione R, Siegel CA, Binion DG, Kane SV, et al. The impact of ulcerative colitis on patients' lives compared to other chronic diseases: a patient survey. Dig Dis Sci. 2010;55(4):1044-52.
63. Constantin J, Atanasov P, Wirth D, Borsi A. Indirect costs associated with ulcerative colitis: a systematic literature review of real-world data. BMC Gastroenterol. 2019;19(1):179.
64. National Institute for Health and Care Excellence. [TA828] Ozanimod for treating moderately to severely active ulcerative colitis. 2022 [Available from: https://www.nice.org.uk/guidance/ta828].
65. National Institute for Health and Care Excellence. [TA792] Filgotinib for treating moderately to severely active ulcerative colitis. 2022 [Available from: https://www.nice.org.uk/guidance/ta792].
66. National Institute for Health and Care Excellence. [TA547] Tofacitinib for moderately to severely active ulcerative colitis. 2018 [Available from: https://www.nice.org.uk/guidance/TA547].
67. Singh H, Wilson L, Pandey A, Tencer T, Kumar J. 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(Supplement_1):S511-S2.
68. Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. Alimentary Pharmacology & Therapeutics. 2016;44(8):807-16.
69. National Institute for Health and Care Excellence. [TA329] Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. 2015 [Available from: https://www.nice.org.uk/guidance/ta329].
70. National Institute for Health and Care Excellence. [TA856] Upadacitinib for treating moderately to severely active ulcerative colitis. 2023 [Available from: https://www.nice.org.uk/guidance/ta856].
71. National Institute for Health and Care Excellence. [TA633] Ustekinumab for treating moderately to severely active ulcerative colitis. 2020 [Available from: https://www.nice.org.uk/guidance/TA633].
72. Blackwell J, Selinger C, Raine T, Parkes G, Smith MA, Pollok R. Steroid use and misuse: a key performance indicator in the management of IBD. Frontline Gastroenterol. 2021;12(3):207-13.
73. Caprioli F, Daperno M, Bravatà I, Brigido A, Frigerio D, Secchi O, et al. Who are the patients with Crohn's disease unsuitable to receive an anti-TNFα therapy? Results from a survey of Italian physicians and literature review. Eur J Gastroenterol Hepatol. 2021;33(8):1082-90.
74. Honap S, Agorogianni A, Colwill MJ, Mehta SK, Donovan F, Pollok R, et al. JAK inhibitors for inflammatory bowel disease: recent advances. Frontline Gastroenterol. 2024;15(1):59-69.

75. Medicines and Healthcare products Regulatory Agency (MHRA). Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality 2023 [Available from: https://www.gov.uk/drug-safety-update/janus-kinase-jak-inhibitors-new-measures-to-reduce-risks-of-major-cardiovascular-events-malignancy-venous-thromboembolism-serious-infections-and-increased-mortality.
76. Bristol-Myers Squibb Pharma EEIG. Zeposia: Summary of Product Characteristics. 2020 [Available from: https://www.medicines.org.uk/emc/product/11906/smpc.
77. Pfizer Limited. Velsipity: Summary of Product Characteristics. 2024 [Available from: https://www.medicines.org.uk/emc/product/15602/smpc.
78. Peyrin-Biroulet L, Sandborn WJ, Panaccione R, Domènech E, Pouillon L, Siegmund B, et al. Tumour necrosis factor inhibitors in inflammatory bowel disease: the story continues. Therap Adv Gastroenterol. 2021;14:17562848211059954.
79. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016;7(1):e135.
80. Marsal J, Barreiro-de Acosta M, Blumenstein I, Cappello M, Bazin T, Sebastian S. Management of Non-response and Loss of Response to Anti-tumor Necrosis Factor Therapy in Inflammatory Bowel Disease. Front Med (Lausanne). 2022;9:897936.
81. Muzammil MA, Fariha F, Patel T, Sohail R, Kumar M, Khan E, et al. Advancements in Inflammatory Bowel Disease: A Narrative Review of Diagnostics, Management, Epidemiology, Prevalence, Patient Outcomes, Quality of Life, and Clinical Presentation. Cureus. 2023;15(6):e41120.
82. Cross RK, Naegeli AN, Harrison RW, Moore PC, Mackey RH, Crabtree MM, et al. Disease Burden and Patient-Reported Outcomes Among Ulcerative Colitis Patients According to Therapy at Enrollment Into CorEvitas' Inflammatory Bowel Disease Registry. Crohns Colitis 360. 2022;4(3):otac007.
83. Gibble TH, Naegeli AN, Grabner M, Isenberg K, Shan M, Teng CC, et al. Identification of inadequate responders to advanced therapy among commercially-insured adult patients with Crohn's disease and ulcerative colitis in the United States. BMC Gastroenterol. 2023;23(1):63.
84. Zhuleku E, Wirth D, Nissinen R, Bravatà I, Ziavra D, Duva A, et al. Switching within versus out of class following first-line TNFi failure in ulcerative colitis: real-world outcomes from a German claims data analysis. Therap Adv Gastroenterol. 2024;17:17562848241262288.
85. 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)? J Clin Med. 2021;10(22).
86. Travis S, Potts Bleakman A, Dubinsky MC, Schreiber S, Panaccione R, Hibi T, et al. The Communicating Needs and Features of IBD Experiences (CONFIDE) Study: US and European Patient and Health Care Professional Perceptions of the Experience and Impact of Symptoms of Moderate-to-Severe Ulcerative Colitis. Inflamm Bowel Dis. 2024;30(6):939-49.

87. Overton PM, Shalet N, Somers F, Allen JA. Patient Preferences for Subcutaneous versus Intravenous Administration of Treatment for Chronic Immune System Disorders: A Systematic Review. Patient Prefer Adherence. 2021;15:811-34.
88. Fiorino G, Bent-Ennakhil N, Varriale P, Braegger F, Hoefkens E. Patient Preferences for Treatment Attributes in Inflammatory Bowel Disease: Results From a Large Survey Across Seven European Countries Using a Discrete Choice Experiment. Inflamm Bowel Dis. 2024.
89. Crohn's & Colitis UK. A guide for employees. 2022 [Available from: https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/employment-and-education/employment-a-guide-for-employees].
90. UK Parliament. Written evidence from Crohn's & Colitis UK DYE0019. 2024 [Available from: https://committees.parliament.uk/writtenevidence/129236/html/].
91. Crohn's & Colitis UK. Weeks not years. 2023 [Available from: https://crohnsandcolitis.org.uk/media/5kefufoj/crohns-colitis-uk_weeks-not-years-briefing.pdf].
92. Arseneau KO, Sultan S, Provenzale DT, Onken J, Bickston SJ, Foley E, et al. Do patient preferences influence decisions on treatment for patients with steroid-refractory ulcerative colitis? Clin Gastroenterol Hepatol. 2006;4(9):1135-42.
93. Royal Pharmaceutical Society of Great Britain. BNF Online. 2024 [Available from: https://www.nice.org.uk/bnf-uk-only].
94. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2024 [Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit].
95. Monthly Index of Medical Specialities. MIMS 2024. 2024 [Available from: https://www.mims.co.uk/].
96. Lindsay JO, Armuzzi A, Gisbert JP, Bokemeyer B, Peyrin-Biroulet L, Nguyen GC, et al. Indicators of suboptimal tumor necrosis factor antagonist therapy in inflammatory bowel disease. Dig Liver Dis. 2017;49(10):1086-91.
97. Department of Health and Social Care. NHS reference costs. 2022/2023. 2024 [Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/].
98. Tsai HH, Punekar YS, Morris J, Fortun P. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2008;28(10):1230-9.
99. Department of Health and Social Care. NHS Payment Scheme. 2024 [Available from: https://www.england.nhs.uk/pay-syst/nhs-payment-scheme/].
100. Johnson & Johnson. [Data on file] Efficacy of guselkumab versus available biologic therapies for the maintenance treatment of moderate to severe ulcerative colitis: A systematic review and meta-analysis 2025.
101. Johnson & Johnson. [Data on file] QUASAR Clinical Protocol Overview. RF-4513342025.
102. Johnson & Johnson. [Data on file] ASTRO clinical protocol overview. RF-4512602025.

103. Geboes K, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000;47(3):404-9.
104. Higgins PD, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. Gut. 2005;54(6):782-8.
105. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994;106(2):287-96.
106. Rubin DT, Allegretti JR, Panes J, Shipitofsky N, Yarandi SS, Huang KG, et al. Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR): phase 3 double-blind, randomised, placebo-controlled induction and maintenance studies. Lancet. 2025;405(10472):33-49.
107. Peyrin-Biroulet L, Allegretti JR, Danese S, Germinaro M, Baker T, Alvarez Y, et al. OP10 Efficacy and safety of subcutaneous guselkumab induction therapy in patients with Ulcerative Colitis: Results through week 12 from the phase 3 ASTRO study. Journal of Crohn's and Colitis. 2025;19(Supplement_1):i19-i20.
108. Johnson & Johnson. Clinical Study Report: QUASAR (Induction Study 1) - A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis 2024.
109. Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S, et al. Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. Clin Gastroenterol Hepatol. 2017;15(2):229-39 e5.
110. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.
111. Sandborn WJ, Baert F, Danese S, Krznaric Z, Kobayashi T, Yao X, et al. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology. 2020;158(3):562-72 e12.
112. S. Navabi GDH, K.H. Samaan, X. Li, V. Arora, I. Redondo, S. Danese. Effect of mirikizumab on clinical and endoscopic outcomes based on prior advanced therapy failure in patients with moderately to severely active ulcerative colitis. JCC. 2023;17(Supplement_1):i598.
113. D'Haens G, Dubinsky M, Kobayashi T, Irving PM, Howaldt S, Pokrotnieks J, et al. Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis. NEJM. 2023;388(26):2444-55.
114. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med. 2015;34(6):984-98.
115. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials 2011 [Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf.

116. National Institute for Health and Care Excellence. [PMG32] User guide for the cost comparison company evidence submission template. 2017 [Available from: https://www.nice.org.uk/process/pmg32/chapter/instructions-for-companies].
117. Takeda Pharma A/S. Entyvio: Summary of Product Characteristics. 2014 [Available from: https://www.medicines.org.uk/emc/product/5442/smpc.
118. Eli Lilly Nederland B.V. Omvoh: Summary of Product Characteristics. 2024 [Available from: https://www.medicines.org.uk/emc/product/14881/smpc.
119. Johnson & Johnson. [Data on file] Summary of calls with UK HCPs. RF-4500872025.
120. British National Formulary. Guselkumab: Medicinal Forms 2025 [Available from: https://bnf.nice.org.uk/drugs/guselkumab/medicinal-forms/.
121. British National Formulary. Vedolizumab: Medicinal Forms 2025 [Available from: https://bnf.nice.org.uk/drugs/vedolizumab/#medicinal-forms.
122. British National Formulary. Mirikizumab: Medicinal Forms 2025 [Available from: https://bnf.nice.org.uk/drugs/mirikizumab/medicinal-forms/.
123. Jonaitis L, Marković S, Farkas K, Gheorghe L, Krznarić Ž, Salupere R, et al. Intravenous versus subcutaneous delivery of biotherapeutics in IBD: an expert's and patient's perspective. BMC Proc. 2021;15(Suppl 17):25.
124. Remy C, Caron B, Gouynou C, Haghnejad V, Jeanbert E, Netter P, et al. Inflammatory Bowel Disease Patients' Acceptance for Switching from Intravenous Infliximab or Vedolizumab to Subcutaneous Formulation: The Nancy Experience. J Clin Med. 2022;11(24).
125. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2023. 2024 [Available from: https://kar.kent.ac.uk/105685/].
126. Johnson & Johnson. [Data on file] Quality check report for the guselkumab cost-comparison model in UC. RF-4513362025.

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's a plain English summary of their submission written for patients participating in the evaluation. It's 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's 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

Both generic and brand name.

Generic name: Guselkumab Brand name: Tremfya®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE
The main patient population that is being appraised by NICE is a subset of the expected full licensed population (marketing authorisation). The population includes adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic or another advanced therapy (ADT) (collectively referred to as the "ADT-failure" population). Advanced therapies include biologic therapies taken as an injection or an infusion such as tumour necrosis factor (TNF)-inhibitors, or oral therapies such as Janus kinase (JAK) inhibitors. The population may also include people for whom TNF-inhibitors are considered unsuitable.

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.
Guselkumab is currently under review by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of people with previously treated ulcerative colitis and is expected to be approved for use in Great Britain in 2025. Guselkumab will initially be available as an induction therapy given by intravenous infusion in a hospital setting, followed by maintenance therapy given via subcutaneous injection at home. Clinical trial data are also being submitted to NICE that demonstrate efficacy of guselkumab as an injection for both induction and maintenance phases of treatment. MHRA review and approval for a fully injectable treatment regimen is expected in early 2026. Details of the proposed label wording and anticipated approval dates are confidential and can be found in the company submission Document B, Section B.1.2., Table 2.

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
J&J works with patient groups on a periodic basis, for example Crohn's & Colitis UK and IBDrelief. As a member of the Association of the British Pharmaceutical Industry (ABPI), J&J is required to publish information about relationships with patient organisations, annually, known as transfer of value (TOV). Table 1 details the TOV information relating to collaborations with Crohn's & Colitis UK and IBDrelief relevant to this appraisal.

Table 1: J&J transfer of value information between the period 2020-2025

Patient group	Engagement/Activity	Financial support provided
Crohn's & Colitis UK	Grant – Online Patient Education programme	£10,000 (2025)
Crohn's & Colitis UK	Sponsorship – IBD Quality of life Dashboard	£40,000 (2024)
Crohn's & Colitis UK	Contracted service – Auto-Immune podcast series	£1,320 (2023)
Crohn's & Colitis UK	Contracted service – Auto-Immune podcast series	£330 (2022)

Crohn's & Colitis UK	Grant – Evidence building programme (ethnicity affects participation in IBD research)	£55,000 (2022)
Crohn's & Colitis UK	Sponsorship – New website	£50,000 (2022)
Crohn's & Colitis UK	Grant – Research project (Economic cost of IBD)	£50,000 (2022)
Crohn's & Colitis UK	Grant – Support services during the COVID-19 pandemic	£20,000 (2020)
Crohn's & Colitis UK	Contracted service – Patient group advisory board	£420 fee, £30 travel expenses (2020)
Crohn's & Colitis UK	Contracted service – Not Every Disability is Visible campaign (partnership)	£53,575 (2020)
Crohn's & Colitis UK	Agency pass through costs – Not Every Disability is Visible campaign (partnership)	£46,425 (2020)
IBDrelief	Contracted service – Auto-Immune podcast series	£1,320 (2022)
IBDrelief	Grant – Online support tool	£15,000 (2022)
IBDrelief	Contracted service – Auto-Immune podcast series	£360 (2022)
IBDrelief	Grant – IBD patient education platform	£15,000 (2022)
IBDrelief	Non-financial support (agency fees) – IBD Quality of life survey (partnership)	£5,000, non-financial (2022)
IBDrelief	Contracted service – Recorded interview with Janssen senior leader	£210 (2022)
IBDrelief	Contracted service – Patient group advisory board	£420 (2020)
IBDrelief	Contracted service – IBD Quality of life survey (partnership)	£12,000 (2020)
IBDrelief	Grant – Support services during the COVID-19 pandemic	£4,600 (2020)
IBDrelief	Grant – Digital education for young people with IBD	£10,000 (2020)
Key: IBD, inflammatory bowel disease		

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 and what are the symptoms?

Ulcerative colitis is a chronic inflammatory condition that affects the colon and rectum, the two parts of the body that make up the large bowel, and is the most common form of inflammatory bowel disease (IBD).(1-3) In people with ulcerative colitis, the immune system does not work properly, causing the body to attack itself resulting in ulcers and inflammation.(3)

The disease is an incurable, life-long condition; people experience periods of no or minimal symptoms, known as remission, followed by flare-ups of more active disease, known as relapse.(4-6) Although the disease improves in approximately 50–70% of people within the first few years(7), up to 80% of people relapse within 5 years of diagnosis(8), and approximately 30–50% of people with the disease only in their rectum will progress to inflammation of their whole rectum and large bowel within 10 years of diagnosis.(9)

People with ulcerative colitis experience a range of debilitating symptoms.(6) The most common symptoms are blood in the stools and diarrhoea; however, people may also experience bowel urgency, stool frequency, incontinence, mucus discharge, fatigue and abdominal pain.(6, 10)

How many people in England are estimated to be living with ulcerative colitis?

At least one in every 227 people are reported to be diagnosed with ulcerative colitis in the UK.(11) Almost 39% of people with ulcerative colitis experience moderately to severely active disease.(12) Therefore, using the Office of National Statistics population estimates for England in 2022, is it estimated that 70,542 people aged 18 years and over are living with moderately to severely active ulcerative colitis. Although ulcerative colitis can occur at any age, it is most commonly diagnosed between the ages of 15–25 years followed by 55–65 years.(13)

What is it like to live with ulcerative colitis?

Ulcerative colitis has a direct negative impact on people with the disease, their families and caregivers.(14) Symptoms of ulcerative colitis, particularly bowel incontinence and urgency, disrupt the daily life of people with the disease, reducing their ability to participate in caregiving, parenting and family planning, and placing unequal burden on the family unit.(15, 16) Uncontrolled disease may also disrupt further education, training and employment. Furthermore, the fatigue that people may experience is associated with a higher likelihood of experiencing extreme difficulties when conducting household activities.(16)

Ulcerative colitis may also have a negative impact on the emotional wellbeing of people living with this disease. People with ulcerative colitis are known to feel anxious, frustrated, scared or angry, and the uncertainty and unpredictability of symptoms may make them feel helpless.(11) These negative feelings can become overwhelming at times, resulting in people not being able to live life to the full.(11)

A recent survey on the quality of life of people with IBD found that more than half of the respondents worry about their disease on a daily basis.(17) The most difficult part for them is managing physical symptoms and making plans for the future. As a result, many of these people avoid stressful situations and miss out on social events, which further compounds emotional and mental health.

What is the economic burden of ulcerative colitis?

As well as the physical symptoms of ulcerative colitis, people often require medical attention or treatment, which can contribute to the economic burden on healthcare systems. This includes outpatient visits for treatment administration, inpatient hospitalisation due to uncontrolled disease and surgery. As the severity of disease worsens, more resources are used and the associated costs are greater compared with people with mild disease severity.(18) Given its chronic and unpredictable nature, ulcerative colitis can also impact a person's ability to work. Up to a quarter of people with ulcerative colitis experience sick leave, up to 17% experience short-term disability and 7% experience long-term disability.(19)

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

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

How is ulcerative colitis diagnosed?

Following initial consultation and investigations in primary care by the general practitioner (GP), ulcerative colitis is diagnosed in secondary care by a gastroenterology hospital specialist.(20) Diagnosis is confirmed by examining the inflammation of the colon and rectum.(20) People with ulcerative colitis can present at various stages of disease severity so assessing its severity is important to guide optimal delivery of care.(21) Various tools are used to measure ulcerative colitis severity, including symptoms, physical examination, analysing stool and blood samples, and imaging of the gastrointestinal tract with an instrument called an endoscope. The most widely used assessment tool for symptom severity is the Mayo score. This measures factors such as stool frequency, rectal bleeding, assessment by a doctor and endoscopy appearance, with higher scores indicating more severe disease.(22, 23) Each aspect is rated from 0–3, giving a total score of 0–12.(24) A score of 3–5 points indicates mildly active disease, a score of 6–10 points indicates moderately active disease, and a score of 11–12 points indicates severely active disease.(24) Should guselkumab be approved for the treatment of adults with moderately to severely active ulcerative colitis, no additional diagnostic tests should be required if the consultant deems the patient to be eligible for this therapy.

Diagnosis and NHS waitlists:

The waiting lists for gastroenterology appointments in England have nearly doubled over the past 5 years(25), and directly impact the time it takes for people to receive a diagnosis from a specialist in gastroenterology. This delay in diagnosis is further compounded by the lengthy hospital-administered induction phase required for many treatment options for ulcerative colitis, which results in significant burden for patients, caregivers, and healthcare providers.

As detailed in the following sections, introducing additional treatments that can be self-administered at home provides an opportunity to reduce outpatient visits and hospitalisations; this would alleviate the burden the healthcare system for the effective treatment of patients with moderately to severely active ulcerative colitis. Should guselkumab be approved for treatment as an induction therapy via subcutaneous injection, it would allow patients to commence treatment without delay. This may be especially helpful within NHS trusts with reduced capacity for infusion appointments.

2c) Current treatment options:

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

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

What are the current treatment options for ulcerative colitis?

Ulcerative colitis is an incurable, life-long condition. The goal of treatment is to manage symptoms of the disease and keep them under control – this may be during flare-ups where symptoms worsen or return after initial improvement and to maintain remission where no gastrointestinal symptoms are present.(6, 13)

People with mild to moderate ulcerative colitis are initially treated with aminosalicylates, thiopurines or corticosteroids.(13) These therapies are collectively known as 'conventional therapies'. When conventional therapies fail, are not tolerated or are not advised because they may be harmful, advanced therapies may be recommended as an alternative. Advanced therapies include classes of drugs such as TNF-inhibitors, JAK inhibitors, IL-12/IL-23 inhibitors, IL-23 inhibitors, integrin inhibitors or spingosine-1 phosphate receptor (S1PR) modulators. They work by targeting different pathways in the immune system that contribute to the inflammatory response observed in ulcerative colitis.

People with ulcerative colitis are treated until they achieve disease control and then usually stay on treatment to maintain remission. Even on advanced therapies, people may still lose response to treatment and require switching to a more effective treatment and may need to cycle through different therapies to achieve and maintain long-term remission.(24, 26)

If the patient continues to have uncontrolled symptoms, surgery will be offered, and the most common is surgical removal of the large bowel. Surgery can lead to long-term complications including small bowel obstruction, inflammation of the pouch formed from the small bowel when the colon is removed, and bowel incontinence.(27) For people who want to avoid or delay surgery, there is a need for additional effective treatments in the current treatment landscape.

Limitations of current options and unmet need

TNF-inhibitors are commonly used to treat ulcerative colitis, but they may not be suitable for all patients and a high proportion of patients that do receive TNF-inhibitors do not respond at all or eventually lose their response over time.(28, 29) There are advanced therapies with different molecular targets, but none are curative, and they only allow symptom control for a limited period of time. Moreover, each class of approved drugs has limitations and may not be appropriate for all patients:

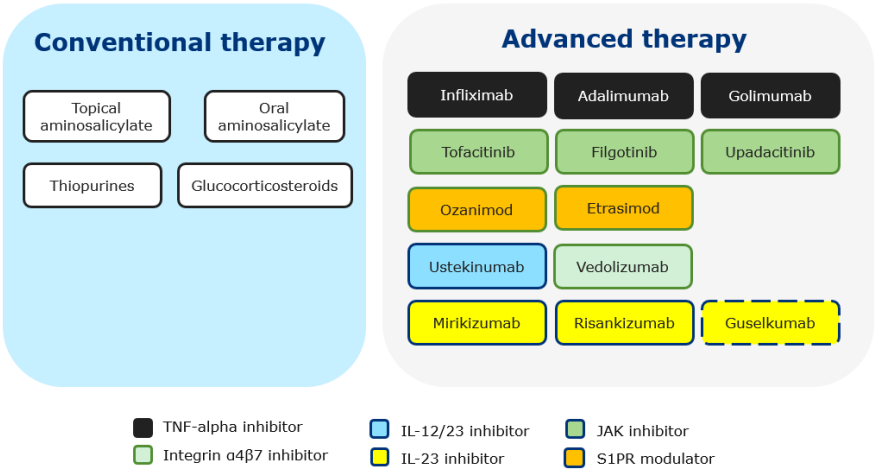
- TNF inhibitors are not suitable for patients with heart disease, high risk of infections, recurrent infections, the elderly and malignancies(30)
- JAK inhibitors should be used at the lowest dose possible and, due to safety concerns, avoided in people with risk factors if alternatives are available.(31, 32) These risk factors include: age 65 years and older, cigarette smokers or significant smoking history, risk factors for cancer, or risk factors for major adverse cardiovascular events
- S1PR modulators are not suitable for patients with heart disease, heart block, severe infections, active malignancies and severe hepatic impairment, or for women of childbearing potential not using effective contraception(33, 34)

Therefore, there is a clear need for more treatment options that can effectively manage ulcerative colitis and maximise patient safety.

Positioning of guselkumab in the treatment pathway

Guselkumab is positioned for use in people with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to an advanced therapy. Guselkumab may also be suitable in some patients for whom TNF-inhibitors are deemed unsuitable, similar to other drugs in this class. Figure 1 provides an overview of the clinical pathway of care for people with ulcerative colitis in England, including the proposed positioning of guselkumab. The accompanying submission to NICE uses vedolizumab and mirikizumab as examples of drugs that may be considered as alternative treatments to guselkumab.

Figure 1: Clinical pathway of care for the management of ulcerative colitis and anticipated positioning of guselkumab



Key: IL, interleukin; JAK, Janus kinase; S1PR, sphingosine-1-receptor; TNF, tumour necrosis factor.
Source: Based on NG130.(13)

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.

Impact of ulcerative colitis on patient lives

The impact of uncontrolled disease in adults with all forms of IBD, including ulcerative colitis, was highlighted in the IBDrelief survey conducted in partnership with J&J in 2021 (n = 167).(35) The majority of respondents reported challenges in performing tasks such as socialising, working or education, playing sports, travelling on public transport, and maintaining their emotional wellbeing.

In 2024, Crohn's & Colitis UK surveyed 970 people in the UK with IBD (53% had Crohn's disease and 41.9% had ulcerative colitis) to find the top 10 impacts of living with IBD.(36) The impacts included fatigue, the unpredictable nature of the disease, physical symptoms and being constantly alert to symptoms, sleep disruption and emotional distress. The majority of other impacts reinforced the burden of issues around bowel movements and consequential effects on other elements of life. These included anxiety about convenient toilet access and having to plan when attending events and activities, embarrassment around the potential social stigma of bowel symptoms and dealing with incontinence and bowel urgency. All of which increase anxiety and the likelihood of people with ulcerative colitis being unable to freely travel and attend social and work events.(36)

Treatment preferences

A literature review conducted in 2021 examined studies conducted globally, on people with chronic immune diseases and their preference to receive treatment either by intravenous infusion or subcutaneous injection.(37) Out of 49 studies reviewed, 36 reported that people favour subcutaneous injection administration, with a preference to have treatment at home to avoid attending hospital as well as having the convenience and comfort of being at home.(37)

Another online survey conducted in Europe in 2020–2021 investigated the treatment preferences of people with IBD (360 people with Crohn's disease and 326 people with ulcerative colitis).(38) Route of administration was the most important aspect when choosing a treatment. People with ulcerative colitis preferred oral tablets and subcutaneous injections over intravenous infusion.

Unmet need in ulcerative colitis

There is a substantial unmet need for additional effective and well-tolerated therapies that can help people with ulcerative colitis to achieve and sustain remission. There is also a need for more flexible treatment administration methods. Currently, many people with ulcerative colitis have no choice but to have intravenous induction therapy for their next treatment. This can be difficult for people for whom attending hospital to receive their treatment is challenging, also for those who prefer under the skin (subcutaneous) administration that can be self-administered conveniently at home (see further information in the next Sections 3a and 3h).

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.

Mechanism of action of guselkumab

Guselkumab is a type of protein called a monoclonal antibody, which can recognise and bind to another protein called interleukin-23 (IL-23) and block its activity. (39) IL-23 is required for the normal functioning of the immune system; however, it is present at increased levels in people with IBD. IL-23 plays an important role in driving inflammation in the colon and rectum, which are characteristic symptoms of ulcerative colitis. Guselkumab blocks IL-23 activity resulting in reduction of inflammation.

In clinical trials, many patients receiving guselkumab treatment reported improvements in symptoms, such as reduced bowel movements, less abdominal pain, and improved quality of life. Guselkumab has also been shown to induce and maintain clinical remission in many patients, whereby, symptoms are under control, with minimal or no signs of inflammation in the colon, allowing them to live a more normal, symptom-free life.

Advantages of guselkumab

Guselkumab can be given either by intravenous infusion, which delivers the drug directly into a vein via a cannula in the hand, or subcutaneous injection, which delivers the drug between the skin and muscle. When starting treatment (induction phase), guselkumab has shown similar positive results when administered via intravenous infusion or when taken as a subcutaneous injection. Depending on patient preference and need, it can either be administered at a hospital or self-administered at home. This is an advantage over other comparable biologic therapies, nearly all of which can only be initiated in a hospital setting, and, therefore, are dependent on NHS capacity.

This reduces the burden on hospitals as people may not need to wait for space in an infusion suite, and do not need to take time off work or education to attend hospital visits and/or rely on carers for help getting to the hospital. Additionally, people may not have to wait as long to begin therapy so spend less time dealing with difficult physical and emotional symptoms, and the negative effects they have on their quality of life.

As a maintenance treatment, guselkumab has shown positive results at two different doses, which dose each patient receives will be decided based on the judgement of the specialist gastroenterology healthcare professional (see also Section 3c below). This dose flexibility allows for a tailored approach for each patient, with the dosage being personalised to their specific disease, rather than being available as a single dose for all.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?
Guselkumab is not intended to be used in combination with any other medicines. In ulcerative colitis studies, concomitant use of immunomodulators (e.g. azathioprine) or corticosteroids did not appear to influence the safety or efficacy of guselkumab.

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?
Treatment with guselkumab is in two phases: the induction phase, which is the start of treatment to reduce symptoms and induce remission, followed by the maintenance phase, which aims to maintain remission and control the disease in the long-term. **Induction therapy:** Guselkumab can be given either by intravenous infusion (delivers the drug directly into a vein via a cannula in the hand) or subcutaneous injection (delivers the drugs between the skin and muscle: • Intravenous infusion: three separate doses of guselkumab 200 mg are given at 4 weekly intervals, over a 12-week period. This is administered in a hospital setting by a trained doctor or nurse • Subcutaneous injection: three separate doses of guselkumab 400 mg are given at 4 weekly intervals, over a 12-week period. Each of these is given as two separate injections of 200 mg each and can be self-administered. The injection can be given under the skin in different locations of the body including abdomen, thigh and upper arm. The subcutaneous injection dose is higher than the intravenous dose, to allow similar amounts of guselkumab reaching the blood and carried to the areas of active inflammation. This can be self-administered at home or given in a hospital setting. **Maintenance therapy:** Guselkumab can be given by subcutaneous injection either with a 100 mg or 200 mg dose. A doctor will decide which maintenance dose should be received based on clinical judgement: • A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks. This is taken as a single injection of 100 mg • A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks. This is taken as a single injection of 200 mg The introduction of an induction therapy that can be taken by subcutaneous injection at home and does not require professional supervision or trips to hospital will reduce the burden on people with ulcerative colitis, carers and hospitals. This is particularly important in the induction phase as there is only one therapy currently available with this option (adalimumab). The flexible maintenance dosing means that people get the most appropriate dose for their disease, rather than a ‘one dose fits all’ approach (further information in Section 3h).

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 efficacy and safety of guselkumab in people with moderately to severely active ulcerative colitis has been studied in two Phase III clinical trial programmes, called QUASAR and ASTRO. All trials were set up to demonstrate statistically and clinically significant differences between guselkumab and placebo, which is a standard method in this disease. In the QUASAR trial, the efficacy of guselkumab was assessed separately for the induction and maintenance phases of treatment. ASTRO was set up specifically to demonstrate the efficacy and safety of guselkumab subcutaneous induction therapy. A summary of these trials is presented in Table 2.

Table 2: Summary of clinical trials

Clinical trial name	QUASAR	ASTRO
Clinical trial number	NCT04033445	NCT05528510
Intervention	**Induction :** Guselkumab intravenous infusion **Maintenance :** Guselkumab subcutaneous injection	**Induction:** Guselkumab subcutaneous injection **Maintenance:** Guselkumab subcutaneous injection
Location	Sites across North America, South America, Europe and Asia-Pacific	Sites across North America, South America, Europe and Asia-Pacific
Number of patients enrolled	1,064	418
Trial completion date	2027 (estimated)	2025 (estimated)
References	**Induction:** • Allegretti, et al. 2023(40) • Clinicaltrials.gov(41) **Maintenance:** • Rubin et al. 2024(42) • Rubin et al. 2024(43) • Clinicaltrials.gov(41)	• Clinicaltrials.gov(44)
Key inclusion criteria	• Age 18 years or older • A confirmed diagnosis of ulcerative colitis at least 3 months before screening • Moderately to severely active ulcerative colitis (a modified Mayo Score of 4 to 9)	• Age 18 years or older • A confirmed diagnosis of ulcerative colitis at least 12 weeks before screening • Moderately to severely active ulcerative colitis (a modified Mayo Score of 5 to 9) • A history of an inadequate response to or intolerance of

	• A history of an inadequate response or failure to tolerate conventional therapies (i.e. 6-mercaptopurine, azathioprine or corticosteroids) or advanced therapies (i.e. TNF-alpha antagonists, vedolizumab or tofacitinib)	conventional therapy (i.e. 6-mercaptopurine, azathioprine or corticosteroids) or advanced therapy (i.e. TNF-alpha antagonists, vedolizumab, ozanimod or approved JAK inhibitors)
Key exclusion criteria	• Severe extensive colitis • Diagnosis of Crohn's disease • Ulcerative colitis limited to the rectum only or to < 20 cm of the colon	• Severe extensive colitis • Diagnosis of Crohn's disease • Ulcerative colitis limited to the rectum only or to < 20 cm of the colon

3e) Efficacy

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

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Key results for the QUASAR Phase III induction trial (Company submission Document B, Section B.3.5.1):(45)

- The main goal or outcome (primary endpoint) of the QUASAR Phase III induction trial was the proportion of patients in clinical remission at 12 weeks (the end of the induction period) after receiving guselkumab intravenous induction treatment compared with placebo. Clinical remission was defined as relative disease improvement based on the Mayo scoring system for stool frequency, rectal bleeding, physician assessment and endoscopy. Major additional outcomes (secondary endpoints) included symptom remission and healing as seen directly via an endoscope
- Guselkumab met its primary endpoint and major secondary endpoints, including reliable and meaningful (statistically significant) rates of symptom remission, endoscopic healing and clinical response at Week 12 compared with placebo

Key results for the QUASAR Phase III maintenance trial (company submission Document B, Section B.3.5.2):(46)

- The primary endpoint of the QUASAR Phase III maintenance trial was the proportion of patients in clinical remission 44 weeks after receiving guselkumab subcutaneous injection maintenance treatment compared with placebo (end of 1-year of treatment). Major secondary endpoints included symptom remission and assessments of healing

- Guselkumab met its primary endpoint and all major secondary endpoints, including statistically significant (reliable and meaningful) rates of symptomatic remission, endoscopic healing and clinical response at Week 44 compared with placebo
- Both maintenance dosing regimens of guselkumab (i.e. 200 mg every 4 weeks and 100 mg every 8 weeks) demonstrated strong efficacy across primary and secondary endpoints at Week 44, including clinical remission observed for guselkumab in up to 50.0% of people compared with only 18.9% with placebo
- Greater efficacy was observed in both guselkumab treatment groups versus placebo for the primary outcome and all major secondary endpoints. This was the case for the whole trial population and people who had received an advanced therapy (ADT-failure subpopulations)
- Through to Week 44, disease-related hospitalisations and surgeries were infrequent in both guselkumab 200 and 100 mg treatment groups

Key results for the ASTRO Phase III trial (company submission document B, Section B.3.5.3):(47)

- The primary endpoint of the ASTRO trial was the proportion of patients in clinical remission 12 weeks after receiving guselkumab subcutaneous induction therapy compared with placebo. Major secondary endpoints included week 12 and week 24 assessment of symptomatic remission and endoscopic improvement
- Guselkumab achieved its primary endpoint and all major secondary endpoints, demonstrating the efficacy of subcutaneous induction therapy
- When comparing data from QUASAR and ASTRO, guselkumab subcutaneous induction demonstrated comparable efficacy to intravenous infusion induction

Indirect evidence for guselkumab in ulcerative colitis (Company submission Document B, Section B.3.8):

- To date, guselkumab has not been directly compared with other comparators relevant to this submission (mirikizumab and vedolizumab). In the absence of such comparisons, a network meta-analysis was performed to determine the relative treatment effect of guselkumab, vedolizumab and mirikizumab in patients with moderately to severely active ulcerative colitis
- The results of the network meta-analysis demonstrate that in the ADT-failure population, guselkumab is numerically more efficacious than vedolizumab in the outcomes of clinical response and remission at the induction stage and at 1 year, and is comparable to mirikizumab. Overall, guselkumab offers favourable outcomes for patients with ulcerative by improving clinical response and remission outcomes

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.

Quality of life was measured in the QUASAR trial using instruments such as the Inflammatory Bowel Disease Questionnaire (IBDQ) and European Quality of Life 5-Dimension 5 Level (EQ-5D-5L). IBDQ is specific for patients with IBD and measures impacts on bowel symptoms (loose stools, abdominal pain), overall functions (fatigue, altered sleep pattern), social function (work attendance, having to cancel social events) and emotional function (anger, depression, irritability). EQ-5D-5L is not a disease-specific instrument and focuses on how patients rate their mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

The results from QUASAR are summarised below and demonstrate the benefits of guselkumab for patients in improving overall well-being and daily life, which is profoundly affected by ulcerative colitis as outlined in Section 2a above.

- At Week 12, the guselkumab induction treatment group had greater improvements in IBDQ bowel, emotional, systemic and social scores when compared with the placebo group
- At Week 12, a greater proportion of patients treated with guselkumab induction treatment achieved clinically meaningful improvement and resolution of bowel urgency and abdominal pain as measured by IBDQ
- By Week 44 in the maintenance study, improvement in the IBDQ bowel, emotional, systemic and social scores were sustained for patients in both guselkumab 200 mg and 100 mg groups
- In comparison, improvements assessed with the IBDQ diminished in the placebo group over time

Further details of quality of life outcomes are presented in the company submission Document B, Section B.3.5.1.5.

Treatment preferences

A survey conducted between 2020–2021, which involved 326 people with ulcerative colitis from seven European countries, including the UK, revealed important treatment preferences.(48) The key findings were:

- The most important factor for choosing a treatment was how the medication was given. Approximately 31% of respondents preferred oral tablets and subcutaneous (under the skin) injections over intravenous injections (received in a hospital setting directly into the vein)
- Other important factors included the risk of serious side effects (23%), achieving remission within a year (18%), healing of the bowel (14%), the chance of long-term remission (8%) and the risk of mild side effects (6%).
- This study emphasises how important it is to provide personalised care and involve people in decisions about their care to ensure they get the most out of the treatments available for ulcerative colitis.

Additionally, a review of 49 studies on the treatment preferences for chronic immune diseases, including ulcerative colitis, supports the preference for subcutaneous (under the skin) treatment over intravenous treatment. (37)

- Out of the 49 studies reviewed, 36 studies found that people preferred subcutaneous treatments
- The main reasons for this preference is that people surveyed value the option of receiving their treatment at home, where they may feel more comfortable than in hospital.

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.

Summary of safety data from QUASAR trial

- The guselkumab induction treatment was well tolerated during the 12-week treatment period. There were low discontinuation rates, meaning patients staying on treatment for longer without needing to switch to another treatment
- The proportion of patients reporting an adverse event (any undesirable experience that occurs after a person is given a treatment) throughout the 12-week treatment period with guselkumab intravenous induction treatment was similar to placebo
- Most patients who were treated with guselkumab intravenous induction treatment and those who reported an adverse event experienced a mild to moderate event
- Safety results for guselkumab 200 mg and 100 mg subcutaneous injection maintenance treatment throughout the 44-week treatment period were consistent with the well-defined and favourable safety profile of guselkumab in its approved indications of psoriasis and psoriatic arthritis
- The most frequent adverse events in any treatment group throughout the study included anaemia, COVID-19, headache, ulcerative colitis and joint pain
- No new safety concerns were identified compared with the safety profile from psoriasis and psoriatic arthritis

Summary of safety data from ASTRO trial

- Safety data for the guselkumab subcutaneous injection induction treatment were consistent with intravenous infusion induction in QUASAR. They were also consistent with the well-defined and favourable safety profile established in the approved indications of plaque psoriasis and psoriatic arthritis

- Discontinuation rates were low, and most adverse events were mild to moderate in severity

Further details of safety outcomes are presented in the company submission Document B, Section B.3.9.

An overall summary of the side effect profile of guselkumab is provided in Table 3.(49) Like all medicines, guselkumab can cause side effects, although not everybody experiences them.

Table 3: List of guselkumab side effects

Type and definition	Side effect
Serious side effects	
Possible serious allergic reaction (may affect up to 1 in 100 people)	• Difficulty breathing or swallowing • Swelling of the face, lips, tongue or throat • Severe itching of the skin, with a red rash or raised bumps • Light-headedness, low blood pressure, or dizziness
Other side effects – mild to moderate	
Very common (may affect more than 1 in 10 people)	• Respiratory tract infections
Common (may affect up to 1 in 10 people)	• Headache • Joint pain (arthralgia) • Diarrhoea • Increased level of liver enzymes in the blood • Skin rash
Uncommon (may affect up to 1 in 100 people)	• Decreased number of a type of white blood cell called neutrophils • Herpes simplex infections • Fungal infection of the skin, for instance between the toes (e.g., athlete's foot) • Stomach flu (gastroenteritis) • Hives • Redness, irritation or pain at the injection site
Rare (may affect up to 1 in 1,000 people)	• Allergic reaction

Source: Guselkumab Prescribing Information.(50)

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

Convenient administration

- Guselkumab offers patients a fully subcutaneous regimen, including the induction phase. This offers several benefits for patients, carers and the NHS healthcare system in England, for example:
  - **Home administration:** people may be able to take guselkumab at their preferred location, typically at home or any other convenient location, allowing them more control over managing their treatment and greater flexibility to suit their lifestyle
  - **Less hospital time:** patients may not need to visit a hospital, reducing the time they need to spend in hospital and travelling to and from hospital. This means less time taken out from responsibilities such as work and/or caring for relatives or from personal time on non-working days. Ultimately, patients can engage in meaningful work or activities of their choosing
  - **Reduced need for carer support:** people with ulcerative colitis who rely on carer support to go to hospital for IV administration may no longer require this support and would manage their treatment independently, easing the burden on their loved ones
  - **Faster treatment start:** Treatment could begin sooner with guselkumab by subcutaneous injection, avoiding long waits for hospital infusion suite appointments. This can help ease frustration and anxiety, leading to quicker relief from the debilitating symptoms of ulcerative colitis
  - **Efficiency for the NHS:** home administration reduces NHS waiting times and healthcare resource utilisation by improving infusion suite capacity.(51) This may lead to less frustration and anxiety for patients waiting for treatment, and timely initiation of treatment may potentially lead to earlier relief of symptoms

Tailored treatment

- Guselkumab offers two dosing options in the maintenance phase of treatment, either 100 mg every 8 weeks or 200 mg every 4 weeks. This is helpful because it provides additional flexibility, allowing doctors to choose the right dose based on the individual patient needs. This offers a tailored approach for each person, rather than a single dose for all, providing a more effective and personalised care. It is currently expected that approximately. Based on the guidance provided in the SmPC, it is expected that patients who achieve sufficient clinical response after 12 weeks of induction therapy will receive the lower dose of guselkumab maintenance therapy (100 mg every 8 weeks). Those patients who are unable to achieve sufficient clinical response after induction will have an option to receive the higher dose of guselkumab (200 mg every 4 weeks) and only continue onto long-term maintenance therapy should they achieve disease control within 24 weeks.

Proven efficacy and safety

- The findings of the QUASAR and ASTRO studies demonstrate the comparable efficacy benefits of guselkumab given as an intravenous infusion or subcutaneous injection for induction treatment, and as either a 100 mg or 200 mg subcutaneous maintenance dose. Having control over the choice of injection and consistent efficacy, patients may

experience relief from their symptoms with more consistent disease management and, ultimately, enjoy a more normal life

- Guselkumab is generally well-tolerated with a favourable safety profile. Clinicians also have many years' experiences with treating people with guselkumab in other approved indications in plaque psoriasis and psoriatic arthritis. Patients can feel confident in their treatment, which can lead to better management of any potential concerns and a more informed approach to their care. Overall, it indicates that guselkumab is a reliable option for treatment

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

Guselkumab is an injectable medication. Although it is available as a convenient self-administered under the skin (subcutaneous) injection from the start of treatment and continued throughout the treatment course, some patients may not prefer an injectable medication (e.g. they may be needle phobic or unable to inject themselves).

Guselkumab may not be suitable for everyone. While the QUASAR and ASTRO trials have shown that guselkumab is effective, not all patients will respond to the treatment. Additionally, some patients may experience side effects; however, these are generally manageable, and the discontinuation rates are low. Physicians have extensive experience using guselkumab and managing side effects as it is approved for other conditions, such as psoriasis and psoriatic arthritis, and no new side effects have been identified.

3j) Value and economic considerations

Introduction for patients:

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

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

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

How the model reflects ulcerative colitis?

The purpose of the model is to compare the costs of using guselkumab as an alternative to other treatment options available for ulcerative colitis in NHS clinical practice. The model is designed to reflect the provision of care received by people with ulcerative colitis who did not respond well to (had an inadequate response, lost response) or had side effects (were intolerant) to an advanced therapy. The induction and maintenance phases are considered in the model to capture the differences in expected costs of people receiving different treatments over a period of 10 years.

Vedolizumab and mirikizumab were considered as relevant comparators in the model. Both are recommended and used in clinical practice for the ADT-failure population, which is the same population of patients considered in this submission. Furthermore, mirikizumab and guselkumab have a similar mechanism of action. Consequently, in NHS clinical practice in England, it is expected that guselkumab would be considered as an alternative treatment to vedolizumab and mirikizumab in the ADT-failure population of ulcerative colitis.

There is no evidence directly comparing guselkumab with vedolizumab or mirikizumab in a randomised clinical trial; therefore, statistical methods must be applied to make indirect comparisons between these using a method called network meta-analysis that takes into account all available evidence on these treatments. The network meta-analysis results (Section 3e) demonstrated that guselkumab can provide similar clinical benefits compared with vedolizumab and mirikizumab. Therefore, the model focuses primarily on cost outcomes as the three may be interchangeably used in terms of efficacy, based on statistical analyses.

How the costs of treatment differ with guselkumab

The model considers treatment acquisition and administration costs during the induction and maintenance phases.

The model includes the following costs:

- Drug acquisition costs (the cost of the medicine)
- Drug administration costs (the cost of giving the medicine)

The acquisition cost of guselkumab is derived from the confidential discounted price that the company has agreed with the NHS. The acquisition costs of vedolizumab and

mirikizumab are derived from the British National Formulary at full price (list price) as any discount the comparators is confidential and therefore unknown.

Guselkumab is administered intravenously or subcutaneously in the induction phase, and subcutaneously in the maintenance phase. Vedolizumab is administered intravenously in the induction phase, and intravenously or subcutaneously in the maintenance phase. Mirikizumab is administered intravenously in the induction phase and subcutaneously in the maintenance phase. Guselkumab is the only treatment that provides the option for subcutaneous administration in the induction phase.

Various dose modifications are allowed for the modelled comparator treatments for patients who lose efficacy during the maintenance phase. Vedolizumab intravenous has a standard and escalated dosing schedule, and mirikizumab allows re-induction in the maintenance period using the intravenous formulation. There are different costs associated with these doses, and this has been represented in the model. No such dose modifications are allowed for guselkumab once a patient commences maintenance therapy.

For guselkumab it is anticipated that patients who achieve sufficient clinical response after 12 weeks of induction therapy will receive 100 mg every 8 weeks of maintenance therapy. Those patients who are unable to achieve sufficient clinical response after induction will receive the 200 mg every 4 weeks and continue into long term maintenance therapy based on the response rate applied at Week 24.

Cost comparison results

It is expected that the External Assessment Group will be provided with confidential discounted prices for vedolizumab and mirikizumab to allow an assessment of all treatments at the discounted prices available to the NHS. It is also expected that any assessments of cost comparability will be made on the results of the External Assessment Group assessment, which will be shared with NICE but not with any of the companies that manufacture these drugs.

In the model analysis provided by the company, guselkumab (at its discounted price) resulted in substantially lower costs than vedolizumab and mirikizumab (at their full price). The introduction of guselkumab in clinical practice is not likely to increase the cost of treatment of ulcerative colitis and may even result in cost savings to the NHS in England.

Uncertainty

The information used in the model could be the source of uncertainties. A test was run (sensitivity analyses) to see how different inputs and assumptions might affect the results. For example, what would happen if more or fewer patients who received guselkumab in the induction phase were given the medication through intravenous infusions instead of subcutaneous injections.

The result of the test showed that making changes to these factors did not change the overall conclusion that the introduction of guselkumab, compared with vedolizumab or mirikizumab, is likely to result in similar or lower costs in the treatment of moderately and

severely active ulcerative colitis in the ADT-failure population. As the price of guselkumab was provided at the discounted price and was compared to vedolizumab and mirikizumab at their full price, the actual difference in costs between guselkumab and the comparators may vary because of confidential discount arrangements and can be cost saving or not.

3k) Innovation

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

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

Guselkumab is a new treatment option for people with moderately to severely ulcerative colitis who have not responded well to other treatments or had side effects. It has been shown to work well in clinical studies.

Unlike many ulcerative colitis treatments recommended by NICE, guselkumab can be given at home as a convenient self-administered injection from the start, which means that the person may not need to go to the hospital for the initial treatment phase. This can be a big relief for patients, their caregivers, and healthcare providers as going to the hospital for treatment can be difficult for some people. Attending hospital can be challenging for those who work or care for others, and for those who are unable to travel without help. Reducing the number of visits patients need to make to the hospital is also important to reduce he strain on an already very stretched NHS. The recently published IBDUK report highlights the challenges facing the UK health system with regards to IBD services and the experiences of people who use them. These include high demand, long waiting times, strained budgets and a workforce under pressure. Together with the impact on the NHS, people with IBD also suffer in terms of finance, physical and emotional health and quality of life.(52)

Guselkumab comes in two different maintenance doses, 100 mg given every 8-weeks and 200 given every 4-weeks mg. This is helpful because it provides additional flexibility and allows doctors to tailor the medication and choose the right dose based on the personal needs of their patient.

In summary, guselkumab is an effective additional option for people with ulcerative colitis that can be given at home from the start, making it less burdensome on the patient, carer, family, and daily life, while helping to ease the strain on the NHS.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Living with IBD is not classed as a disability under the Equality Act. This creates a challenge for IBD patients, including those with ulcerative colitis, as they do not qualify for the same benefits as people with other long-term illnesses.(53) For instance, while some patients can get free prescriptions because of their conditions, many IBD patients only receive assistance if they have a permanent stoma that needs a continuous surgical dressing or an appliance (this happens in IBD following surgery).(54) As a result, individuals often must endure severe illness before getting the support they need, highlighting the importance of ensuring that IBD patients have access to effective treatments. IBD may be considered as a disability depending on the effect it has on a person's daily life.(55) People living with IBD often require specialist medications and surgery, hospital admissions, investigations, and outpatient appointments. Relapses are unpredictable in nature, and approximately 50% of people with Crohn's disease and ulcerative colitis experience at least one flare-up per year.(56) More than a quarter of people with Crohn's disease and ulcerative colitis had to wait over a year for diagnosis, with almost half ending up in accident and emergency departments during this time.(57) Availability of an additional treatment option that can be safely administered at home may reduce inequalities between people with IBD with varying degrees of disability who are restricted from visiting a healthcare setting i.e. hospital visits and reduce reliance on an overburdened healthcare system. (58) This strain on the NHS is further emphasised in the recently published IBDUK report which states that 'Challenges facing the UK health system are reflected in UK IBD services and the experiences of people who use them. These include high demand, long waiting times, strained budgets and a workforce under pressure'. Together with the impact on the NHS, people with IBD also suffer in terms of finance, physical and emotional health and quality of life.(52) Ulcerative colitis as a type of IBD is often called an invisible disability because it is not easy to see how it affects someone. People ulcerative colitis can struggle to manage work, education or social activities, and they may not want others to know they have the condition. Many patients feel embarrassed about their symptoms and worry about having accidents, which can lead them to avoid work and social events. An effective treatment can help them feel better and can allow them to live a more normal life, giving them the same chances at work or education and helping them maintain their relationships (emotional and physical), just like anyone without IBD.

In summary, it's important to tackle the challenges faced by IBD patients to make the healthcare system more equitable to ensure access to timely care, equal treatment, and a better quality of life.

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. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on ulcerative colitis:

- Crohn's & Colitis UK: https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis?parent=4107&page=1&tags=&category=&sort=
- IBDrelief: https://www.ibdrelief.com/learn/what-is-ibd/what-is-ulcerative-colitis
- NICE guidance for ulcerative colitis: https://www.nice.org.uk/guidance/ng130

Further information on QUASAR:

- Clinicaltrials.gov (NCT04033445): https://clinicaltrials.gov/study/NCT04033445

Further information on ASTRO:

- Clinicaltrials.gov (NCT05528510): https://clinicaltrials.gov/study/NCT05528510

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Active substance: the main ingredient of a medicine that causes the desired treatment effect.

ADT-failure population: patients who have had an inadequate response, lost response or were intolerant to advanced therapies.

Adverse event: any undesirable experience that occurs after a person is given a treatment. This may be related to the treatment but is not necessarily caused by it. Treatment in a clinical trial may either be the intervention (the drug of interest) or a placebo (see definition below).

Anaemia: a condition where the amount of healthy red blood cells in the blood is low.

Arthralgia: pain experienced in joints.

Clinical remission: disease is currently inactive and minimal to no symptoms. It indicates that the symptoms are under control with minimal bowel movements, no rectal bleeding, and minimal or no signs of inflammation in the colon and rectum, allowing individuals to live a more normal, symptom-free life. This is definition is based on the Mayo scoring system, which uses stool frequency, rectal bleeding, physician assessment and endoscopy scores.

Clinical response: a positive improvement in symptoms and overall condition, meaning significant relief in symptoms such as diarrhoea, abdominal pain, urgency to pass stools, and rectal bleeding. It indicates that the condition is getting better and that the treatment is helping to control the disease.

Colectomy: surgery where the large bowel is removed.

Contraindicated: a situation where a drug is not recommended because it could be harmful to the patient.

Diarrhoea: passing three or more loose or liquid stools per day.

Endoscopy or endoscope: a procedure where a long, thin flexible tube containing a camera is inserted into the body to look at the appearance of the colon and extent of inflammation.

Endoscopic healing: when the colon appears to be in a relatively healthy state, with minimal or no signs of inflammation or tissue damage during the endoscopic examination.

Endoscopic healing or improvement: where the colon appears to be in a relatively healthy state, with minimal or no signs of inflammation or tissue damage during the endoscopic examination.

IL-23: interleukin-23, which is a protein that plays an important role in the formation of inflamed regions in people with ulcerative colitis.

Immune system: a network of organs, cells and proteins that defend the body against infections.

Induction phase: the beginning of treatment that aims to rapidly reduce symptoms.

Inflammation: when a part of the body experiences an injury or infection, the body releases chemicals that makes the immune system react. This response makes the area red and swollen, but can also make people generally feel unwell.

Intravenous infusion: when drugs are delivered directly into a vein via a cannula placed in the hand.

Maintenance phase: conducted after the induction phase to maintain no or minimal symptoms and control the disease over a long period of time.

Mayo score: commonly used to assess the severity of ulcerative colitis. It includes four parts: rectal bleeding, stool frequency, physician assessment and endoscopy appearance. Higher scores in these areas indicate more severe disease.

Monoclonal antibody: a laboratory-made protein that can target and bind specific molecules in the body – in the case of guselkumab, the immune protein IL-23.

Network meta-analysis: in the absence of evidence directly comparing treatments, statistical methods are applied to make indirect comparisons between these. Network meta-analysis compares multiple treatments for a health condition by combining data from various studies. This may help patients and doctors make informed treatment decisions about treatment options.

Phase III trial: a large-scale study that looks at whether a new treatment works well and is safe before it can be approved for use.

Placebo: a treatment that is designed to have no therapeutic effect but is administered in the same way as the study drug. It is used as a control in clinical trials.

Primary outcome: the main result that is measured in a clinical trial to find out if the treatment being tested is effective.

Protein: naturally occurring, large and complex molecules required for the structure, function and regulation of the body's tissues and organs.

Psoriasis: a skin disease causing scaly patches of skin that are itchy and red.

Psoriatic arthritis: joint pain, swelling and stiffness that occur with the skin condition, psoriasis.

Relapse or flare-ups: periods where disease symptoms worsen or return after initial improvement.

Remission: periods where no or minimal symptoms of disease are experienced.

Secondary outcome: an additional result that is measured in a clinical trial to provide more information on the effects of a treatment.

Statistically significant: where the results observed are unlikely to have occurred by chance alone.

Subcutaneous injection: an injection delivering a drug between the skin and muscle.

Symptomatic remission: a period of relative disease improvement and defined based on the Mayo scoring system. It uses stool frequency and rectal bleeding scores.

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. NICE CKS. Ulcerative colitis: Summary 2024 [updated March 2024. Available from: https://cks.nice.org.uk/topics/ulcerative-colitis/.

2. NICE CKS. Ulcerative colitis: How common is it? 2024 [updated March 2024. Available from: https://cks.nice.org.uk/topics/ulcerative-colitis/background-information/prevalence/.
3. Crohn's and colitis UK. Crohn's and Colitis Care in the UK: The Hidden Cost and a Vision for Change 2021 [Available from: https://crohnsandcolitis.org.uk/media/4swaomlx/croj8096-ibd-national-report-web-210427_-2.pdf?_gl=1*1lhqxyv*_up*MQ..*_ga*NDU4NzQ1NjAuMTcyMTIyNTkxOQ..*_ga_5THF1XE73Q*MTcyMTIyNTkxOC4xLjAuMTcyMTIyNTkxOC4wLjAuMA..
4. Annese V. Genetics and epigenetics of IBD. Pharmacol Res 2020;159(104892).
5. Le Berre C DS, Peyrin-Biroulet L. Can we change the natural course of inflammatory bowel disease? Therap Adv Gastroenterol. 2023;16:1-19.
6. Le Berre C HS, Peyrin-Biroulet L. Ulcerative colitis. Lancet. 2023;402.
7. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(3):343-56.e3.
8. Zhao M, Gönczi L, Lakatos PL, Burisch J. The Burden of Inflammatory Bowel Disease in Europe in 2020. J Crohns Colitis. 2021;15(9):1573-87.
9. Verstockt B, Bressler B, Martinez-Lozano H, McGovern D, Silverberg MS. Time to Revisit Disease Classification in Inflammatory Bowel Disease: Is the Current Classification of Inflammatory Bowel Disease Good Enough for Optimal Clinical Management? Gastroenterology. 2022;162(5):1370-82.
10. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389(10080):1756-70.
11. Crohn's and colitis UK. Ulcerative colitis 2021 [updated May 2021. Available from: https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/understanding-crohns-and-colitis/ulcerative-colitis?ref=vzk.ru.
12. Pilon D, Ding Z, Muser E, Obando C, Voelker J, Manceur AM, et al. Long-term direct and indirect costs of ulcerative colitis in a privately-insured United States population. Curr Med Res Opin. 2020;36(8):1285-94.
13. NICE guideline. NG130; Ulcerative colitis: management 2019 [Available from: https://www.nice.org.uk/guidance/ng130.
14. Liu R, Tang A, Wang X, Shen S. Assessment of Quality of Life in Chinese Patients With Inflammatory Bowel Disease and their Caregivers. Inflamm Bowel Dis. 2018;24(9):2039-47.
15. Hibi T, Ishibashi T, Ikenoue Y, Yoshihara R, Nihei A, Kobayashi T. Ulcerative Colitis: Disease Burden, Impact on Daily Life, and Reluctance to Consult Medical Professionals: Results from a Japanese Internet Survey. Inflamm Intest Dis. 2020;5(1):27-35.
16. Paulides E, Cornelissen D, Vries ACd, Woude CJvd. Inflammatory bowel disease negatively impacts household and family life. Frontline Gastroenterology. 2022;13(5):402-8.
17. IBDreflief. Impact of IBD on physical and emotional health: Findings from an IBDrelief survey 2022 [Available from: https://www.ibdrelief.com/impact-of-ibd-on-physical-and-emotional-health.
18. Naegeli AN, Balkaran BL, Shan M, Hunter TM, Lee LK, Jairath V. The impact of symptom severity on the humanistic and economic burden of

inflammatory bowel disease: a real-world data linkage study. Curr Med Res Opin. 2022;38(4):541-51.
19. Constantin J, Atanasov P, Wirth D, Borsi A. Indirect costs associated with ulcerative colitis: a systematic literature review of real-world data. BMC Gastroenterol. 2019;19(1):179.
20. NHS. Ulcerative colitis: diagnosis 2022 [Available from: https://www.nhs.uk/conditions/ulcerative-colitis/diagnosis/.
21. Pabla BS SD. Assessing Severity of Disease in Patients with Ulcerative Colitis. . Gastroenterol Clin North Am. 2020;49(4):671-88.
22. Sturm A MC, Calabrese E, Annese V, Fiorino G. 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(3):273-84.
23. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114(3):384-413.
24. Lamb CA KN, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68:s1–s106.
25. Lane Clark & Peacock (LCP). NHS waiting list tracker 2024 [Available from: https://waitinglist.health.lcp.com/.
26. Singh H, Wilson L, Pandey A, Tencer T, Kumar J. 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(Supplement_1):S511-S2.
27. Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. Alimentary Pharmacology & Therapeutics. 2016;44(8):807-16.
28. Peyrin-Biroulet L, Sandborn WJ, Panaccione R, Domènech E, Pouillon L, Siegmund B, et al. Tumour necrosis factor inhibitors in inflammatory bowel disease: the story continues. Therap Adv Gastroenterol. 2021;14:17562848211059954.
29. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016;7(1):e135.
30. Caprioli F, Daperno M, Bravatà I, Brigido A, Frigerio D, Secchi O, et al. Who are the patients with Crohn's disease unsuitable to receive an anti-TNFα therapy? Results from a survey of Italian physicians and literature review. Eur J Gastroenterol Hepatol. 2021;33(8):1082-90.
31. Honap S, Agorogianni A, Colwill MJ, Mehta SK, Donovan F, Pollok R, et al. JAK inhibitors for inflammatory bowel disease: recent advances. Frontline Gastroenterol. 2024;15(1):59-69.
32. Medicines and Healthcare products Regulatory Agency (MHRA). Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality 2023 [Available from: https://www.gov.uk/drug-safety-update/janus-kinase-jak-inhibitors-new-measures-to-reduce-risks-of-major-cardiovascular-events-malignancy-venous-thromboembolism-serious-infections-and-increased-mortality.
33. European Medicines Agency (EMA). Summary of Product Characteristics (SmPC). Zeposia (ozanimod) 2024 [Available from:

https://www.ema.europa.eu/en/documents/product-information/zeposia-epar-product-information_en.pdf.
34. European Medicines Agency (EMA). Summary of Product Characteristics (SmPC). Velsipity (estrasimod) 2024 [Available from: https://www.ema.europa.eu/en/documents/product-information/velsipity-epar-product-information_en.pdf.
35. IBDrelief. Quality of Life Impact of IBD on physical and emotional health: Findings from an IBDrelief survey 2022 [Available from: https://www.ibdrelief.com/impact-of-ibd-on-physical-and-emotional-health.pdf.
36. Crohn's and Colitis UK. Crohn's and Colitis Top 10 Impacts Final Report 2024 [Available from: https://crohnsandcolitis.org.uk/media/ozvb3rch/top-10-impacts-of-living-with-crohns-and-colitis.pdf.
37. Overton PM, Shalet N, Somers F, Allen JA. Patient Preferences for Subcutaneous versus Intravenous Administration of Treatment for Chronic Immune System Disorders: A Systematic Review. Patient Prefer Adherence. 2021;15:811-34.
38. Fiorino G, Bent-Ennakhil N, Varriale P, Braegger F, Hoefkens E. Patient Preferences for Treatment Attributes in Inflammatory Bowel Disease: Results From a Large Survey Across Seven European Countries Using a Discrete Choice Experiment. Inflamm Bowel Dis. 2024.
39. J&J Innovative Medicine. Tremfya. Tremfya 100 mg and 200 mg solution for injection or infusion2024.
40. Allgretti J. The Efficacy and Safety of Guselkumab Induction Therapy in Patients with Moderately to Severely Active Ulcerative Colitis: Results from the Phase 3 QUASAR Induction Study. Digestive Disease Week2023.
41. Clinicaltrials.gov. A Study of Guselkumab in Participants With Moderately to Severely Active Ulcerative Colitis (QUASAR). Identifier: NCT04033445 2024 [Available from: https://clinicaltrials.gov/study/NCT04033445.
42. Rubin D. Oral presentation (abstract #759): The efficacy and safety of guselkumab as maintenance therapy in patients with moderately to severely active ulcerative colitis: Results from the Phase 3 QUASAR Maintenance Study. Digestive Disease Week2024.
43. Rubin D. The Efficacy and Safety of Guselkumab as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis: Results from the Phase 3 Quasar Maintenance Study. Digestive Disease Week2024.
44. Clinicaltrials.gov. A Study of Guselkumab Therapy in Participants With Moderately to Severely Active Ulcerative Colitis (ASTRO). Identifier: NCT05528510 2024 [Available from: https://clinicaltrials.gov/study/NCT05528510.
45. J&J Innovative Medicine. Induction Study 2 (Phase 3) Clinical Study Report; A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis (QUASAR).
46. J&J Innovative Medicine. Maintenance Study (Phase 3) Week 44 Clinical Study Report; A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis (QUASAR).
47. J&J Innovative Medicine. A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of

Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Ulcerative Colitis (ASTRO). 2024.
48. Fiorino G, Bent-Ennakhil N, Varriale P, Braegger F, Hoefkens E. Patient Preferences for Treatment Attributes in Inflammatory Bowel Disease: Results From a Large Survey Across Seven European Countries Using a Discrete Choice Experiment. Inflammatory Bowel Diseases. 2024:izae015.
49. J&J Innovative Medicine. Guselkumab package leaflet: information for the user. 2024.
50. J&J Innovative Medicine. [Data on File] Package leaflet: Information for the user - Tremfya 200 mg concentrate for solution for infusion guselkumab 2024.
51. Department of Health and Social Care Media centre. How we're tackling the NHS backlog? 2023 [Available from: https://healthmedia.blog.gov.uk/2023/05/11/how-were-reducing-the-nhs-backlog/.
53. Crohn's and Colitis UK. Ending prescription charges for people with Crohn's and Colitis. 2024 [Available from: https://crohnsandcolitis.org.uk/our-work/campaigns/policy-and-influencing/prescription-charges.
54. NHS Business Services Authority. Medical exemption certificates, Who is entitled [Available from: https://www.nhsbsa.nhs.uk/check-if-you-have-nhs-exemption/medical-exemption-certificates.
55. Crohn's and colitis UK. A guide for employees 2022 [Available from: https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis/employment-and-education/employment-a-guide-for-employees.
56. UK Parliament. Written evidence from Crohn's & Colitis UK DYE0019 2024 [Available from: https://committees.parliament.uk/writtenevidence/129236/html/.
57. Crohn's and colitis UK. Weeks not years 2023 [Available from: https://crohnsandcolitis.org.uk/media/5kefufoj/crohns-colitis-uk_weeks-not-years-briefing.pdf.
58. Healthwatch. NHS travel troubles: Five barriers patients face getting to appointments. 2024 [Available from: https://www.healthwatch.co.uk/blog/2024-11-14/nhs-travel-troubles-five-barriers-patients-face-getting-appointments.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison

Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6237 Guselkumab UC_Clarification Response_CON_Redacted	**Final**	**Yes**	**27.03.2025**

Section A: Clarification on effectiveness data

Systematic literature review and network meta-analyses

A1. Priority question. Company submission (CS), Document B, section B.3.8.1. Please clarify whether any relevant data from the trials included in the network meta-analyses (NMAs), or any relevant new trials, have been published since the systematic literature review searches were last conducted in July 2023.

Company response: In order to identify any additional relevant data from the trials included in the network meta-analyses (NMAs) or any relevant new trials that have been published since July 2023, we undertook a two-step approach as outlined below. The searches described below were conducted on 4th and 5th March 2025.

1. We first conducted a search on ClinicalTrials.gov to identify all Phase 2, 3, 4 trials in ulcerative colitis that may be active or completed (Table 1). A total of 41 records were identified, of which 36 records were excluded due to study termination (n=3), population (n=10), intervention (n=11), outcomes (n=7), study design (n=3), duplicate (n=1) outcome data not available (n=1). The five remaining records included those identified in the July 2023 SLR and included data that informed the NMAs presented in the company submission: QUASAR, GEMINI-1, LUCENT-1, LUCENT-2 and VISIBLE-1

   Table 1: Search strategy for ClinicalTrials.gov

Search strategy	Results
Ulcerative Colitis | vedolizumab OR mirikizumab OR Guselkumab | Active, not recruiting, Completed, Terminated, Enrolling by invitation, Suspended, Withdrawn, Unknown status studies | Phase: 2, 3, 4 | Interventional studies	41

2. We also conducted a targeted literature review (TLR) to further identify any trial data in the public domain, that may not yet be captured on Clinicaltrials.gov. The search strategy for the TLR was limited to the PICOS

described in the company's decision problem (Table 2) and conducted on PubMed and Embase electronic databases (described in Table 3 and Table 4 respectively).

In total 485 records were identified, of which 463 were excluded after screening due to: Population (n=74), Intervention (n=9), Comparator (n=39), Outcomes (n=121), Study design (n=188), Duplicate (n=11), non-English language (n=5), Publication type (n=16). Of the 22 included records, 21 of these relate to QUASAR, LUCENT-1 and LUCENT-2, which were identified in the July 2023 SLR and included data that informed the NMAs presented in the company submission. A single record was identified relevant to this submission describing the Week 12 outcomes from the ASTRO trial.(1) ASTRO is a Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of guselkumab SC induction therapy in adult participants with moderately to severely active UC.(2)

The results of these searches indicate that ASTRO is the only new trial that may be included in an update of the induction NMAs presented in the company submission. Updated NMAs including ASTRO are planned however, these will not be available in the timeframe of the appraisal.

For the perspective of the cost comparison process, the NMAs are intended to demonstrate equivalent efficacy between guselkumab and the selected comparators. Results described in Section 3.8 of the company submission show that GUS 200 mg IV has similar or greater efficacy vs MIRI 300mg IV and VDZ 300 mg IV. The clinical outcomes from ASTRO and QUASAR Phase III induction are comparable, as discussed in Document B, Section 3.5.4, and with a similar manageable safety profile as reported in QUASAR (discussed in Document B, Section B.3.10 and B.4.2.4). Therefore, it is anticipated that alongside guselkumab 200mg IV induction therapy, guselkumab 400mg SC induction therapy would also have similar efficacy to mirikizumab and vedolizumab.

Table 2: PICO criteria used for the TLR

	Inclusion Criteria	Exclusion Criteria
Population	• Adults and select adolescents (age ≥ 16 years) with moderately to severely active ulcerative colitis (as defined by study)	• Any population not in inclusion criteria
Interventions	The following therapies alone or in combination with conventional therapy: • Guselkumab • Mirikizumab • Vedolizumab	Surgery Non-pharmacological interventions Studies that do not include guselkumab, mirikizumab or vedolizumab
Comparators	• Active comparator or placebo	• Any other comparator
Outcomes	Efficacy outcomes (as defined by study) • Clinical remission • Clinical response • Symptomatic remission • Corticosteroid-free remission • Histological-endoscopic mucosal improvement • Reduction in hospitalisation/surgery (tracking only) Safety outcomes • Serious infections • Discontinuations due to serious adverse events (tracking only) • Serious adverse events (tracking only) Quality of life outcomes • Inflammatory Bowel Disease Questionnaire (IBDQ) remission • Fatigue • EuroQol-5D (EQ-5D-5L and EQ-5D-3L) • PROMIS-29 (tracking only)	• Outcomes other than those listed
Study Design	• Randomised, double-blinded or open label, placebo- and active-controlled, parallel-group trials evaluating efficacy and safety in Phase II, III, or IV	• Observational/real world studies, including cohort,

	Inclusion Criteria	Exclusion Criteria
		case-control, and cross-sectional studies • Single-arm trials • Non-randomised trials
Publication type	• Full-text published articles or conference abstracts (from 2023 to present) reporting on eligible trials	• Pre-clinical studies • Study protocols • Narrative reviews (i.e., not systematic) • Opinion pieces, commentaries, letters, editorials, case reports, prognostic studies, pharmacodynamics • Conference abstracts prior to 2022 • SLRs of RCTs[a]
Language[a]	• English	• Non-English
Dates	• Published articles: 2023 to present • Conference abstracts: 2023 to present	• Published articles: < 2023 • Conference abstracts: < 2023
Key: EQ-5D-5L EuroQol-5D; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; JAK, Janus kinase; PICOS, population, interventions, comparators, outcomes, study design; RCTs, randomised controlled trials; SLRs, systematic literature reviews; TNF, tumour necrosis factor. **Notes:** Systematic reviews will not be included in the present review; however, bibliographies of relevant systematic reviews will be reviewed to identify additional eligible citations. [a] Search will capture all languages, but non-English citations will be excluded during screening.		

Table 3: PubMed search strategy and results

#	Searches	Results
1	colitis, ulcerative"[mh] OR (colitis OR colitides OR colorectitis OR "colo rectitis" OR proctocolitis OR "procto colitis" OR rectocolitis OR "recto colitis") AND (ulcerative OR ulcerous OR ulceration OR idiopathic OR gravis OR mucosal)	75,019
2	943609-66-3"[tiab] or 9rv78q2002[tiab] or Entyvio*2[tiab] or kynteles*2[tiab] or ldp02[tiab] or "ldp-02"[tiab] or mln0002[tiab] or "mln-0002"[tiab] or mln02[tiab] or "mln-02"[tiab] or "mln02- antibody"[tiab] or "mln-02-antibody"[tiab] or "mln02-monoclonal- antibody"[tiab] or "mln-02-monoclonal-antibody"[tiab] or "monoclonal-antibody-ldp-02"[tiab] or "monoclonal-antibody-mln- 02"[tiab] or pb016[tiab] or "pb-016"[tiab] or vedolizumab*2[tiab] OR vedolizumab[nm]	1,151
3	guselkumab*[tiab] or "Cnto-1959"[tiab] or cnto1959[tiab] or Tremfya*2[tiab] or 089658A12D[tiab] or "1350289-85-8"[tiab] OR guselkumab[nm]	848
4	mirikizumab*2[tiab] or "ly-3074828"[tiab] or ly3074828[tiab] or Z7HVY03PHP[tiab] or "1884201-71-1"[tiab] OR mirikizumab[nm]	37
5	#2 OR #3 OR #4	2,030
6	#1 and #5	744
7	(("randomized controlled trial"[pt] or "controlled clinical trial"[pt]) or (randomized[tiab] or placebo[tiab] or randomly[tiab]) or "clinical trials as topic"[mh] or trial[ti]) not (animals[mh] not humans[mh])	1,634,535
8	Randomized Controlled Trial[MeSH] OR controlled clinical trial[MeSH] OR clinical trial[MeSH] OR "Clinical Trials as Topic" [MeSH] OR "Random Allocation"[MeSH] OR Clinical Trial, Phase II[MeSH] OR Clinical Trial, Phase III[MeSH] OR "Randomized Controlled Trials as Topic"[MeSH] OR "Double-Blind Method"[MeSH] OR "Single-Blind Method"[MeSH] OR "Cross-Over Studies"[MeSH] OR triple blind procedure[MeSH] OR rct[tiab] OR randomisation* [tiab] OR randomization*[tiab] OR randomly[tiab] OR placebo*[tiab] OR (((double[tiab] OR single[tiab] OR doubly[tiab] OR singly[tiab] OR triple[tiab] OR treble[tiab]) AND (mask*[tiab] OR blind*[tiab] OR dumm*[tiab]))) OR ((study[tiab] OR trial[tiab] OR ct[tiab]) AND ("phase 2"[tiab] OR "phase 2a"[tiab] OR "phase 2b"[tiab] OR "phase 2c"[tiab] OR "phase ii"[tiab] OR "phase iia"[tiab] OR "phase iib"[tiab] OR "phase iic"[tiab] OR "phase 3"[tiab] OR "phase 3a"[tiab] OR "phase 3b"[tiab] OR "phase 3c"[tiab] OR "phase iii"[tiab] OR "phase iiia"[tiab] OR "phase iiib"[tiab] OR "phase iiic"[tiab] OR "phase 2/3" [tiab] OR "phase ii/iii"[tiab]))	1,384,187
9	#7 or #8	1,921,299
10	#6 and #9	188
11	(Child[mh] or Infant[mh]) not ((Adult[mh] or Adolescent[mh]) and (Child[mh] or Infant[mh]))	1,521,943
12	(Animals[mh] not (Animals[mh] and Humans[mh]))	5,313,187
13	(address[pt] or autobiography[pt] or bibliography[pt] or biography[pt] or comment[pt] or dictionary[pt] or directory[pt] or editorial[pt] or "expression of concern"[pt] or festschrift[pt] or historical article[pt] or interactive tutorial[pt] or lecture[pt] or legal case[pt] or	3,013,165

#	Searches	Results
	legislation[pt] or news[pt] or newspaper article[pt] or patient education handout[pt] or personal narrative[pt] or portrait[pt] or video-audio media[pt] or webcast[pt] or (letter[pt] not (letter[pt] and randomized controlled trial[pt]))	
14	#10 not (#11 or #12 or #13)	183
15	#10 not (#11 or #12 or #13) Filters: from 2023/7/23 - 2025/3/5	43

Table 4: Embase search strategy and results

#	Searches	Results
1	'ulcerative colitis'/syn	121,546
2	((colitis* OR colitides OR colorectitis OR 'cola rectitis' OR proctocolitis OR 'procto colitis' OR rectocolitis OR 'recto colitis') NEAR/3 (ulcer* OR idiopathic* OR gravis OR mucosa*)):ab,ti,kw	97,454
3	(((colon OR colonic) NEAR/3 ulceration):ab,ti,kw) AND chronic*:ab,ti,kw	122
4	(uc:ab,ti,kw OR asuc:ab,ti,kw) AND (ulcer*:ab,ti,kw OR colitis*:ab,ti,kw)	45,346
5	#1 OR #2 OR #3 OR #4	123,791
6	'vedolizumab'/syn OR 'guselkumab'/syn OR 'mirikizumab'/syn OR vedolizumab*:ab,ti,kw OR guselkumab*:ab,ti,kw OR mirikizumab*:ab,ti,kw	14,120
7	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'randomization'/exp OR 'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'triple blind procedure'/exp OR rct:ab,ti,kw OR randomi?ation*:ab,ti,kw OR randomly:ab,ti,kw OR placebo*:ab,ti,kw OR (((double OR single OR doubly OR singly OR triple OR treble) NEAR/1 (mask* OR blind* OR dumm*)):ab,ti,kw) OR (((study OR trial OR ct) NEAR/3 ('phase 2' OR 'phase 2a' OR 'phase 2b' OR 'phase 2c' OR 'phase ii' OR 'phase iia' OR 'phase iib' OR 'phase iic' OR 'phase 3' OR 'phase 3a' OR 'phase 3b' OR 'phase 3c' OR 'phase iii' OR 'phase iiia' OR 'phase iiib' OR 'phase iiic' OR 'phase 2/3' OR 'phase ii/iii')):ab,ti,kw)	3,110,572
8	#5 AND #6 AND #7	2,376
9	('cross-sectional study'/exp NOT ('randomized controlled trial'/exp OR 'controlled clinical study'/exp OR 'controlled study'/exp OR ((random* NEAR/1 controlled):ti,ab) OR ((control NEAR/1 group*):ab,ti)) OR ((case NEAR/1 control*) AND random*)) NOT random* NEAR/1 controlled OR (nonrandom* NOT random*) OR 'random field*' OR (('random cluster' NEAR/3 sampl*):ab,ti)	473,160

#	Searches	Results
10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti,kw OR 'meta analysis':ab,ti,kw)	3,171,033
11	('animal'/exp OR 'animal experimentation'/exp OR 'animal model'/exp OR 'animal experiment'/exp OR 'nonhuman'/exp OR 'vertebrate'/exp) NOT ('animal'/exp AND 'human'/exp OR 'human experimentation'/exp OR 'human experiment'/exp) OR ((rat OR rats OR mouse OR mice OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset*:ti) AND 'animal experiment'/exp)	8,738,787
12	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	6,129,064
13	('child'/exp OR 'fetus'/exp) NOT (('adult'/exp OR 'adolescent'/exp) AND ('child'/exp OR 'fetus'/exp))	2,260,256
14	#9 OR #10 OR #11 OR #12 OR #13	19,378,748
15	#8 NOT #14	1,803
16	#15 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	1,149
17	#15 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2022-2025]/py	459
18	#16 NOT#17	690
19	#15 NOT #18	1,113
20	#15 NOT #18 AND [23-07-2023]/sd	454
21	#15 NOT #18 AND [23-07-2023]/sd AND [embase]/lim	442

A2. Priority question. CS, Document B, section B.3.8.5. Please provide the outcome data that were used as the inputs into the NMAs.

Company response: The outcome data from the trials that were used as inputs in the NMAs presented in Document B.3.8 and Appendix J are shown in Table 5.(3)

Table 5: Outcome data used in the NMAs

Study	Treatment	Analysis Timepoint	Population	Sample size (N)	Analysis Responders (n)	Analysis Response (%)	Analysis Remitters (n)	Analysis Remission (%)
GEMINI-1	PBO	Induction	ADT failure	63	13	20.63%	2	3.17%
GEMINI-1	VDZ 300mg	Induction	ADT failure	82	32	39.02%	8	9.76%
LUCENT-1	PBO	Induction	ADT failure	118	35	29.66%	10	8.47%
LUCENT-1	MIRI 300mg	Induction	ADT failure	361	197	54.57%	55	15.24%
QUASAR Induction 1	PBO	Induction	ADT failure	51	14	27.45%	4	7.84%
QUASAR Induction 1	GUS 200mg	Induction	ADT failure	46	27	58.70%	7	15.22%
QUASAR Induction 1	GUS 400mg	Induction	ADT failure	51	25	49.02%	8	15.69%
QUASAR Induction 2	PBO	Induction	ADT failure	136	30	22.06%	5	3.68%
QUASAR Induction 2	GUS 200mg	Induction	ADT failure	208	114	54.81%	23	11.06%
GEMINI 1	PBO	1 year with delayed	ADT failure	63	10	15.87%	4	6.35%
GEMINI 1	VDZ 300mg Q4W	1 year with delayed	ADT failure	27	9	33.33%	6	22.22%
GEMINI 1	VDZ 300mg Q8W	1 year with delayed	ADT failure	29	10	34.48%	7	24.14%
LUCENT-2	PBO	1 year with delayed	ADT failure	118	23	19.49%	8	6.78%
LUCENT-2	MIRI 200mg	1 year with delayed	ADT failure	241	125	51.87%	77	31.95%

Study	Treatment	Analysis Timepoint	Population	Sample size (N)	Analysis Responders (n)	Analysis Response (%)	Analysis Remitters (n)	Analysis Remission (%)
QUASAR	PBO	1 year with delayed	ADT failure	187	32	17.11%	12	6.42%
QUASAR	GUS 100mg Q8W	1 year with delayed	ADT failure	85	48	56.47%	23	27.06%
QUASAR	GUS 200mg Q4W	1 year with delayed	ADT failure	91	47	51.65%	25	27.47%
VISIBLE 1	VDZ 108mg Q2W	1 year with delayed	ADT failure	73	NR	NR	16	21.92%
VISIBLE 1	VDZ 300mg Q8W	1 year with delayed	ADT failure	41	NR	NR	8	19.51%
GEMINI 1	PBO	1 year without delayed	ADT failure	63	6	9.52%	2	3.17%
GEMINI 1	VDZ 300mg Q4W	1 year without delayed	ADT failure	27	5	18.52%	4	14.81%
GEMINI 1	VDZ 300mg Q8W	1 year without delayed	ADT failure	29	5	17.24%	4	13.79%
LUCENT-2	PBO	1 year without delayed	ADT failure	118	17	14.41%	5	4.24%
LUCENT-2	MIRI 200mg	1 year without delayed	ADT failure	241	94	39.00%	61	25.31%
QUASAR	PBO	1 year without delayed	ADT failure	187	20	10.70%	7	3.74%
QUASAR	GUS 100mg Q8W	1 year without delayed	ADT failure	85	32	37.65%	18	21.18%
QUASAR	GUS 200mg Q4W	1 year without delayed	ADT failure	91	30	32.97%	19	20.88%
VISIBLE 1	VDZ 108mg Q2W	1 year without delayed	ADT failure	73	NR	NR	11	15.07%
VISIBLE 1	VDZ 300mg Q8W	1 year without delayed	ADT failure	41	NR	NR	5	12.20%

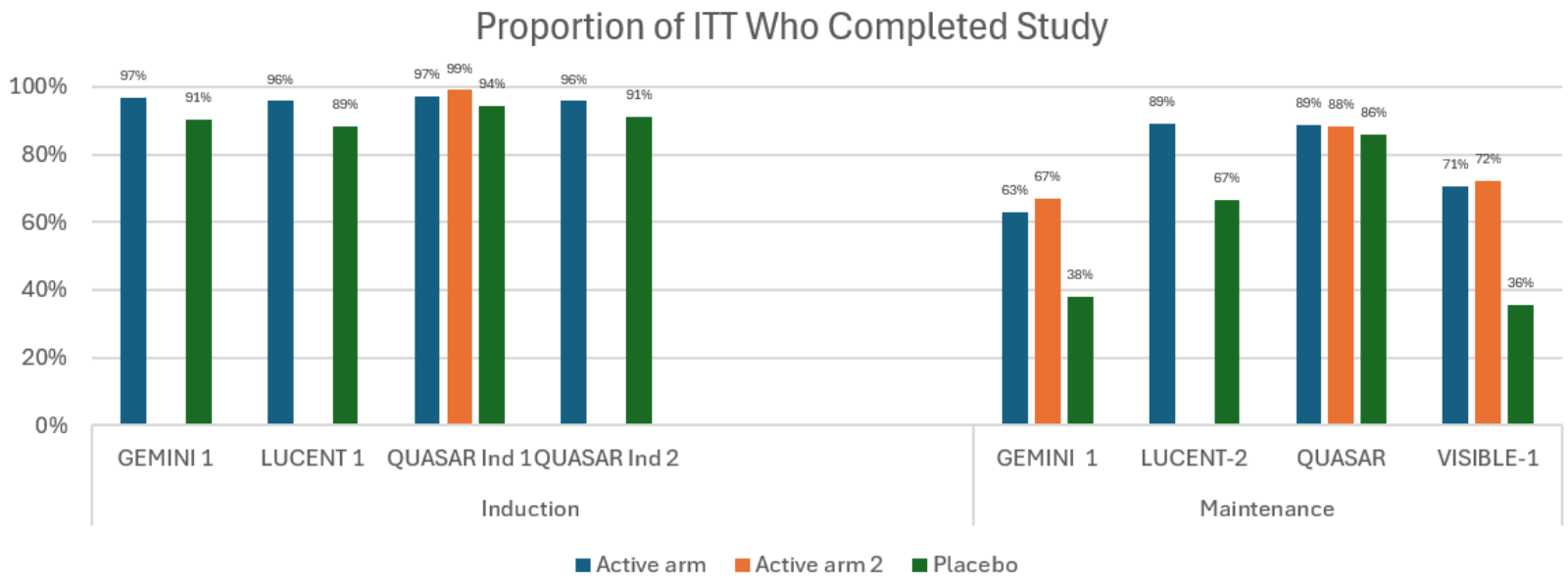
Abbreviations: ADT = Advance therapy; GUS = guselkumab; MIRI = mirikizumab; NR = not reported; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; VDZ = vedolizumab

A3. Priority question. CS, Document B, section B.3.8.6. The company submission states "Dropout rates varied across trials, which may impact results." (p98). However, in the next sentence, it is stated that dropout rates were similar across trials. Please clarify whether dropout rates varied or were similar and please provide the relevant data on dropout rates.

Company response: The statement above refers to a general observation regarding dropout rates (the proportion of patients in the intention to treat population that did not complete the study) in UC trials identified in the global SLR. Specifically, while dropout rates were generally similar during the induction phase, there was variation in the maintenance phase. Although this variability in the maintenance phase has the potential to impact the outcomes, it is anticipated that the results will be consistent with NMAs presented in previous appraisals which included these trials.(4, 5) .

Considering the trials informing induction analyses i.e., QUASAR induction study 1 and 2, GEMINI-1 and LUCENT-1, dropout rates across trials were broadly homogeneous, typically under 10% and similar between treatment arms of the same trial, as shown in Figure 1. The dropout rates from the trials informing 1 year maintenance analysis ranged more widely (36% to 89% considering isolated treatment arms) and were greatest in the GEMINI 1 and VISIBLE-1 trials. For these trials as well as LUCENT-2, dropout rates for placebo arms were substantially higher (36% to 67%). However, the method of non-responder imputation used in each trial's analysis would mitigate risks of bias related to varied dropout rate. It should also be noted that NMAs of efficacy outcomes have indicated variable dropout rates in previous appraisals, (e.g. TA998). It is anticipated that the variations in dropout rates will have a limited impact on the NMA conclusions.

Figure 1: Proportion of patients in the intention to treat population that completed the trials that inform the NMAs included in the company submission



Abbreviations: ITT = Intention-to-treat

Table 6: Proportion of patients completing the trials informing the NMAs included in the company submission

Trial	Intervention	Route of administration and dosing frequency	Timepoint	Proportion of ITT who completed trial (%)	Source
<u>Induction phase</u>					
GEMINI 1	Vedolizumab	300mg IV at weeks 0,2,6	6 weeks	97%	ITT from CT.gov; induction
GEMINI 1	Placebo	-	6 weeks	91%	ITT from CT.gov; induction

LUCENT 1	Mirikizumab	300mg IV at weeks 0,4,8	12 weeks	96%	ITT from CT.gov
LUCENT 1	Placebo	-	12 weeks	89%	ITT from CT.gov
QUASAR Ind 1	Guselkumab	200mg IV at weeks 0,4,8	12 weeks	97%	ITT from CT.gov; Period 1
QUASAR Ind 1	Guselkumab	400mg IV at weeks 0,4,8	12 weeks	99%	ITT from CT.gov; Period 1
QUASAR Ind 1	Placebo	-	12 weeks	94%	ITT from CT.gov; Period 1
QUASAR Ind 2	Guselkumab	200mg IV at weeks 0,4,8	12 weeks	96%	ITT from CT.gov; Period 1
QUASAR Ind 2	Placebo	-	12 weeks	91%	ITT from CT.gov; Period 1
Maintenance phase					
GEMINI 1	Vedolizumab	300 mg IV Q8W	46 weeks	63%	ITT from CT.gov; Maintenance study
GEMINI 1	Vedolizumab	300 mg IV Q4W	46 weeks	67%	ITT from CT.gov; Maintenance study
GEMINI 1	Placebo	-	46 weeks	38%	ITT from CT.gov; Maintenance study
LUCENT-2	Mirikizumab	200 mg SC Q4W	40 weeks	89%	ITT from CT.gov; Maintenance study
LUCENT-2	Placebo	-	40 weeks	67%	ITT from CT.gov; Maintenance study
QUASAR	Guselkumab	100 mg SC Q8W	44 weeks	89%	ITT from CT.gov; Maintenance study
QUASAR	Guselkumab	200 mg SC Q4W	44 weeks	88%	ITT from CT.gov; Maintenance study
QUASAR	Placebo	-	44 weeks	86%	ITT from CT.gov; Maintenance study
VISIBLE-1	Vedolizumab	108mg SC Q2W	46 weeks	71%	ITT from CT.gov; Maintenance study
VISIBLE-1	Vedolizumab	300 mg IV Q8W	46 weeks	72%	ITT from CT.gov; Maintenance study
VISIBLE-1	Placebo	-	46 weeks	36%	ITT from CT.gov; Maintenance study

Abbreviations: Q4W= Every 4 weeks; Q8W = Every 8 Weeks; SC= Subcutaneous; ITT = intention to treat

A4. Priority question. CS, Document B, section B.3.8.2.2 and Appendix D, section D.1.9.1.4. The company submission states "Differences were noted between QUASAR and comparator trials with regards to disease duration, baseline Mayo Clinic score, prior failure, and extent of disease … [and] with regards to prior therapies received and prior therapies received within a specific time period" (p88). However, the data for all these characteristics are not presented in Table 9 of Appendix D.1.9.1.4. Please provide the data extracted for all these characteristics for all the trials.

Company response: A revised version of Table 9 of Appendix D.1.9.1.4 presenting key patient baseline characteristics for all trials informing the NMAs are presented in Table 7. An additional column has been added pertaining to prior ADT failure, which was not included in the company submission. The population considered for all trials included in the NMA are presented in Table 7. The language used in the company submission, "prior therapies received within a specific time period", referred to differences in trial eligibility criteria, particularly with respect to exclusion criteria. For example, there was variation noted with regard to extent of prior use of B-cell or T-cell depleting agents. QUASAR and LUCENT did not include patients with natalizumab use within the past 12 months, whereas GEMINI 1 and VISIBLE 1 excluded patients with any prior use of natalizumab. In general, upon restriction of analyses to only ADT-failed patients, these cross-trial differences were considered minor and are not expected to impact the assumption of transitivity.

Table 7: Key patient baseline characteristics for all trials included in the NMA

Trial*	Population considered for reported patient baseline traits	NCT	Sex (female, %)	Mean age (years)	Mean BMI (kg/m^2)	Mean disease duration (years)	Mean Mayo Score	Mean CRP (mg/L)	Mean FCP (ug/g)	Concomitant therapies			Disease location	
										IMM (%)	CS (%)	ASA (%)	Left side of colon, %	Extensive disease, %
QUASAR induction 1 (n = 313)	Mixed ADT failure, FAS	NCT04033445	41	41.6	24.1	7.55	9.2	10.5	2,579.6	22	40	77	51	49
QUASAR induction 2 (n = 701)	Mixed ADT failure, FAS	NCT04033445	43	40.5	NR	7.52	9.1	8.7	3,132.8	21	35	73	52	48
QUASAR (n = 805)	Mixed ADT failure, FAS	NCT04033445	45	40.7	NR	7.64	9.1	8.6	2,999.2	22	40	76	53	47
GEMINI 1	Mixed ADT failure, FAS	NCT00783718	40	40.1	24.3	6.5	8.5	NR	2,524[a]	12[b]	37[c]	NR	40[d]	36[d]
LUCENT-1, LUCENT-2	Mixed ADT failure, FAS	NCT03518086	40	42.5	NR	7.12	NR	7.23	2,287.54	24[b]	40	74	63	NR
VISIBLE 1	Mixed ADT failure, FAS	NCT02611830	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

* Note: Baseline characteristics data reported here were manually pooled across select trial arms and pertain to induction baseline.
[a] Mean was calculated using the box-cox method where median and IQR/range were reported.
[b] Data were reported for patients with only concomitant immunomodulator therapy.
[c] Data were reported for patients with only concomitant corticosteroids.
[d] Trial reported additional data on patients with different disease locations that are not presented here.
Abbreviations: ADT = advanced therapy; ASA = aminosalicylates; BMI = Body-Mass Index; CRP = C-reactive protein; CS = corticosteroids; FAS = full analysis set; FCP = fecal calprotectin; IMM = immunomodulators; NCT = National Clinical Trial; NR = not reported

Table 8: Population considered and percentage of patients with prior ADT failure for all trials included in the NMA

Trial*	Population considered for reported patient baseline traits	NCT	Prior ADT failure (%)
QUASAR induction 1	FAS	NCT04033445	53
QUASAR induction 2	FAS	NCT04033445	49.1
QUASAR	FAS	NCT04033445	45
GEMINI 1	FAS	NCT00783718	41
LUCENT-1, LUCENT-2	FAS	NCT03518086	36
VISIBLE 1	FAS	NCT02611830	39

Abbreviations: FAS = full analysis set; NCT = national clinical trial; ADT = advanced therapy

A5. Priority question. CS, Document B, section B.3.8.2.4. Please conduct NMAs for the following outcomes which were analysed in NMAs for the mirikizumab appraisal (TA925): histological-endoscopic mucosal healing and safety outcomes (all cause discontinuation and serious adverse events). Alternatively, please justify why these NMAs were not considered to be necessary.

Company response: As guselkumab is the third interleukin-23 (IL-23) inhibitor to be appraised via the cost comparison route, a pragmatic approach has been adopted to ensure that the most relevant and necessary information is included. With reference to TA925, comparable outcomes were previously presented, specifically concerning the histological-endoscopic mucosal endpoint and safety. Since guselkumab and mirikizumab are in the same therapeutic class, and comparable efficacy has been demonstrated between guselkumab and mirikizumab in the clinical response and clinical remission NMAs presented in Document B, Section 3.8 of this submission, it is anticipated that guselkumab will by extension have similar efficacy in the histological-endoscopic and safety outcomes.

Histological-endoscopic mucosal healing NMAs were not planned in the original NMA protocol, and it will not be feasible to conduct these in the timeframe of clarification response. However, it should be considered that endoscopic healing may be correlated within the clinical remission outcome assessed in the NMA, given that the definition of the Mayo score used includes an endoscopic component (mucosal appearance at endoscopy, accounting for three of twelve maximum assignable points).

NMAs for safety outcomes (adverse events [AEs] leading to discontinuation and serious adverse events [SAEs]) were conducted between guselkumab and its comparators in the induction phase and included publicly available data for licensed doses of these therapies. NMAs for SAEs included vedolizumab and mirikizumab as comparators and NMAs for AEs leading to discontinuation only included mirikizumab as a comparator as data was unavailable for vedolizumab, the networks are shown in Figure 2 and Figure 3, respectively.(6)

Figure 2: NMA network diagram for serious adverse events

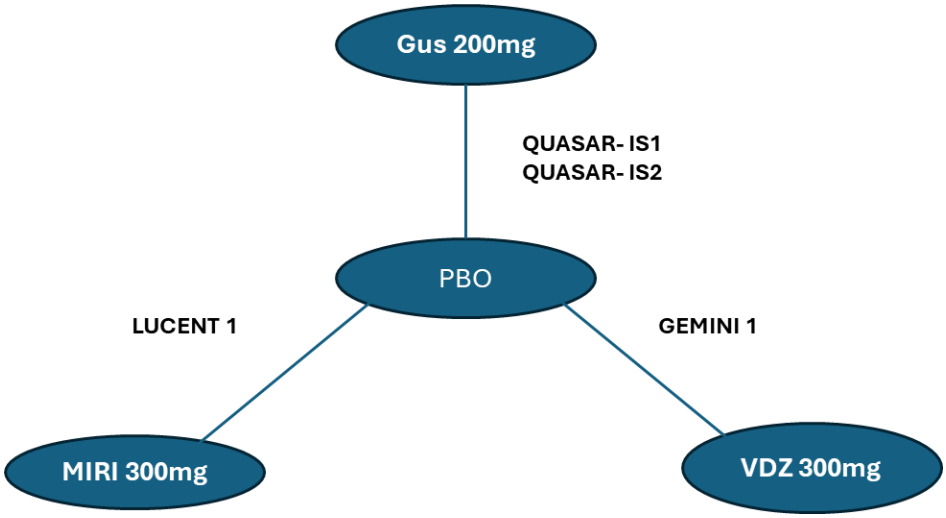
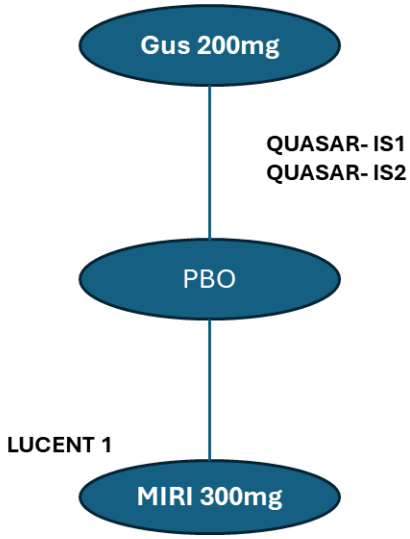


Figure 3: NMA network diagram for adverse events leading to discontinuation



The NMAs for safety outcomes were performed using a similar approach as the clinical response and clinical remission NMAs, in line with the NICE TSD 2 guidelines.(3, 7) These Bayesian NMA analyses were performed in winbugs (version 1.4.3), using three chains with a 50,000 run-in iteration phase and a 50,000-iteration phase for parameter estimation. Both the fixed effect (FE) and the random effect (RE) model were fit. To avoid prior beliefs influencing the results of the model, non-informative prior distributions were used for the baseline and treatment effects, and in RE models, a Uniform(0,1) distribution was used for the between-study standard deviation. Convergence was monitored using the Gelman-Rubin diagnostic and no issues were detected.

It is important to note that there are some limitations of these NMAs. For example, the event rate for both serious adverse events and adverse events leading to discontinuation are low, which can result in the outcomes being uncertain and difficult to interpret.

Serious adverse event NMA for the induction phase

In the random and fixed effect NMAs of serious adverse events, safety for guselkumab was comparable to vedolizumab and mirikizumab with both credible intervals overlapping with an OR of 1. The forest plots of both the RE and FE model are presented in the figures below. (6)

Figure 4: Forest plot for random effect NMA of serious adverse events in the induction phase of guselkumab 200mg IV versus comparators, full population

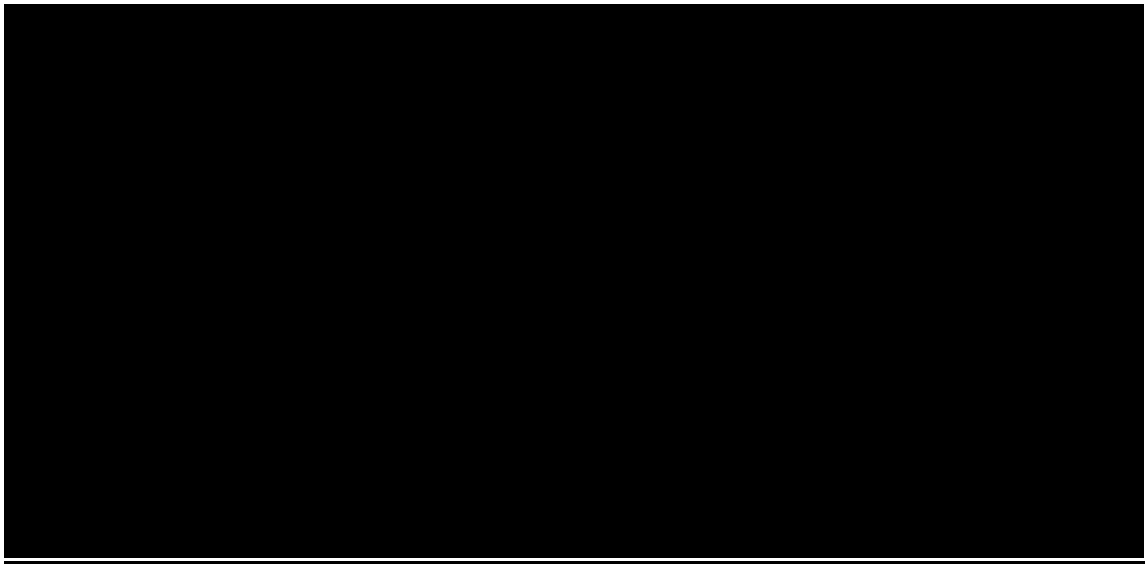
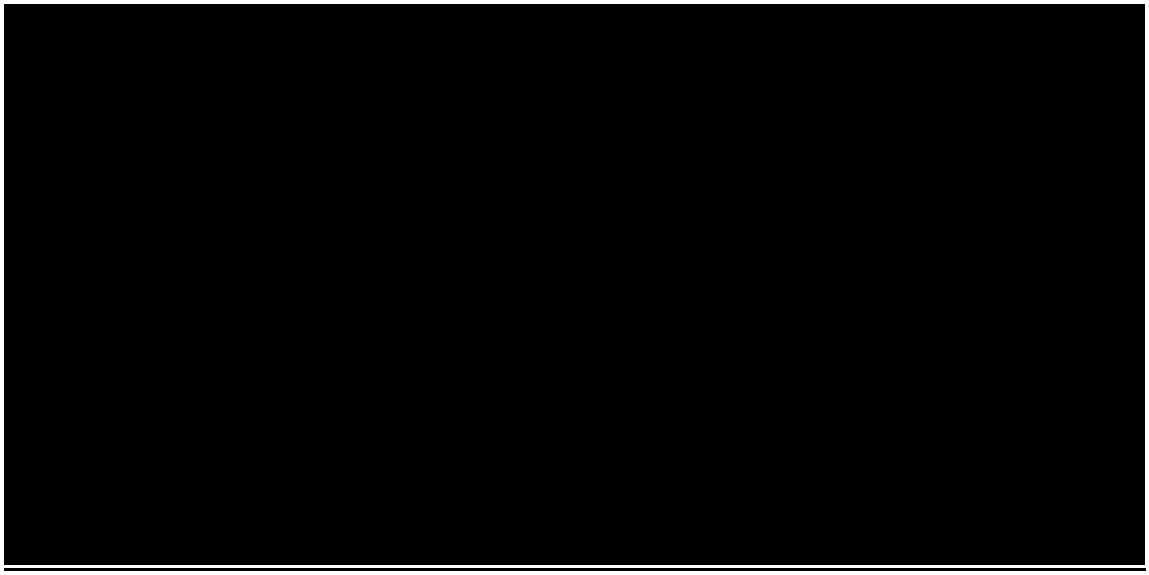


Figure 5: Forest plot for fixed effect NMA of serious adverse events in the induction phase of guselkumab 200mg IV versus comparators, full population



Adverse events leading to discontinuation NMA for the induction phase

In the random effect and fixed effect NMAs of AEs leading to discontinuation, safety for guselkumab was comparable to mirikizumab as the credible interval overlaps with an OR of 1. The forest plots of both the RE and FE model are presented in the figures below. (6)

Figure 6: Forest plot for random effect NMA of AEs leading to discontinuation in the induction phase of guselkumab 200mg IV versus comparators, full population

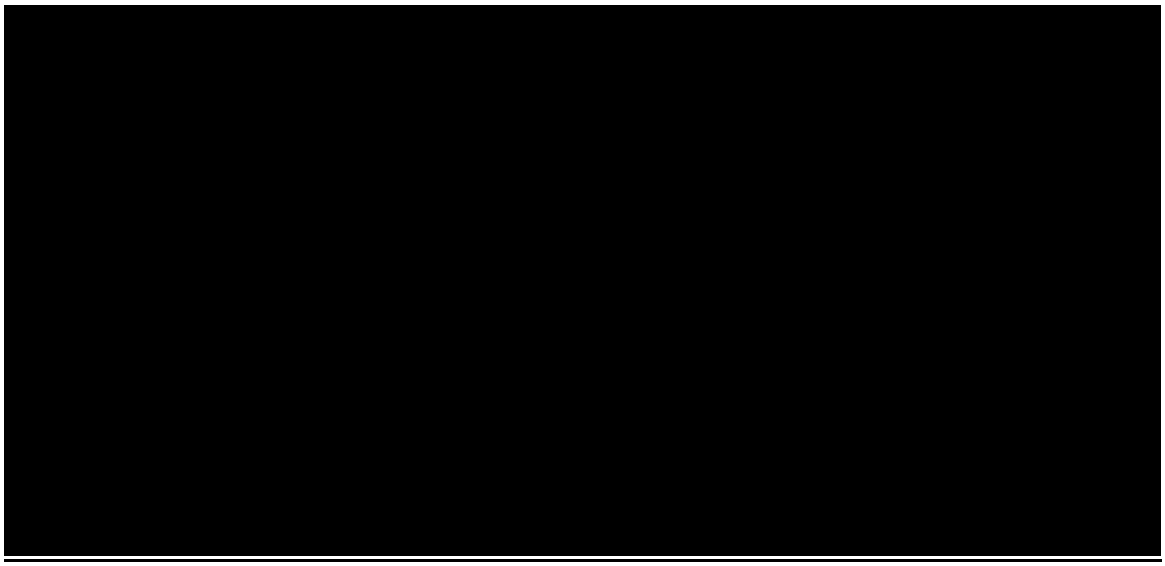


Figure 7: Forest plot for fixed effect NMA of AEs leading to discontinuation in the induction phase of guselkumab 200mg UV versus comparators, full population

A6. Priority question. CS, Document B, section B.3.8.3. Were the methods used to conduct the NMAs pre-specified in a protocol or statistical analysis plan? If so, please provide this document.

Company response: The methods used to conduct the NMAs were pre-specified in the protocol titled 'TREMFYA (Guselkumab) for the Treatment of Ulcerative Colitis: Network Meta-analysis of Randomized Controlled Trials'. As requested, Johnson and Johnson have attached the report as part of the response.

A7. Priority question. CS, Appendix, section D.1.9.1.4. For Table 9:

i) **Please provide the accompanying footnotes.**

ii) **Please clarify the source of the QUASAR trial data, that is, QUASAR IIb induction trial, QUASAR III induction trial or QUASAR III maintenance trial.**

iii) **Please clarify the population for all listed trials (that is, full analysis set, advanced therapy [ADT] population, etc).**

Company response:

i) Table 9 from Appendix D, Section D.1.9.1.4 has been reproduced below with the missing footnotes (Table 9).

ii) These data pertain to the QUASAR maintenance trial, however the data from both QUASAR induction trials have been included for completeness.

iii) The population for which baseline traits pertain to is now detailed in a dedicated column titled 'population considered for reported patient baseline traits'.

Table 9: Baseline characteristics of NMA included trials

Trial*	Population considered for reported patient baseline traits	NCT	Sex (female, %)	Mean age (years)	Mean BMI (kg/m^2)	Mean disease duration (years)	Mean Mayo Score	Mean CRP (mg/L)	Mean Faecal calprotectin (ug/g)	Concomitant therapies			Disease location	
										IMM (%)	CS (%)	ASA (%)	Left side of colon, %	Extensive disease, %
QUASAR induction 1 (n = 313)	Mixed ADT failure, FAS	NCT04033445	41	41.6	24.1	7.55	9.2	10.5	2,579.6	22	40	77	51	49
QUASAR induction 2 (n = 701)	Mixed ADT failure, FAS	NCT04033445	43	40.5	NR	7.52	9.1	8.7	3,132.8	21	35	73	52	48
QUASAR (n = 805)	Mixed ADT failure, FAS	NCT04033445	45	40.7	NR	7.64	9.1	8.6	2,999.2	22	40	76	53	47
GEMINI 1	Mixed ADT failure, FAS	NCT00783718	40	40.1	24.3	6.5	8.5	NR	2,524[a]	12[b]	37[c]	NR	40[d]	36[d]
LUCENT-1, LUCENT-2	Mixed ADT failure, FAS	NCT03518086	40	42.5	NR	7.12	NR	7.23	2,287.54	24[b]	40	74	63	NR
VISIBLE 1	Mixed ADT failure, FAS	NCT02611830	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

* Note: Baseline characteristics data reported here were manually pooled across select trial arms and pertain to induction baseline.
[a] Mean was calculated using the box-cox method where median and IQR/range were reported.
[b] Data were reported for patients with only concomitant immunomodulator therapy.
[c] Data were reported for patients with only concomitant corticosteroids.
[d] Trial reported additional data on patients with different disease locations that are not presented here.
Abbreviations: ADT = advanced therapy; ASA = aminosalicylates; BMI = Body-Mass Index; CRP = C-reactive protein; CS = corticosteroids; FAS = full analysis set; IMM = immunomodulators; NCT = National Clinical Trial; NR = not reported

Safety data

A8. Priority question. CS, Document B, section B.2.1. Please provide data that supports the statement that "comparable safety was demonstrated across all treatments" (Table 3, p35).

Company response: Section B.2.1 outlines the key drivers of the cost-effectiveness of comparators, particularly the clinical outcomes and measures. The statement above relates to the serious adverse events NMA that was presented in the company submission of mirikizumab for treating moderately to severely active ulcerative colitis (TA925). Although the outcomes of the serious adverse events NMA are redacted and not publicly available, in section 3.1.2 of the addendum, as part of the key model assumptions, it is stated that "adverse events were not included in the model due to the NMA results demonstrating broadly similar safety outcomes for mirikizumab, ustekinumab and vedolizumab", suggesting comparable safety.(4)

Regarding safety versus vedolizumab and mirikizumab, when comparing across the QUASAR, GEMINI-1 and LUCENT-1 trials, the overall rates of AEs, serious AEs and serious infections are similar.(8-10) The most frequently reported AEs (>5%) are worsening symptoms of ulcerative colitis, anaemia, upper respiratory tract infection, headache, arthralgia and nasopharyngitis in all three trials. Additionally, the safety of guselkumab has been demonstrated in the safety NMAs (serious adverse events and AEs leading to discontinuation) provided in the response to question A5.

QUASAR trial

A9. Priority question. CS, Document B, section B.3.5. The results achieved by patients in the placebo arms of the induction and maintenance phases of the QUASAR trial appear to be notably worse (for example, much lower proportion of patients in remission/responded to treatment) than those achieved by patients in the placebo arms of the LUCENT-1 and LUCENT-2 trials. Please provide reasons that may account for these differences.

Company response: Generally, response rates in placebo-treated patients can vary from <5 to >40% across ulcerative colitis clinical trials and are influenced by factors including trial duration, number of study visits, design features used to enrol patients

with more active disease and intensity of endoscopic follow-up.(11) These factors can influence the observed treatment effect and the resulting deltas.

When specifically assessing the QUASAR and LUCENT trial designs, most variables are similar i.e., both were randomised withdrawal trials, both have the same definition of clinical response and clinical remission, and baseline characteristics including inflammatory burden (faecal calprotectin, C-reactive protein), disease severity and disease duration are all comparable. Another factor that can influence placebo rates is perceived unmet need of the treatment and the timing of the trials. The LUCENT trial programme was conducted between 2018 and 2021 compared to the QUASAR trial programme which was conducted between 2019 and 2023. As such, the LUCENT programme was conducted in a period where there was a higher unmet need due to the later emergence of some advanced drug therapies such as IL-12/23 inhibitors, S1P modulators and JAK inhibitors from 2020 onwards, depending on the market. Thus, aside from this timing, there are no obvious causes for the differences between the outcomes between the two trials.

A10. Priority question. CS, Document B, section B.3.3.1. Please provide the statistical analysis plans (SAPs) for the QUASAR phase IIb induction trial and the QUASAR phase III induction trial.

Company response: As requested, Johnson & Johnson have attached the statistical analysis plans for the QUASAR phase IIb induction trial and QUASAR phase III induction as part of the response

A11. Priority question. Please provide the clinical study report (CSR) for the QUASAR phase IIb induction trial.

Company response: As requested, Johnson & Johnson have attached the clinical study report for the QUASAR phase IIb induction trial as part of the response.

A12. Priority question. CS, Document B, section B.3.3.1.3. Please provide baseline characteristics and disease characteristics in the ADT population for the QUASAR phase IIb induction trial.

Company response: The baseline characteristics and disease characteristics in the total ADT failure population from the QUASAR phase IIb induction study are presented below.(12)

Table 10: Baseline demographics and disease characteristics in the ADT population (QUASAR Phase IIb induction study)

Characteristic, n (%)	Placebo (N 50)	GUS 400 mg IV (N = 51)	GUS 200 mg IV (N = 47)	Total (N = 148)
Age, years				
Mean (SD)	42.48 (16.14)	42.08 (13.575)	45.3 (13.975)	43.24 (14.582)
Sex, n (%)				
Male, n (%)	34 (68%)	28 (54.9%)	31 (66%)	93 (62.8%)
Female, n (%)	16 (32%)	23 (45.1%)	16 (34%)	55 (37.2%
Weight, Kg				
Mean (SD)	69.96 (17.488)	71.56 (21.173)	72.6 (18.394)	71.35 (19.012)
Mean (SD)	170.31 (9.54)	168.89 (10.025)	169.71 (10.116)	169.63 (9.843)
Region				
Asia	15 (30%)	16 (31.4%)	15 (31.9%)	46 (31.1%)
Eastern Europe	12 (24%)	11 (21.6%)	12 (25.5%)	35 (23.6%)
Rest of World	23 (46%)	24 (47.1%)	20 (42.6%)	67 (45.3%)
Latin America	0	0	2 (4.3%)	2 (1.4%)
North America	4 (8%)	3 (5.9%)	2 (4.3%)	9 (6.1%)
Western Europe	18 (36%)	17 (33.3%)	16 (34%)	51 (34.5%)
Other	1 (2%)	4 (7.8%)	0	5 (3.4%)
Race				
Asian	15 (30%)	16 (31.4%)	15 (31.9%)	46 (31.1%)
White	32 (64%)	29 (56.9%)	28 (59.6%)	89 (60.1%)
Black or African American	0	1 (2%)	1 (2.1%)	2 (1.4%)
Not Reported	3 (6%)	5 (9.8%)	3 (6.4%)	11 (7.4%)
Ethnicity				
Hispanic or Latino	2 (4%)	0	3 (6.4%)	5 (3.4%)
Not Hispanic or Latino	46 (92%)	46 (90.2%)	40 (85.1%)	132 (89.2%)
Not Reported	2 (4%)	5 (9.8%)	4 (8.5%)	11 (7.4%
Extent of disease, n (%)				
Limited to left side of colon	27 (54%)	24 (47.1%)	20 (42.6%)	71 (48%)
Extensive	23 (46%)	27 (52.9%)	27 (57.4%)	77 (52%)
Mayo score				
Mean (SD)	9.26 (1.44)	9.27 (1.168)	9.19 (1.076)	9.24 (1.232)
Range	(6-12)	(7-12)	(7-12)	(6-12)
Severity of UC disease, n (%)				
Moderate (6 =< Mayo score =< 10)	39 (78%)	43 (84.3%)	42 (89.4%)	124 (83.8%)

Characteristic, n (%)	Placebo (N 50)	GUS 400 mg IV (N = 51)	GUS 200 mg IV (N = 47)	Total (N = 148)
Severe (Mayo score > 10)	11 (22%)	8 (15.7%)	5 (10.6%)	24 (16.2%)
Modified Mayo score				
Mean (SD)	7.1 (1.147)	7.04 (0.848)	7 (0.885)	7.05 (0.964)
Median (range)	7.0 (5-9)	7.0 (5-9)	7.0 (5-9)	7.0 (5-9)
Partial Mayo score				
Mean (SD)	6.44 (1.28)	6.41 (1.062)	6.43 (0.994)	6.43 (1.113)
Median (range)	6.5 (3-9)	6.0 (5-9)	6.0 (4-9)	6.0 (3-9)
Severity of endoscopic subscore				
Moderate (endoscopy subscore = 2)	9 (18%)	7 (13.7%)	11 (23.4%)	27 (18.2%)
Moderate (endoscopy subscore = 3)	41 (82%)	44 (86.3%)	36 (76.6%)	121 (81.8%)
Extraintestinal manifestations				
Present	7 (14%)	17 (33.3%)	7 (14.9%)	31 (20.9%)
Absent	43 (86%)	34 (66.7%)	40 (85.1%)	117 (79.1%)
CRP, mg/L				
Mean (SD)	13.02 (24.993)	8.55 (9.955)	9.83 (12.536)	10.48 (17.233)
Median (range)	6.0 (0.1- 163)	4.8 (0.2- 51.7)	3.9 (0.1- 52.6)	4.9 (0.1- 163)
Abnormal CRP (> 3 mg/L)	34 (68%)	35 (70%)	29 (63%)	98 (67.1%)
=< 3 mg/L	16 (32%)	15 (30%)	17 (37%)	48 (32.9%)
Fecal calprotectin, mg/kg				
Mean (SD)	2835.55 (3467.398)	2253.42 (2291.166)	3170.95 (5785.416)	2737.16 (4066.028)
Median (range)	1638.5 (221-20856	1572.5 (81-10697)	1625.5 (15-36000)	1586.5 (15-36000)
Abnormal fecal calprotectin (> 250 mg/kg)	40 (95.2%)	46 (95.8%)	38 (86.4%)	124 (92.5%)
< 250 mg/kg	2 (4.8%)	2 (4.2%)	6 (13.6%)	10 (7.5%)
Albumin (g/L)				
Mean (SD)	42.68 (3.56)	42.86 (3.889)	42.4 (3.899)	42.66 (3.763)
Median (range)	42.5 (31-51)	43.0 (33-50)	43.0 (32-51)	43.0 (31-51)
Abnormal albumin (< 33 g/L)	1 (2%)	0	1 (2.1%)	2 (1.4%)
>= 33 g/L	49 (98%)	51 (100%)	46 (97.9%)	146 (98.6%)

Key: ADT, advanced therapy; CRP, C-reactive protein; SD, standard deviation; UC, ulcerative colitis.

Source: Data on file, 2025.(12)

A13. Priority question. CS, Document B, section B.3.3.1.3 and Appendices, section H.1.2. Please provide baseline characteristics and disease characteristics in the total ADT population (that is, summarised across all treatment arms) for the QUASAR phase III maintenance trial. This is not provided in Table 31 of Appendix H.

Company response: The baseline characteristics and disease characteristics in the total ADT failure population from the QUASAR phase III maintenance trial are presented below.(13)

Table 11: Baseline demographics and disease characteristics in the ADT population (QUASAR maintenance study)

Characteristic	Randomised patients – induction guselkumab responders					Nonrandomised patients		Overall total (N = 358)
	Placebo[a] SC (N = 75)	Guselkumab			Total (N = 240)	Induction placebo IV responders	Induction guselkumab 24-week responders[c]	
		100 mg SC Q8W (N = 77)	200 mg SC Q4W (N = 88)	Combined (N = 165)		Placebo SC[b] (N = 45)	Guselkumab 200 mg SC Q4W (N = 73)	
Age, years								
Mean (SD)	42.8 (13.88)	42.5 (13.88)	42.7 (14.61)	42.6 (14.23)	42.7 (14.09)	40.4 (12.72)	41.4 (14.03)	42.1 (13.90)
Median (IQR)	41.0 (33.0–54.0)	42.0 (32.0–49.0)	41.0 (30.0–56.0)	41.0 (32.0–54.0)	41.0 (32.0–54.0)	39.0 (30.0–48.0)	41.0 (31.0–53.0)	41.0 (31.0–53.0)
Sex, n (%)								
Female	37 (49.3)	34 (44.2)	33 (37.5)	67 (40.6)	104 (43.3)	23 (51.1)	33 (45.2)	160 (44.7)
Male	38 (50.7)	43 (55.8)	55 (62.5)	98 (59.4)	136 (56.7)	22 (48.9)	40 (54.8)	198 (55.3)
Weight, kg								
Mean (SD)	72.51 (16.817)	71.66 (18.459)	72.89 (17.410)	72.32 (17.863)	72.38 (17.508)	72.28 (18.837)	69.98 (17.248)	71.88 (17.603)
Height (cm)								
Mean (SD)	170.75 (9.782)	168.91 (9.249)	170.53 (9.925)	169.77 (9.620)	170.08 (9.661)	168.50 (11.325)	168.12 (10.829)	169.48 (10.133)

Characteristic	Randomised patients – induction guselkumab responders					Nonrandomised patients		Overall total (N = 358)
	Placebo[a] SC (N = 75)	Guselkumab			Total (N = 240)	Induction placebo IV responders	Induction guselkumab 24-week responders[c]	
		100 mg SC Q8W (N = 77)	200 mg SC Q4W (N = 88)	Combined (N = 165)		Placebo SC[b] (N = 45)	Guselkumab 200 mg SC Q4W (N = 73)	
Region								
Asia	16 (21.3%)	16 (20.8%)	23 (26.1%)	39 (23.6%)	55 (22.9%)	10 (22.2%)	21 (28.8%)	86 (24.0%)
Eastern Europe	20 (26.7%)	15 (19.5%)	23 (26.1%)	38 (23.0%)	58 (24.2%)	6 (13.3%)	20 (27.4%)	84 (23.5%)
Rest of World	39 (52.0%)	46 (59.7%)	42 (47.7%)	88 (53.3%)	127 (52.9%)	29 (64.4%)	32 (43.8%)	188 (52.5%)
Latin America	5 (6.7%)	5 (6.5%)	7 (8.0%)	12 (7.3%)	17 (7.1%)	5 (11.1%)	3 (4.1%)	25 (7.0%)
North America	5 (6.7%)	4 (5.2%)	7 (8.0%)	11 (6.7%)	16 (6.7%)	4 (8.9%)	4 (5.5%)	24 (6.7%)
Western Europe	23 (30.7%)	29 (37.7%)	21 (23.9%)	50 (30.3%)	73 (30.4%)	14 (31.1%)	14 (19.2%)	101 (28.2%)
Other[d]	6 (8.0%)	8 (10.4%)	7 (8.0%)	15 (9.1%)	21 (8.8%)	6 (13.3%)	11 (15.1%)	38 (10.6%)
Race								
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Asian	18 (24.0%)	17 (22.1%)	23 (26.1%)	40 (24.2%)	58 (24.2%)	10 (22.2%)	21 (28.8%)	89 (24.9%)
Black or African American	2 (2.7%)	2 (2.6%)	1 (1.1%)	3 (1.8%)	5 (2.1%)	1 (2.2%)	1 (1.4%)	7 (2.0%)
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0	0	0
White	46 (61.3%)	50 (64.9%)	56 (63.6%)	106 (64.2%)	152 (63.3%)	32 (71.1%)	45 (61.6%)	229 (64.0%)
Multiple	0	0	0	0	0	0	1 (1.4%)	1 (0.3%)
Not Reported	9 (12.0%)	8 (10.4%)	8 (9.1%)	16 (9.7%)	25 (10.4%)	2 (4.4%)	5 (6.8%)	32 (8.9%)
Ethnicity								
Hispanic or Latino	5 (6.7%)	5 (6.5%)	8 (9.1%)	13 (7.9%)	18 (7.5%)	7 (15.6%)	3 (4.1%)	28 (7.8%)

Characteristic	Randomised patients – induction guselkumab responders					Nonrandomised patients		Overall total (N = 358)
	Placebo[a] SC (N = 75)	Guselkumab			Total (N = 240)	Induction placebo IV responders	Induction guselkumab 24-week responders[c]	
		100 mg SC Q8W (N = 77)	200 mg SC Q4W (N = 88)	Combined (N = 165)		Placebo SC[b] (N = 45)	Guselkumab 200 mg SC Q4W (N = 73)	
Not Hispanic or Latino	62 (82.7%)	62 (80.5%)	70 (79.5%)	132 (80.0%)	194 (80.8%)	37 (82.2%)	62 (84.9%)	293 (81.8%)
Not reported	8 (10.7%)	10 (13.0%)	10 (11.4%)	20 (12.1%)	28 (11.7%)	1 (2.2%)	8 (11.0%)	37 (10.3%)
UC disease duration, years								
Mean (SD)	9.03 (7.019)	11.04 (9.219)	9.76 (8.937)	10.36 (9.065)	9.94 (8.486)	8.40 (7.502)	7.48 (5.028)	9.25 (7.830)
Median (IQR)	7.34 (3.48–12.78)	8.27 (4.88–13.10)	6.88 (3.73–12.68)	7.44 (4.15–13.00)	7.42 (3.85–13.00)	6.89 (3.41–9.60)	6.18 (3.63–9.86)	7.25 (3.73–11.87)
Extent of disease, n (%)								
Limited to left side of colon	34 (45.3)	40 (51.9)	50 (56.8)	90 (54.5)	124 (51.7)	23 (51.1)	43 (58.9)	190 (53.1)
Extensive	41 (54.7)	37 (48.1)	38 (43.2)	75 (45.5)	116 (48.3)	22 (48.9)	30 (41.1)	168 (46.9)
Mayo score								
Mean (SD)	9.5 (1.29)	8.9 (1.31)	9.3 (1.25)	9.1 (1.28)	9.2 (1.30)	9.3 (1.34)	9.2 (1.12)	9.2 (1.27)
Median (IQR)	10.0 (9.0–11.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	10.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
Severity of UC disease, n (%)								
Moderate (Mayo score 6–10)	56 (74.7)	67 (87.0)	73 (83.0)	140 (84.8)	196 (81.7)	35 (77.8)	63 (86.3)	294 (82.1)
Severe (Mayo score 11–12)	19 (25.3)	10 (13.0)	15 (17.0)	25 (15.2)	44 (18.3)	10 (22.2)	10 (13.7)	64 (17.9)
Modified Mayo score								
Mean (SD)	7.3 (0.98)	6.7 (1.12)	7.0 (1.06)	6.9 (1.09)	7.0 (1.07)	7.0 (1.04)	6.9 (0.94)	7.0 (1.04)
Median (IQR)	7.0 (7.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (7.0-8.0)	7.0 (6.0-8.0)

Characteristic	Randomised patients – induction guselkumab responders					Nonrandomised patients		Overall total (N = 358)
	Placebo[a] SC (N = 75)	Guselkumab			Total (N = 240)	Induction placebo IV responders	Induction guselkumab 24-week responders[c]	
		100 mg SC Q8W (N = 77)	200 mg SC Q4W (N = 88)	Combined (N = 165)		Placebo SC[b] (N = 45)	Guselkumab 200 mg SC Q4W (N = 73)	
Modified Mayo score of 7-9	61 (81.3%)	45 (58.4%)	60 (68.2%)	105 (63.6%)	166 (69.2%)	28 (62.2%)	55 (75.3%)	249 (69.6%)
Severity of UC disease by modified Mayo Score								
Moderate (modified Mayo score 5-6)	14 (18.7%)	32 (41.6%)	28 (31.8%)	60 (36.4%)	74 (30.8%)	17 (37.8%)	18 (24.7%)	109 (30.4%)
Severe (modified Mayo score 7-9)	61 (81.3%)	45 (58.4%)	60 (68.2%)	105 (63.6%)	166 (69.2%)	28 (62.2%)	55 (75.3%)	249 (69.6%)
Partial Mayo score								
Mean (SD)	6.7 (1.19)	6.1 (1.21)	6.5 (1.13)	6.3 (1.18)	6.4 (1.20)	6.6 (1.20)	6.3 (1.05)	6.4 (1.17)
Median (IQR)	7.0 (6.0-8.0)	6.0 (5.0-7.0)	6.0 (6.0-7.0)	6.0 (6.0-7.0)	6.0 (6.0-7.0)	7.0 (6.0-8.0)	6.0 (6.0-7.0)	6.0 (6.0-7.0)
Severity of endoscopy subscore								
Moderate (endoscopy subscore n =2)	15 (20.0%)	15 (19.5%)	19 (21.6%)	34 (20.6%)	49 (20.4%)	14 (31.1%)	10 (13.7%)	73 (20.4%)
Severe (endoscopy subscore n =3)	60 (80.0%)	62 (80.5%)	69 (78.4%)	131 (79.4%)	191 (79.6%)	31 (68.9%)	63 (86.3%)	285 (79.6%)
Extraintestinal manifestations								
Present	18 (24.0%)	10 (13.0%)	13 (14.8%)	23 (13.9%)	41 (17.1%)	3 (6.7%)	19 (26.0%)	63 (17.6%)
Absent	57 (76.0%)	67 (87.0%)	75 (85.2%)	142 (86.1%)	199 (82.9%)	42 (93.3%)	54 (74.0%)	295 (82.4%)
CRP, mg/L								
Mean (SD)	11.1 (15.46)	9.6 (10.25)	8.0 (10.59)	8.7 (10.43)	9.5 (12.26)	8.2 (8.86)	9.4 (11.39)	9.3 (11.69)

Characteristic	Randomised patients – induction guselkumab responders					Nonrandomised patients		Overall total (N = 358)
	Placebo[a] SC (N = 75)	Guselkumab			Total (N = 240)	Induction placebo IV responders	Induction guselkumab 24-week responders[c]	
		100 mg SC Q8W (N = 77)	200 mg SC Q4W (N = 88)	Combined (N = 165)		Placebo SC[b] (N = 45)	Guselkumab 200 mg SC Q4W (N = 73)	
Median (IQR)	4.3 (1.8-14.0)	4.9 (2.1-15.3)	4.1 (1.5-10.1)	4.5 (1.7-11.8)	4.4 (1.8-12.7)	6.5 (2.5-8.9)	4.8 (1.5-14.6)	5.0 (1.7-12.8)
Abnormal CRP (> 3 mg/L), n (%)	48 (64.0)	49 (64.5)	51 (59.3)	100 (61.7)	148 (62.4)	33 (73.3)	45 (61.6)	226 (63.7)
Faecal calprotectin, mg/kg								
Mean (SD)	3,441.5 (5,368.37)	4,378.4 (6,555.10)	3,537.9 (5,171.02)	3,916.7 (5,829.03)	3,759.8 (5,672.74)	2,099.7 (1,907.43)	3,119.4 (3,950.75)	3,413.0 (5,028.96)
Median (IQR)	1631.5 (831.0-3741.0)	1647.0 (1003.0-4834.0)	1605.5 (751.0-3434.0)	1642.5 (848.0-3557.0)	1641.5 (839.5-3649.0)	1577.0 (1138.0-2170.0)	1690.0 (918.0-3275.0)	1631.0 (854.0-3472.5)
Abnormal faecal calprotectin (> 250 mg/kg), n (%)	64 (91.4)	57 (89.1)	69 (88.5)	126 (88.7)	190 (89.6)	38 (92.7)	65 (97.0)	293 (91.6)
Fecal calprotectin > 150 mg/kg	66 (94.3%)	59 (92.2%)	73 (93.6%)	132 (93.0%)	198 (93.4%)	39 (95.1%)	65 (97.0%)	302 (94.4%)
Albumin (g/L)								
Mean (SD)	42.1 (3.91)	43.2 (3.32)	42.0 (3.84)	42.6 (3.65)	42.5 (3.73)	43.3 (3.22)	42.7 (3.35)	42.6 (3.60)
Median (IQR)	43.0 (40.0–45.0)	43.0 (41.0–45.0)	42.0 (40.0-44.0)	43.0 (40.0-45.0)	43.0 (40.0-45.0)	43.0 (42.0-45.0)	43.0 (40.0-45.0)	43.0 (40.0-45.0)

Key: ADT, advanced therapy; CRP, C-reactive protein; SC; subcutaneous; IQR, interquartile range; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation; UC, ulcerative colitis.

Notes: Includes only patients with modified Mayo score 5–9 at induction baseline.
Note: Includes only subjects with modified Mayo score 5-9 at induction baseline.
Note: Subjects were presented in the treatment group assigned at Week M-0.

Characteristic	Randomised patients – induction guselkumab responders				Nonrandomised patients		Overall total (N = 358)
	Placebo[a] SC (N = 75)	Guselkumab		Total (N = 240)	Induction placebo IV responders	Induction guselkumab 24-week responders[c]	
		100 mg SC Q8W (N = 77)	200 mg SC Q4W (N = 88)	Combined (N = 165)	Placebo SC[b] (N = 45)	Guselkumab 200 mg SC Q4W (N = 73)	

a Subjects who were in clinical response to guselkumab IV induction dosing and were randomized to placebo SC on entry into this maintenance study.
b Subjects who were in clinical response to placebo IV induction dosing and received placebo SC on entry into this maintenance study.
c Subjects who were not in clinical response to guselkumab IV at Week I-12 but were in clinical response at Week I-24 after receiving SC administrations of guselkumab from Week I-12.
d Includes countries Australia, Israel, Jordan and New Zealand.

Source: QUASAR maintenance study, clinical study report. (13)

ASTRO trial

A14. Priority question. CS, Document B, section B.3.3.2.3. Please provide the baseline characteristics by treatment arm for patients in the advanced therapy inadequate responder (ADT-IR) subpopulation of the ASTRO trial.

Company response: The baseline characteristics and disease characteristics in the total ADT-IR population from the ASTRO trial are presented below. (14)

Table 12: Baseline demographics and disease characteristics in the ADT-IR population (ASTRO study)

Characteristic	Placebo (N = 56)	Guselkumab			Total (N = 168)
		400 mg SC Q4W → 100 mg SC Q8W (N = 57)	400 mg SC Q4W → 200 mg SC Q4W (N = 55)	Combined (N = 112)	
Age, years					
Mean (SD)	41.1 (13.11)	43.2 (15.20)	46.2 (14.51)	44.7 (14.88)	43.5 (14.38)
Median (range)	38.0 (30.0–52.0)	43.0 (31.0–54.0)	48.0 (34.0–58.0)	45.5 (31.5–55.0)	43.5 (30.5–54.0)
Sex, n (%)					
Female	17 (30.4)	29 (50.9)	17 (30.9)	46 (41.1)	63 (37.5)
Male	39 (69.6)	28 (49.1)	38 (69.1)	66 (58.9)	105 (62.5)
Weight, kg					
Mean (SD)	71.70 (16.196)	68.46 (13.556)	75.21 (16.793)	71.77 (15.536)	71.75 (15.711)
Height, cm					
Mean (SD)	171.59 (9.424)	165.28 (9.864)	169.83 (8.233)	167.51 (9.343)	168.87 (9.538)
Race					
American Indian or Alaska Native	0	0	0	0	0
Asian	23 (41.1%)	19 (33.3%)	19 (34.5%)	38 (33.9%)	61 (36.3%)

Characteristic	Placebo (N = 56)	Guselkumab			Total (N = 168)
		400 mg SC Q4W → 100 mg SC Q8W (N = 57)	400 mg SC Q4W → 200 mg SC Q4W (N = 55)	Combined (N = 112)	
Black or African American	0	4 (7.0%)	3 (5.5%)	7 (6.3%)	7 (4.2%)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
White	31 (55.4%)	33 (57.9%)	33 (60.0%)	66 (58.9%)	97 (57.7%)
Multiple[a]	0	0	0	0	0
Not Reported	2 (3.6%)	1 (1.8%)	0	1 (0.9%)	3 (1.8%)
Ethnicity					
Hispanic or Latino	9 (16.1%)	14 (24.6%)	14 (25.5%)	28 (25.0%)	37 (22.0%)
Not Hispanic or Latino	43 (76.8%)	41 (71.9%)	41 (74.5%)	82 (73.2%)	125 (74.4%)
Not reported	3 (5.4%)	1 (1.8%)	0	1 (0.9%)	4 (2.4%)
Unknown	1 (1.8%)	1 (1.8%)	0	1 (0.9%)	2 (1.2%)
Region					
Asia	22 (39.3%)	18 (31.6%)	19 (34.5%)	37 (33.0%)	59 (35.1%)
Eastern Europe	7 (12.5%)	11 (19.3%)	8 (14.5%)	19 (17.0%)	26 (15.5%)
Rest of World	27 (48.2%)	28 (49.1%)	28 (50.9%)	56 (50.0%)	83 (49.4%)
Latin America	10 (17.9%)	14 (24.6%)	14 (25.5%)	28 (25.0%)	38 (22.6%)
North America	4 (7.1%)	4 (7.0%)	7 (12.7%)	11 (9.8%)	15 (8.9%)
Western Europe	7 (12.5%)	7 (12.3%)	2 (3.6%)	9 (8.0%)	16 (9.5%)
Other[b]	6 (10.7%)	3 (5.3%)	5 (9.1%)	8 (7.1%)	14 (8.3%)
UC disease duration, years					
Mean (SD)	6.83 (4.619)	9.35 (8.012)	8.76 (6.168)	9.06 (7.140)	8.32 (6.482)
Median (IQR)	5.45 (3.35–9.93)	6.59 (4.04–11.28)	7.75 (3.73–12.67)	6.97 (3.88–11.79)	6.56 (3.59–11.40)
Extent of disease, n (%)					
Limited to left side of colon	17 (30.4)	19 (33.3)	24 (43.6)	43 (38.4)	60 (35.7)

Characteristic	Placebo (N = 56)	Guselkumab			Total (N = 168)
		400 mg SC Q4W → 100 mg SC Q8W (N = 57)	400 mg SC Q4W → 200 mg SC Q4W (N = 55)	Combined (N = 112)	
Extensive	39 (69.6)	38 (66.7)	31 (56.4)	69 (61.6)	108 (64.3)
Mayo score					
Mean (SD)	9.4 (1.17)	9.0 (1.26)	9.2 (1.14)	9.1 (1.20)	9.2 (1.19)
Median (IQR)	9.0 (9.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
Severity of UC disease, by Mayo score n (%)					
Moderate (Mayo score 6–10)	44 (78.6)	51 (89.5)	50 (90.9)	101 (90.2)	145 (86.3)
Severe (Mayo score 11–12)	12 (21.4)	6 (10.5)	5 (9.1)	11 (9.8)	23 (13.7)
Modified Mayo score					
Mean (SD)	6.9 (0.96)	6.8 (1.11)	6.8 (1.03)	6.8 (1.07)	6.8 (1.03)
Median (IQR)	7.0 (6.0-8.0)	7.0 (6.0-7.0)	7.0 (6.0-7.0)	7.0 (6.0-7.0)	7.0 (6.0-7.0)
Severity of UC disease by modified Mayo Score					
Moderate (modified Mayo score 5-6)	18 (32.1%)	16 (28.1%)	16 (29.1%)	32 (28.6%)	50 (29.8%)
Severe (modified Mayo score 7-9)	38 (67.9%)	40 (70.2%)	37 (67.3%)	77 (68.8%)	115 (68.5%)
Partial Mayo score					
Mean (SD)	6.6 (1.02)	6.4 (1.08)	6.5 (1.00)	6.4 (1.04)	6.5 (1.03)
Median (IQR)	6.0 (6.0-7.0)	6.0 (5.0-7.0)	6.0 (6.0-7.0)	6.0 (6.0-7.0)	6.0 (6.0-7.0)
Severity of endoscopy subscore					
Moderate (endoscopy subscore n =2)	15 (26.8%)	19 (33.3%)	16 (29.1%)	35 (31.3%)	50 (29.8%)
Severe (endoscopy subscore n =3)	41 (73.2%)	38 (66.7%)	39 (70.9%)	77 (68.8%)	118 (70.2%)
CRP, mg/L					

Characteristic	Placebo (N = 56)	Guselkumab			Total (N = 168)
		400 mg SC Q4W → 100 mg SC Q8W (N = 57)	400 mg SC Q4W → 200 mg SC Q4W (N = 55)	Combined (N = 112)	
Mean (SD)	13.8 (18.77)	9.4 (14.51)	7.4 (7.34)	8.4 (11.55)	10.2 (14.53)
Median (IQR)	6.4 (3.0-14.6)	4.1 (2.3-11.5)	6.0 (3.1-9.5)	4.9 (2.5-11.0)	5.2 (2.6-11.4)
Abnormal CRP (> 3 mg/L), n (%)	42 (75.0)	38 (66.7)	42 (76.4)	80 (71.4)	122 (72.6)
Faecal calprotectin, mg/kg					
Mean (SD)	3,287.7 (4,019.39)	2,810.6 (3,800.13)	3,902.2 (5,636.71)	3,366.9 (4,832.32)	3,340.2 (4,561.19)
Median (IQR)	1919.0 (1425.0-3202.0_	1466.0 (633.0-2982.0)	1598.0 (929.0-3480.0)	1571.5 (802.0-3238.0)	1629.0 (862.0-3202.0)
Abnormal faecal calprotectin (> 250 mg/kg), n (%)	50 (94.3)	44 (86.3)	51 (96.2)	95 (91.3)	145 (92.4)
Albumin (g/L)					
Mean (SD)	42.4 (4.42)	42.8 (3.76)	42.2 (4.00)	42.5 (3.87)	42.5 (4.05)
Median (IQR)	43.0 (41.0–45.0)	42.0 (41.0–45.0)	43.0 (40.0–45.0)	43.0 (40.0–45.0)	43.0 (40.0–45.0)

Key: ADT-IR, inadequate response to or intolerance of advanced therapy; CRP, C-reactive protein; SC; subcutaneous; IQR, interquartile range; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation; UC, ulcerative colitis.

Note: Ns for each parameter reflect non-missing values.
a Race = Multiple when more than one race is selected.
b Other includes countries Australia, Israel, Jordan and New Zealand.

Source: Data on file, 2025 (14)

A15. Priority question. CS, Document B, section B.3.3.2. Please provide the statistical analysis plan (SAP) for the ASTRO trial.

Company response: As requested, Johnson & Johnson have attached the statistical analysis plan for ASTRO as part of the response

A16. CS, Document B, section B.3.5.3. No ASTRO trial results are presented in the company submission for the maintenance phase. Please provide these results or clarify when they will become available.

Company response: The ASTRO maintenance outcomes (week 48 data) are not provided in this submission as they will only be available in October 2025.

Section B: Clarification on cost-effectiveness data

B1. Priority question. The draft SmPC does not make any reference to dose adjustment during the maintenance period. However, in the QUASAR Maintenance Study, participants meeting the criteria for loss of clinical response were eligible for a single dose adjustment. It is reported in the QUASAR CSR that 19 patients randomised to 100mg SC Q8W subsequently met loss of response criteria and received a dose adjustment to 200mg Q4W. Please explain whether or not the difference in approach to dose adjustments between the QUASAR Maintenance Study and the SmPC are reflected in the economic model. Please justify the approach taken to guselkumab dose adjustments in the economic analysis.

Company response: Relevant text from Section 4.2 of the draft summary of product characteristics (SmPC) for guselkumab is pasted below.

The recommended induction dose is 200 mg administered by intravenous infusion at Week 0, Week 4 and Week 8. After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered. (15)

There is, therefore, a binary choice upon completion of induction therapy, whereby patients may initiate on maintenance regimen of 100mg Q8W SC or 200mg Q4W SC. However, there is no provision for dose adjustment within maintenance therapy such that patients who lose response may increase from 100 mg Q8W to 200 mg Q4W dosing. Consequently, the economic analysis does not incorporate any dose adjustments for guselkumab.

The recommendations outlined in the in posology of the draft SmPC are based on robust clinical data derived from the QUASAR trial which was designed to assess the efficacy and safety of guselkumab in patients with moderately to severely active UC. Although the QUASAR maintenance trial did allow for 19 patients on guselkumab 100mg Q8W to receive guselkumab 200mg Q4W, the data supporting this dose escalation was not sufficiently extensive or conclusive to justify being included in the posology section. Additionally, the trial was not powered to assess and evaluate the differences between patients who received guselkumab 100mg SC Q8W and those who escalated from the 100mg dose to 200mg SC Q4W. Out of the patients that received dose adjustments, 11 of these patients (58%) achieved symptomatic response and 5 patients (26%) achieved symptomatic remission after 12 weeks.(8) The recaptured response for these patients are lower than for the overall population, and the very low number of patients precludes drawing any robust conclusions.

The decision tree for guselkumab maintenance dosing contrasts with the comparator treatments in the model, e.g. vedolizumab which would be set up as a 300 mg Q8W IV regimen in the base case. However, patients who experienced a decrease in their response may benefit from an increase in dosing frequency to intravenous vedolizumab 300 mg every 4 weeks based on Section 4.2 of the Entyvio SmPC, and this has been modelled in our submission, as well as previous appraisals in UC. (16)

B2. Priority question. CS, Document B, section B.4.2.1.3. The company submission states that "the proportion of responders are assumed to discontinue treatment at a constant rate during the maintenance phase" (p113). This constant discontinuation rate is derived from the combined probability of discontinuation before completing maintenance dosing at week

44. Please justify extending this same discontinuation rate from week 45 until the end of the model time horizon (10 years).

Company response: The cost comparison model was designed to reflect and consider clinical practice pragmatically whilst reducing unnecessary complexity. All-cause discontinuation was incorporated to accurately depict patients discontinuing treatment due to loss of efficacy or adverse events. This rate is derived from the week 44 time point from the QUASAR maintenance trial as longer-term data is unavailable from the trial to suggest any changes in the discontinuation rate over time.(8). Since the all-cause discontinuation rate applies uniformly to all treatments within the model, based on the assumption of similar efficacy, any potential changes in this rate are expected to have a minimal impact on overall outcomes. This approach is also consistent with the methods in the mirikizumab cost comparison NICE appraisal (TA925), where a constant discontinuation rate was modelled over a 10-year horizon.(4)

B3. Company Excel model. In the company model, extended induction costs are included in total induction costs for vedolizumab and mirikizumab, and in total maintenance costs for guselkumab. Although this does not affect overall costs, it makes it challenging to track patient movements through the model. Please justify the choice to include extended induction costs in different parts of the model trace depending on treatment.

Company response: In the model, extended induction and delayed responder costs are structured according to the dosing regimens and formulations specified in the SmPC for vedolizumab, mirikizumab, and the draft SmPC for guselkumab.(15-17) The dosing regimens for extended induction and delayed response assessment are detailed below:

- Mirikizumab extended induction: The SmPC for mirikizumab outlines a dosing regimen of 300 mg intravenously (IV) at weeks 12, 16, and 20.(17)
- Vedolizumab extended induction: Although the extended induction dosing for vedolizumab (300 mg IV at week 10) is mentioned under the Crohn's disease section of its SmPC, the model uses a consistent extended induction regimen in alignment with TA925, adhering to assumptions of equivalence.(4, 16)

- Guselkumab delayed response: The draft SmPC states consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment. (15) Therefore, delayed responders in the model receive 200 mg SC at weeks 12, 16, and 20, followed by response assessment at week 24.

Extended induction applies to mirikizumab and vedolizumab, as it is based on additional induction doses (300 mg IV for mirikizumab or 300 mg IV for vedolizumab) before the decision to initiate maintenance therapy. In the case of guselkumab (200 mg IV or 400 mg SC), there is no data available for extended induction. Rather, a 200 mg SC Q4W maintenance dosing regimen would be selected for inadequate responders to induction therapy at Week 12 and continued after a secondary assessment point at Week 24.

The additional doses during extended induction for mirikizumab and vedolizumab follow the same regimen and administration route as the induction phase therefore, their costs are included in the induction phase. In comparison, the extra doses for delayed responders on guselkumab are administered subcutaneously and follow the 200 mg maintenance regimen and thus are accounted for in the maintenance phase.

Section C: Textual clarification and additional points

C1. Some data provided for the QUASAR trial and which are marked as confidential appear to have been published by Rubin et al 2025 (Lancet 405:33-49). Please clarify which data should no longer be marked as confidential.

Company response: As requested, revised documents have been provided by Johnson and Johnson where data included in the Rubin et al, 2025 publication and Peyrin-Biroulet et al, 2025 oral presentation have been unmarked as confidential.(1, 8)

C2. CS, Document B, Figure 6. Please clarify whether the shading in Figure 6 should be blue or green.

Company response: The shading should be blue to reflect that the figure is considered confidential

C3. CS, Appendix, section D.1.9.1.2. Please provide footnotes to Table 7 in Appendix D.

Company response: The accompanying footnotes to Table 7 presented in section D.1.9.1.2 of the appendices have been provided below. (3)

Table 13: Characteristics of trials included in the NMA

Trial Name	NCT	Phase	Trial Design	Reference ID	Setting	Blinding	Funding Source	Trial Duration (weeks)	Tx Design	Trial Period	Treatment Arms	N randomised
QUASAR	NCT04033445	2b/3	RCT	CSR-IS-1, CSR-IS-2, CSR-MS, 491, 824	Multi-centre	Double-blind	Janssen Research and Development	12 (induction), 60[a] (maintenance)	RR	Induction study 1	Placebo	105
											Guselkumab 200mg Week 0, 4, 8	101
											Guselkumab 400mg Week 0, 4, 8	107
										Induction study 2	Placebo	280
											Guselkumab 200mg Week 0, 4, 8	421
										Maintenance	Placebo	190
											Guselkumab 200mg Q4W	190
											Guselkumab 100mg Q8W	188
		3	RCT		Multi-				RR	Induction	Placebo	149

Trial Name	NCT	Phase	Trial Design	Reference ID	Setting	Blinding	Funding Source	Trial Duration (weeks)	Tx Design	Trial Period	Treatment Arms	N randomised
GEMINI 1	NCT00783718			2610, 2072	centre	Double-blind	Millenium Pharmaceuticals	6 (induction), 52 (maintenance)			Vedolizumab 300mg Week 0, 2, 6	225
										Maintenance	Placebo	126
											Vedolizumab 300mg Q8W	122
LUCENT-1	NCT03518086	3	RCT	250, 121	Multi-centre	Double-blind	Eli Lilly	12 (induction)	RR	Induction	Placebo	294
											Mirikizumab 300mg Week 0, 4, 8	868
LUCENT-2	NCT03524092	3	RCT	250, 121	Multi-centre	Double-blind	Eli Lilly	12 (induction), 52[b] (maintenance)	RR	Maintenance	Placebo	179
											Mirikizumab 200mg Q4W	365
VISIBLE 1	NCT02611830	3	RCT	1367	Multi-centre	Double-blind	Takeda Development Centre	68	RR	Maintenance	Placebo	56
											Vedolizumab 108mg Q2W	106
											Vedolizumab 300mg Q8W	54

[a] Reported as week 44 in reference, calculated to represent the total period from initiation of treatment including 12-week induction.
[b] Reported as week 40 in reference, calculated to represent total period from initiation of treatment including 12-week induction.
Abbreviations: N = number; NCT = National Clinical Trial; NR = not reported; RCT = randomized controlled trial; RR = responder re-randomization; Tx = treatment; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks

C4. CS, Appendix, section I.1.1.2. Figure 15 in Appendix I.1.1.2 is labelled ‘Forest plot for random effects NMA of clinical response in the 1-year analysis, ADT-failure subgroup without delayed responders’. Please clarify that the outcome referred to in the title should be ‘clinical remission’ and not ‘clinical response’.

Company response: Johnson and Johnson apologise for the error and can confirm that the outcomes presented in Figure 15 in Appendix I, section 1.1.2 relates to clinical remission. (3)

C5. Please provide the documents for the following references:

i. CS, reference 100: Johnson & Johnson. [Data on file] Efficacy of guselkumab versus available biologic therapies for the maintenance treatment of moderate to severe ulcerative colitis: A systematic review and meta-analysis 2025.

ii. CS, Appendix, reference 94: Johnson & Johnson. [Data on File] A Systematic Literature Review of Economic Evidence for the Treatment of Moderately to Severely Active Ulcerative colitis. 2025.

Company response: As requested, Johnson & Johnson have attached the two references detailed above as part of the response.

Section D: Additional questions relating to NMA report provided by company for C5

- (CS, reference 100 (NMA report): Johnson & Johnson. [Data on file] Efficacy of guselkumab versus available biologic therapies for the maintenance treatment of moderate to severe ulcerative colitis: A systematic review and meta-analysis 2025)

For all requests that relate to providing the source of data values, if the values are from published sources (that is, rather than individual patient data) please provide sufficient information so that the EAG can verify the source (for example, a journal article reference and table number).

D1. Priority question. CS, reference 100 (NMA report), section L.1.3, Table L-6 (Table L 6. RR for conversion of mixed to subgroup for GEMINI 1):

a. **The footnotes to Table L-6 appear to be incorrect. Please clarify and provide the source for all values in this table.**

b. **For the estimation of maintenance response in GEMINI-1 patients who were induction non-responders, it seems that the company used values relating to the maintenance response for induction responders. Please confirm whether this is correct. If correct, please justify this approach with reference to the rules for generating subgroup data outlined in Section 5.1.5.2.2 of the NMA report.**

Company response:

a. Johnson & Johnson apologise for the error and Table L-6 from the original submission has been reproduced below as Table 14 with corrected information, sources and footnotes.

b. The maintenance response/remission among induction non-responders for subgroups of ADT-failure and ADT-non-failure in GEMINI-1 was estimated by converting the available maintenance response/remission among induction non-

responders from the mixed population data of GEMINI-1 via risk ratios (RR) of response/remission in ADT-failure versus ADT-non-failure subgroups (those shown in Table L-6). Although the mixed population data for GEMINI-1 was among the induction non-responders, indeed the RRs required to convert to subgroups were estimated among induction responders. This was because maintenance outcomes among induction non-responders by ADT-failure vs. ADT-non-failure subgroups was not available in GEMINI-1, nor other trials. The next best data available to estimate the RR was for the same maintenance outcomes but from the induction responder population of UNIFI for placebo (sourced from IPD on file, and as per TA633) and GEMINI-1 for vedolizumab arms (sourced from G-BA filing referenced in Table L-6, and as per TA633), under the assumption that the RRs for maintenance response/remission would not differ between induction responders and induction non-responders. Importantly, this assumption only applies to the RR used to convert the mixed population maintenance outcomes among induction non-responders to subgroup data – the outcome data used for the induction non-responder population of GEMINI-1 is fundamentally representing an induction non-responder population; only the RR to facilitate conversion to subgroups is estimated from induction responders.

With reference to the rules in Section 5.1.5.2.2 of the NMA report, this corresponds to the second bullet of “If subgroup data is not available for maintenance response/remission in induction non-responders/delayed responders: mixed data was converted to subgroup data based on the rules below.”. Then per the rules stated below that bullet, step number 1 is suitable for GEMINI-1’s vedolizumab Q4W arm, given the availability of data for the relevant treatment, timepoint, and dose from GEMINI-1 in Feagan 2017 (as referenced in Table L-6)(9). However, GEMINI-1 does not report the equivalent data for the treat-through placebo arm. Instead, we therefore relied on treat-through placebo data from UNIFI IPD on file, as per TA633; step number 3 in Section 5.1.5.2.2 of the NMA report.

Table L-6 shows the estimation of the RRs, while Table L-7 shows the maintenance response/remission among induction non-responder data for mixed and then for converted-to subgroup data (using those RRs). The updated sources and

descriptions in Table L-7 included in our response to Priority Question D2, can also clarify the methods further.

Table 14: Estimation of RR for conversion of mixed to subgroup for GEMINI 1

Population	Treatment	Response	Remission	Description
ADT non-failure	Placebo	47.4%[a]	26.3%[a]	Maintenance response in non responders
ADT-failure	Placebo	43.5% [a]	13% [a]	Maintenance response in non responders
RR (non fail vs fail)	-	43.5% / 47.4% = 0.918	13% / 26.3% = 0.494	Maintenance response in non responders
ADT non-failure	Vedolizumab Q4W	56.2%[b]	47.9%[b]	Maintenance response in non responders
ADT-failure	Vedolizumab Q4W	42.5%[b]	35%[b]	Maintenance response in non responders
RR (non fail vs fail)	-	42.5% / 56.2% = 0.756	35% / 47.9% = 0.731	Maintenance response in non responders

Sources: [a] UNIFI IPD end of maintenance in PBO induction responders; [b]GEMINI end of maintenance VDZ Q4W induction responders 2072-Feagan-2017 Supplementary table 2 durable clinical response (response), clinical remission (assumes all remission at maintenance were remission at induction).

Notes: VDZ Q4W RR used for both doses

D2. Priority question. CS, reference 100 (NMA report), section L.1.3, Table L-7 (Conversion of mixed to subgroup for GEMINI 1). The EAG cannot locate the values provided in this table in the source referenced. Please reproduce the table below and provide the source of all values (except for those shaded in blue in the last column).

Johnson & Johnson apologise for the error and have reproduced Table L-7 from the NMA report below (Table 15) with corrected and clarified sources.

Table 15. Conversion of mixed population to the ADT-failure population for GEMINI 1(updated in response to Priority Question D1)

Treatment	Population	Outcome	N	% split	Outcome in mixed population (%)	Outcome in subgroup (%)
Placebo	ADT non-failure	Response in induction non responders	56 [a]	52.8	7 / 82 * 100 = 8.54 [b]	8.88 [c]
Placebo	ADT failure	Response in induction non responders	50 [a]	47.2		8.15 [c]
Placebo	ADT non-failure	Remission in induction non responders	56 [a]	52.8	4 / 82 * 100 = 5.88 [b]	6.40 [c]
Placebo	ADT failure	Remission in induction non responders	50 [a]	47.2		3.17 [c]
Vedolizumab Q4W	ADT non-failure	Response in induction non responders	61 [a]	47	93 / 322 * 100 = 28.88 [b]	32.44 [c]
Vedolizumab Q4W	ADT failure	Response in induction non responders	50 [a]	61		24.53 [c]
Vedolizumab Q4W	ADT non-failure	Remission in induction non responders	61 [a]	47	52 / 322 * 100 = 16.15 [b]	18.38 [c]
Vedolizumab Q4W	ADT failure	Remission in induction non responders	50 [a]	61		13.43 [c]

Values in blue have been imputed

Sources: [a] 2072-Feagan-2017, Table 2 reporting number of induction responders, from which to back-calculate induction non-responders. [b] https://www.g-ba.de/downloads/92-975-565/2014-07-10_Modul4A_Vedolizumab.pdf, Table 4-38

reporting response and remission at week 52 among induction non-responders. [c] Converted from mixed % using RRs reported in Table L-6 and formulas reported in Section 5.1.5.2.2 of NMA report.

NB: The EAG highlights that '% splits' for the outcomes "response in vedolizumab Q4W induction non-responders" and "remission in vedolizumab Q4W induction non responders" add up to 108%.

Company response: Johnson & Johnson apologises for the typographical error, the calculation of % split should read as 61/(61+50) = 54.95% for the ADT non-failure population and 50/(61+50)= 45.05% for the ADT failure population. It should be noted that, although these calculations were presented inaccurately in the table, Johnson & Johnson can confirm that the correct values were used in the NMA analyses. The table has been reproduced with the correct values as part of the response to the question below (Table 1).

The EAG considers that it should be true that when you multiply the outcome in each subgroup by the '% split', and then add these values together, you would obtain the outcome in the mixed population. This holds true for "response in placebo induction non-responders", that is, (0.528*8.88) + (0.472*8.15) = 8.54. However, it does not hold true for "remission in placebo induction non-responders", or for "response/remission in vedolizumab Q4W induction non-responders". Please clarify why this is the case.

Company response: Johnson & Johnson agrees with the rationale and confirm that the calculations do not hold true due to transcription errors. The correct calculations should be:

- **Induction remission placebo:** (0.528*8.88) + (0.472*8.15) = 8.54
- **Induction remission placebo:** (0.528*6.40) + (0.472*3.17) = 4.88
- **Induction response vedolizumab:** (0.5495*32.44) + (0.4505*24.53) = 28.88
- **Induction remission vedolizumab:** (0.5495*18.38) + (0.4505*13.43) = 16.15

We confirm that although the incorrect values were presented in Table L-7, the correct values were used in the NMA analyses. Table L-7 has been reproduced as Table 1 with the corrected calculations.

Table 1. Reproduced Table L-7, conversion of the mixed population to subgroups for GEMINI 1, with corrected transcription errors

Treatment	Population	Outcome	N	% split	Outcome in mixed population (%)	Outcome in subgroup (%)
Placebo	ADT non-failure	Response in induction non responders	56	52.8	8.54	8.88
Placebo	ADT failure	Response in induction non responders	50	47.2		8.15
Placebo	ADT non-failure	Remission in induction non responders	56	52.8	4.88	6.40
Placebo	ADT failure	Remission in induction non responders	50	47.2		3.17
Vedolizumab Q4W	ADT non-failure	Response in induction non responders	61	54.95	28.88	32.44
Vedolizumab Q4W	ADT failure	Response in induction non responders	50	45.05		24.53
Vedolizumab Q4W	ADT non-failure	Remission in induction non responders	61	54.95	16.15	18.38
Vedolizumab Q4W	ADT failure	Remission in induction non responders	50	45.05		13.43

Note: Values in blue have been imputed
Sources: https://www.g-ba.de/downloads/92-975-565/2014-07-10_Modul4A_Vedolizumab.pdf tables 4-27and 4-28

D3. Priority question. CS, reference 100 (NMA report), section L.2.1, Table L-28 (Re-calculation of ITT sample size for VISIBLE 1). Please clarify the source of data values in the column "Maintenance N (re-randomized induction responders)".

Company response: An updated version of Table L-28 has been provided below with the description of the location of the relevant data within the Sandborn et al. 2020 publication presented in the footnotes.

Table 2. Reproduced Table L-28, re-calculation of ITT sample size for VISIBLE 1, with sources

Treatment Sequence	Population	Induction ITT (N)	Proportion in subgroup in RR portion of trial	Maintenance N (re-randomized induction responders)	% maintenance N of the total re-randomized	Re-calculated ITT N for treatment sequence
Vedolizumab IV 400mg to vedolizumab 108mg Q2W	ADT non-failure	383	1 – (84/216)[a] = 61.1%	67[b]	67 / 136 = 49.26%	49.26% X 61.1% X 383 = 115.3
Vedolizumab IV 400mg to vedolizumab 108mg Q8W	ADT non-failure			32[c]	32 / 136 = 23.53%	23.53% X 61.1% X 383 = 55.1
Vedolizumab IV 400mg to placebo	ADT non-failure			37[b]	NA	NA
Total	NA		NA	136[d]	NA	NA
Vedolizumab IV 400mg to vedolizumab 108mg Q2W	ADT-failure		84 / 216[a] = 38.9%	39[b]	39 / 80 = 48.75%	48.75% X 38.9% X 383 = 72.6
Vedolizumab IV 400mg to vedolizumab 108mg Q8W	ADT-failure			22[c]	22 / 80 = 27.5%	27.5% X 38.9% X 383 = 40.9
Vedolizumab IV 400mg to placebo	ADT-failure			19[b]		
Total	NA		NA	80[d]	NA	NA

Percentages are rounded for display however, re-calculated Ns were calculated without rounding during intermediary steps.
Sources: Sandborn, 2020, [a] Sandborn, 2020 – Table 1, [b] Sandborn, 2020 – Supplementary Figure 2, [c] Sandborn, 2020, [d] Sandborn, 2020 – Figure 2.

D4. Priority question. CS, reference 100 (NMA report), section L.2.4, Table L-30 (Clinical Response Imputations for VISIBLE 1). Please clarify the reason for including this table , given that the VISIBLE-1 trial was not included in the 1-year NMA for clinical response.

Company response: Johnson & Johnson can confirm that data from VISIBLE-1 is not included in the 1-year NMA for clinical response as the relevant subgroup data were unavailable. The table was included in error and is relevant for the broader NMA that was conducted outside of the UK decision problem.

D5. Priority question. CS, reference 100 (NMA report), section L.3.1, Table L-46 (Re-calculation of ITT sample size for QUASAR). Please clarify why values in the column "Maintenance N (re-randomized induction responders)" sum to 334. The number of re-randomized induction responders in the QUASAR maintenance trial was 568.

Company response: The one-year maintenance NMAs consider patients that responded to the guselkumab 200mg IV induction dose only; therefore, the number of re-randomised induction responders sums to 334. Patients that responded to the guselkumab 400mg IV dose in the QUASAR Phase IIb dose ranging study were excluded from the analysis since the 400mg IV dose is not being considered by the Medicines and Healthcare products Regulatory Agency (MHRA) and will not be included in the anticipated marketing authorisation. Excluding these patients ensured that the relative efficacy of guselkumab to vedolizumab and risankizumab was based on the expected treatment sequence in clinical practice of guselkumab 200mg IV → guselkumab 100mg SC Q8W or guselkumab 200mg IV → guselkumab 200mg SC Q4W. The induction NMAs included the guselkumab 400mg IV dose for completeness, given the QUASAR Phase IIb induction trial design, without any expected impact to estimated relative treatment effects given the structure of the network.

D6. Priority question. CS, reference 100 (NMA report), section L.3.4, Table L-47 (Clinical Response Imputations for QUASAR):

a) Please clarify why the values in the column "Maintenance response in induction responders)" for the ADT-failure population do not match the values provided in Table 29 of the company submission (Document B, section B.3.5.2.5).

Company response: Johnson & Johnson confirms that the difference in values reported is due to the exclusion of the 400mg IV dose responders. As discussed in question D5, the maintenance NMAs include patients that responded to the 200mg IV dose only, in line with anticipated marketing authorisation and use in clinical practice.

b) Please clarify which (if any) values were imputed from the GEMINI-1 trial (as per footnote b).

Company response: The placebo maintenance response in induction non-responders (D) is imputed utilizing GEMINI-1 (per footnote b) and is incorrectly labelled as coming from ACT-1 (per footnote a) currently. Please find the updated table below as Table 3, with the imputed values highlighted in orange

Table 3. Reproduced Table L-47, clinical response imputations for QUASAR

Treatment arm	Population	Induction responders (%) (A)	Induction non-responders (%) (B)	Responder at intermediate time point of induction non-responders (%) (B2)	Maintenance Response in induction responders (%) (C)	Maintenance response in induction non-responders (PBO) or delayed responders (GUS) (%) (D)	1 year % induction responders (A X C)	1 year % induction non-responders PBO: (B X D) GUS: (B X B2 X D)	1 year Total % induction responders + % induction non-responders	n*	N
Placebo	ADT non-failure	33.84	66.16	-	66.67	7.89[a]	22.56	5.22	27.78	55	198
Guselkumab 100mg Q8W	ADT non-failure	70.52	29.48	60.66	86.15	72.5	60.76	12.96	73.72	65	88.4
Guselkumab 200mg Q4W	ADT non-failure	70.52	29.48	60.66	83.87	72.5	59.15	12.96	72.11	61	84.3
Placebo	ADT-failure	21.39	78.61	-	51.11	8.15[b]	10.93	6.41	17.34	32	187
Guselkumab 100mg Q8W	ADT-failure	51.97	48.03	51.06	71.74	77.05	37.28	18.90	56.18	48	85.3
Guselkumab 200mg Q4W	ADT-failure	51.97	48.03	51.06	63.27	77.05	32.88	18.9	51.78	47	90.8

Values in orange have been imputed. Individual cells are rounded for display but only final values were rounded in the NMA. n* calculated from unrounded values and used for NMA.
Sources: QUASAR IPD; [a]Imputed from ACT 1 IPD; [b]Imputed from GEMINI 1 per Table L-7

c) For the column "Maintenance response in induction non-responders (PBO) or delayed responders (GUS)", please provide the source of values (except those shaded in blue). The EAG highlights that the response rate provided in the QUASAR maintenance study CSR (page 1059) for the mixed population of delayed responders to guselkumab is lower than both the rates provided for ADT-failure and ADT-non-failure subgroups reported in this table.

Company response: Johnson & Johnson confirms that the values used in the "Maintenance response in induction non-responders (PBO) or delayed responders (GUS)" are derived from QUASAR IPD. There are differences compared to the data in the CSR as patients that responded to the guselkumab 400mg IV induction dose were excluded from the 1-year maintenance analyses to align with the anticipated marketing authorisation and use in clinical practice (as discussed in the response to question D5).

D7. Priority question. CS, reference 100 (NMA report), section L.3.4, Table L-48 (Clinical Remission Imputations for QUASAR). Please clarify why values in the column "Maintenance response in induction responders)" for the ADT-failure population do not match values provided in Table 25 of the company submission (Document B, section B.3.5.2.1).

Company response: Johnson & Johnson confirms that the values used in the "maintenance response in induction responders" for the ADT-failure population are based on the guselkumab 200mg IV induction dose responders only (as discussed in the response to question D5).

D8. Priority question. CS, reference 100 (NMA report), section L.3.4, Table L-47 and Table L-48. As the company calculates "1 year % induction non-responders" as follows: B X B2 X D, it seems to the EAG that the company is assuming that if patients do not respond at initial guselkumab induction, or experience a delayed response at the intermediate timepoint, then they will not

have a response at the maintenance time point. Please clarify whether this interpretation is correct. If so, please justify this approach.

Company response: Johnson & Johnson confirms that the interpretation of the EAG regarding induction non-responders is correct. The objective of our normalisation process is to impute 1-year, end of maintenance outcomes among the full set of patients randomised at induction, as a treat-through study (i.e., regardless of their response status at the end of induction). However, there often lacks data to support the imputation of outcomes among induction non-responders for example, the subset of patients that is innately missing from re-randomised trials like QUASAR. Where there is a lack of data to support the imputation of induction non-responders, we sought to, at the minimum, impute among induction non-responders that had a delayed response by a certain timepoint, if that data was available. This was the approach taken for the guselkumab arms in the QUASAR trial, where we leveraged available data for induction delayed responder data by week 24. The assumption is that induction non-responders who did not obtain a response by the delayed response timepoint of 24 weeks would not achieve response or remission by the end of maintenance for our 1-year NMAs. We believe this assumption to be reasonable and applicable in clinical practice as the draft SmPC for guselkumab includes a recommendation to consider discontinuing treatment in patients who have shown no evidence of therapeutic benefit after 24 weeks of treatment.(1) A similar recommendation of discontinuing at week 24 is also included in the SmPC for mirikizumab.(2)

Finally, the assumption that these patients are not expected to achieve response or remission in the maintenance phase leads to a conservative estimate, where imputing values other than zero (without evidence) may increase response or remission rates of guselkumab relative to placebo. It should be noted that the same approach was adopted for LUCENT-2 and is applied consistently across the studies included in the NMAs.

D9. Priority question. CS, reference 100 (NMA report), section L.4.3, Table L-53 (Conversion of mixed to subgroup for LUCENT-2). Please clarify how the outcome in each subgroup has been calculated using the % split and the outcome in the mixed population.

Company response: Johnson & Johnson can confirm that Table L-53 contained transcription errors, and the table has been reproduced below as Table 4 with the appropriate corrections**.** The % splits were presented in the reverse order for the subgroup populations, and the proportion of patients considered ADT non-failure should be 64.93% as opposed to 64.25%. We confirm that the correct values have been used in the NMAs and therefore these transcription errors do not impact the NMA outcomes.

Table 4. Reproduced Table L-53, conversion of the mixed population to subgroups for LUCENT-2, with corrected transcription errors

Treatment	Population	Outcome	N	% split	Outcome in mixed population (%)	Outcome in subgroup (%)
Mirikizumab	ADT-failure	clinical response - delayed induction	128	35.07	53.7[a]	45.34
Mirikizumab	ADT non-failure	clinical response - delayed induction	237	64.93		58.21
Mirikizumab	ADT-failure	clinical response - maintenance - delayed responders	128	35.07	72.2[a]	64.22
Mirikizumab	ADT non-failure	clinical response - maintenance - delayed responders	237	64.93		76.51
Mirikizumab	ADT-failure	clinical remission - maintenance - delayed responders	128	35.07	36.1[a]	33.55
Mirikizumab	ADT non-failure	clinical remission - maintenance - delayed responders	237	64.93		37.48
Values in blue have been imputed						

Sources: Navabi, 2023; [a]https://www.ema.europa.eu/en/documents/product-information/omvoh-epar-product-information_en.pdf

References

1. Peyrin-Biroulet L, Allegretti JR, Danese S, Germinaro M, Baker T, Alvarez Y, et al. OP10 Efficacy and safety of subcutaneous guselkumab induction therapy in patients with Ulcerative Colitis: Results through week 12 from the phase 3 ASTRO study. Journal of Crohn's and Colitis. 2025;19(Supplement_1):i19-i20.
2. Johnson & Johnson. [Data on file] ASTRO clinical protocol overview. RF-4512602025.
3. Johnson & Johnson. Efficacy of guselkumab versus available biologic therapies for the maintenance treatment of moderate to severe ulcerative colitis: A systematic review and meta-analysis 2025.
4. National Institute for Health and Care Excellence. [TA925] Mirikizumab for treating moderately to severely active ulcerative colitis. 2023 [Available from: https://www.nice.org.uk/guidance/ta925].
5. National Institute for Health and Care Excellence. [TA342] Vedolizumab for treating moderately to severely active ulcerative colitis. 2015 [Available from: https://www.nice.org.uk/guidance/ta342].
6. Johnson & Johnson. [Data on file] Safety NMAs. RF-4562742025.
7. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials 2011 [Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf.
8. Rubin DT, Allegretti JR, Panes J, Shipitofsky N, Yarandi SS, Huang KG, et al. Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR): phase 3 double-blind, randomised, placebo-controlled induction and maintenance studies. Lancet. 2025;405(10472):33-49.
9. Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S, et al. Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists. Clin Gastroenterol Hepatol. 2017;15(2):229-39 e5.
10. D'Haens G, Dubinsky M, Kobayashi T, Irving PM, Howaldt S, Pokrotnieks J, et al. Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis. NEJM. 2023;388(26):2444-55.
11. Travis SPL, Higgins PDR, Orchard T, Van Der Woude CJ, Panaccione R, Bitton A, et al. Review article: defining remission in ulcerative colitis. Alimentary Pharmacology & Therapeutics. 2011;34(2):113-24.
12. Johnson & Johnson. [Data on file] QUASAR IS1 ADT-failure characteristics. RF-4562482025.
13. Janssen Research and Development. Clinical Study Report: QUASAR (Maintenance Study) - A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis 2024.
14. Johnson & Johnson. [Data on file] ASTRO ADT-IR characteristics. RF-4562992025.

15. Janssen-Cilag Ltd (a Johnson & Johnson Company). Tremfya: Summary of Product Characteristics (draft). 2025.
16. Takeda Pharma A/S. Entyvio: Summary of Product Characteristics. 2014 [Available from: https://www.medicines.org.uk/emc/product/5442/smpc.
17. Eli Lilly Nederland B.V. Omvoh: Summary of Product Characteristics. 2024 [Available from: https://www.medicines.org.uk/emc/product/14881/smpc.

1. Janssen-Cilag Ltd (a Johnson & Johnson Company). Tremfya: Summary of Product Characteristics (draft). 2025.
2. Eli Lilly Nederland B.V. Omvoh: Summary of Product Characteristics. 2024 [Available from: https://www.medicines.org.uk/emc/product/14881/smpc.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]

NICE medicines optimisation briefing

July 2024

Key issues

- The specific licensed indication for guselkumab in ulcerative colitis is not yet known, nor is it yet known where the marketing authorisation holder will position it in the treatment pathway.
- The most likely comparators for a cost comparison would be other monoclonal antibodies which have a similar mechanism of action (mirikizumab and ustekinumab), but evidence from system intelligence demonstrates that other classes of medicines may also be used at the same point in the pathway as these.
- Administration route (intravenous [IV], subcutaneous or oral) and adverse effects may influence treatment choice.
- The patent for ustekinumab is nearing expiry. This may affect the comparative cost-effectiveness of guselkumab if biosimilars becomes available.

Technology overview

Guselkumab is a recombinant human monoclonal antibody that selectively binds to interleukin-23 (IL-23), a cytokine involved in inflammatory and immune responses. Blocking IL-23 reduces inflammation in several immune-related disorders (SPC).

Guselkumab is currently licensed in the UK for treating:

- moderate to severe plaque psoriasis in adults
- active psoriatic arthritis in adults whose condition has responded inadequately to a prior disease-modifying antirheumatic drug (DMARD), or who have not tolerated a DMARD (SPC).

NICE has made optimised recommendations in relation to its use in these indications (TA521 and TA815 respectively).

Guselkumab has been studied in clinical trials in adults with moderately to severely active ulcerative colitis whose condition has responded inadequately to, or has lost response to, conventional or biologic treatment or a Janus Kinase (JAK) inhibitor (tofacitinib), or in whom these have not been tolerated. Guselkumab is also currently being assessed by NICE for previously treated moderately to severely active Crohn's disease (ID6238).

Context

Ulcerative colitis is a long-term condition in which parts of the large bowel become inflamed, causing urgent bloody diarrhoea, abdominal pain and other symptoms. For treating moderately to severely active ulcerative colitis, NICE has assessed:

- 3 TNF-alpha inhibitors: adalimumab, golimumab and infliximab (TA329).
- 3 monoclonal antibodies: mirikizumab (TA925), ustekinumab (TA633) and vedolizumab (TA342).
- 3 JAK inhibitors: upadacitinib (TA856), filgotinib (TA792) and tofacitinib (TA547).
- 2 sphingosine-1-phosphate (S1P) receptor modulators: etrasimod (TA956) and ozanimod (TA828).

NICE is also assessing another monoclonal antibody for treating moderately to severely active ulcerative colitis, risankizumab (ID6209), and may assess another TNF-alpha inhibitor, etrolizumab (ID3827]).

Table 1: Characteristics of guselkumab compared with other medicines used for treating moderately to severely active ulcerative colitis in adults at a similar point in the treatment pathway

	Guselkumab	Mirikizumab and Ustekinumab	Vedolizumab	Adalimumab, golimumab and infliximab	Filgotinib, tofacitinib and upadacitinib	Etrasimod and ozanimod
Mechanism of action	Monoclonal antibody (IL-23 inhibitor)	Monoclonal antibodies: (mirikizumab: IL-23 inhibitor; ustekinumab: IL-12 and IL-23 inhibitor)	Monoclonal antibody (αlpha-4-beta-7 integrin blocker)	TNF-alpha inhibitors	JAK inhibitors	S1P receptor modulators
Indication	Moderate to severely active ulcerative colitis with inadequate response, lost response, or intolerance to conventional or biologic treatment or a JAK inhibitor (details to be confirmed when marketing authorisation is granted)	Moderately to severely active ulcerative colitis with an inadequate response, lost response, intolerance to conventional therapy or a biologic agent. (Mirikizumab SPC) (Ustekinumab SPC)	Moderately to severely active ulcerative colitis with an inadequate response, lost response or intolerance to conventional therapy or a TNF-alpha inhibitor (Vedolizumab SPC)	Moderately to severely active ulcerative colitis with an inadequate response intolerance or contraindication to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine. (Adalimumab SPC) (Golimumab SPC) (Infliximab SPC)	Moderately to severely active ulcerative colitis with an inadequate response, lost response or intolerance to conventional therapy or a biologic agent. (Filgotinib SPC) (Tofacitinib SPC) (Upadacitinib SPC)	Moderately to severely active ulcerative colitis with an inadequate response, lost response, or intolerance to conventional therapy or a biologic agent. (Etrasimod SPC) (Ozanimod SPC)
Technology appraisal	Not applicable	Moderately to severely active ulcerative colitis when conventional	Moderately to severely active ulcerative colitis, within its marketing	Moderately to severely active ulcerative colitis within their	Moderately to severely active ulcerative colitis within their	**Etrasimod**: Moderately to severely active ulcerative colitis

recommendation		or biological treatment cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if: a TNF-alpha inhibitor has not worked cannot be tolerated or is not suitable (TA925, TA633)	authorisation (TA342)	marketing authorisations if the disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or these cannot be tolerated or are contraindicated (TA329)	marketing authorisations when conventional or biological treatment cannot be tolerated, or the disease has responded inadequately or lost response to treatment (TA792, TA547)	within its marketing authorisation when conventional or biological treatments cannot be tolerated or the condition has not responded well enough, or lost response to treatment. (TA956). **Ozanimod**: Moderately to severely active ulcerative colitis only if conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable, or biological treatment cannot be tolerated or is not working well enough (TA828)
Dosage and route of administration	Dosage and route to be confirmed when the marketing authorisation is granted	**Mirikizumab** 300 mg IV infusion at weeks 0, 4, and 8 (can be extended for a further 12 weeks), then	**Vedolizumab**: 300 mg IV infusion at weeks 0 and 2, then either 300 mg by IV infusion at week 6 repeated	**Adalimumab:** 160 mg by SC injection at week 0 and 80 mg at week 2, then 40 mg every	**Filgotinib:** 200 mg orally once daily for 10 weeks, then maintenance 200 mg once daily (100 mg in age 65 –	**Etrasimod:** 2 mg orally once daily. **Ozanimod** – 0.23 mg orally once daily on days 1–4, then 0.46 mg orally

		200 mg by SC injection every 4 weeks. **Ustekinumab:** 260 mg (≤55 kg), 390 mg (>55 to ≤85 kg) or 520 mg (>85 kg) as a single IV dose, then 90 mg by SC injection every 8 to 12 weeks	every 8 weeks, or 108 mg by SC injection at week 6 repeated every 2 weeks	2 weeks (increased if needed to 40 mg weekly or 80 mg every 2 weeks). **Golimumab**: 200 mg by SC injection at week 0 and 100 mg at week 2, then 50 mg to 100 mg every 4 weeks. **Infliximab:** 5 mg/kg (IV infusion) at weeks 0 and 2, followed by either 5 mg/kg IV infusion at week 6 then every 8 weeks, or 120 mg SC injection at week 6 then every 2 weeks	74 years or with certain risk factors). **Tofacitinib:** 10 mg orally twice daily for 8 weeks (can be extended for a further 8 weeks), then 5 mg twice daily. **Upadacitinib:** 45 mg once daily orally for 12 weeks (can be extended for a further 8 weeks), then 15mg or 30 mg once daily orally	once daily on days 5–7, then 0.92 mg orally once daily from day 8 onwards
Resource impact	Dosage and route to be confirmed when marketing authorisation is granted.	IV treatment: invasive, higher service delivery costs than oral or SC treatments (clinic costs, health professional time) SC treatment: lower service delivery costs than IV (delivered by homecare, can be	IV treatment: invasive, higher service delivery costs than oral or SC treatments (clinic costs, health professional time) SC treatment: lower service delivery costs than IV (delivered by homecare, can be	IV invasive, higher service delivery costs than oral or SC treatments (clinic costs, health professional time) SC treatment: lower service delivery costs than IV (delivered by homecare, can be self-administered	Oral treatment: convenient, non-invasive, lower service delivery costs than injections	Oral treatment: convenient, non-invasive, lower service delivery costs than injections

		self-administered at home after training)	self-administered at home after training)	at home after training)		
Abbreviations: IV, intravenous; SC, subcutaneous						

Current practice

Medicines for treating moderately to severely active ulcerative colitis in adults are commissioned by integrated care boards.

System intelligence indicates that local treatment pathways for initial management follow the NICE guideline on the management of ulcerative colitis (CG130), which recommends treatment according to disease presentation and severity. Conventional treatment to induce remission include topical or oral aminosalicylates, topical, oral or IV corticosteroids and IV ciclosporin. To maintain remission, conventional treatments include topical or oral aminosalicylates, azathioprine and mercaptopurine. For moderately to severely active disease the guideline directs users to the NICE technology appraisals.

Further system intelligence suggests that prescribing practice follows 3 or 4 treatment choices for moderately to severely active ulcerative colitis. Typically, TNF-alpha inhibitors are used first line. Adalimumab and infliximab are licensed as subcutaneous injections for maintenance therapy, and golimumab is given by subcutaneous injection only; adalimumab is available as biosimilar Subcutaneous formulations can be delivered by homecare services and self-administered at home. Infliximab is also licensed as an infusion (also available as a biosimilar) which, when administered in specialist settings, is likely to increase service delivery costs (clinic costs and healthcare professionals' time).

Other treatments with a different mode of action from the TNF-alpha inhibitors are used in practice if TNF-alpha inhibitors are not effective, or if they are contraindicated or not tolerated. This is usually the lowest cost clinically appropriate alternative, but in practice there is variation between centres in order of treatment used. System intelligence suggests monoclonal antibodies are used second or third line in practice. There is an expectation that guselkumab will likely sit as an option at this

point in the pathway, alongside mirikizumab and ustekinumab, as well as other treatments with a different mode of action.

The treatment pathways for moderately to severely active ulcerative colitis have changed as newer treatments have been recommended by NICE. From system intelligence, the main uncertainty identified for guselkumab use was the effectiveness, cost and cost-effectiveness of the medicine compared, , to other monoclonal antibodies with a similar mechanism of action (mirikizumab and ustekinumab), and less costly biosimilars for other treatments. The patent for ustekinumab is nearing expiry. This may affect the comparative cost-effectiveness of guselkumab if a biosimilar becomes available.

Patient centred factors

Most treatments used for moderately to severely active ulcerative colitis are initiated with IV infusions, followed by maintenance therapy with IV or subcutaneous injection. This requires attendance at clinics (for IV therapy) or home visits by the care team (for subcutaneous therapy if not self-administering), or training for the individual or carer to give subcutaneous injections at home. However, the JAK inhibitors (filgotinib, tofacitinib and upadacitinib) and the S1P receptor modulators (etrasimod and ozanimod) are oral medicines. Some people may prefer oral therapy, particularly if they have dexterity problems, needle phobia, or problems travelling to clinic. JAK inhibitors should be avoided (unless there are no suitable alternatives) in people aged 65 years or older, with current or past long-time smoking, or other risk factors for cardiovascular disease or malignancy (MHRA Drug Safety Update, April 2023).

Health inequalities

Ulcerative colitis usually develops in people between 15 and 25 years, with a second peak between 55 and 65 years, but can develop at any age. It is most common in Black people and Caucasian people of European descent and is less frequent in people from Asian

communities. There is an equal split in prevalence between men and women, although women with ulcerative colitis are at greater risk of relapse. Although not identified by name as a disability, people who have ulcerative colitis may be defined as disabled (under the Equality Act 2010) if the condition has a substantial and long-term adverse effect on their ability to carry out normal day-to-day activities.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]

Patient Organisation Submission

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Crohn's & Colitis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's & Colitis UK is the UK's leading charity for everyone affected by Crohn's and Colitis. We're working to improve diagnosis and treatment, and to fund research into a cure; to raise awareness and to give people hope, comfort, and confidence to live freer, fuller lives. We want: • To drive world-class research that improves lives today and brings us closer to a world free from Crohn's and Colitis tomorrow • Everyone to understand Crohn's and Colitis • To support and empower everyone to manage their conditions • To drive high-quality and sustainable clinical care • Early and accurate diagnosis for all. Founded as a patients' association in 1979, we now have nearly 48,000 members across the UK. Our members include people living with the conditions, their families and friends, health professionals and others who support our work. We have 50 Local Networks which arrange educational meetings, generate publicity and organise fundraising. Funding is through membership subscriptions and a wide range of fundraising activities, including events, grants, legacies and corporate partnerships. Full details are available in our annual accounts Crohn's & Colitis UK's annual reports and accounts (crohnsandColitis.org.uk)

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	In the last 12 months we received a total of £50,000 from Janssen. £40,000 was for our evidence and insight dashboard and £10,000 went towards patient education. For context, our total income in 2023 was £7.7m.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; and • research - our own and that of external organisations.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The symptoms of Ulcerative Colitis, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships.[1] [2] *"Life with UC has been difficult, as I was constantly ill over a period of years, I had my relationship break down. I have been lucky that my previous line manager at work had a daughter of his own who suffered from UC, so any hospital stays weren't a problem and he allowed me to work from home on particularly bad days."* **Quote from a person living with Ulcerative Colitis.** Given that disease severity is wide-ranging, and while each person has their own individual experience, we would like to take this opportunity to describe the impact and experience of the specific cohort of patients with moderate to severe Ulcerative Colitis that this guidance is targeting. This cohort is likely to comprise of patients with Ulcerative Colitis who experience more severe flares, weight loss, fever and constitutional symptoms, and whose disease has not responded to or are unable to tolerate other treatments, and/or can benefit from this treatment in particular. For this subgroup of patients with moderate to severe Ulcerative Colitis, the condition is more than challenging, but frequently overwhelming and detrimentally life-altering, as described below: *"I had 3 blood transfusions, multiple steroids, sleepless drained nights, cannula paracetamol, Iron deficiency, stomach ulcers and multiple drugs and many blood tests, not being able to eat and losing a huge amount of weight over 2 and a half stone in just 2 weeks wasn't expected out the blue in my life."* **Quote from a person living with Ulcerative Colitis.** **Mortality** There are risks and mortality associated with untreated and uncontrolled disease. NICE Guideline on Ulcerative Colitis states: 'Ulcerative Colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled'.[3] This is echoed by BSG Guidelines that state that 'acute severe Colitis is a potentially life-threatening condition'.[4]

	Acute severe Colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy).[5] 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.[6] When a flare occurs in acute severe Colitis, deterioration can occur rapidly. Patients will require close monitoring and review by appropriate specialists. It's also vitally important to make decisions quickly to avoid severe complications. The very real risks associated with acute severe Colitis include: • Life-threatening haemorrhage • Toxic megacolon - can occur in up to 1 in 40 people with Colitis [7] • Perforation of the bowel [8] 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 [9] • Anaemia [10] • Increased risk of cancer [11] **Impact on emotional and mental health**

[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) Guideline on Ulcerative Colitis: Management: Overview | Ulcerative Colitis: management | Guidance | NICE
[4] The British Society of Gastroenterology (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://gut.bmj.com/content/60/5/571.long
[5] Ibid
[6] Ibid
[7] Parray, F. Q. et al. (2012). Ulcerative Colitis: a challenge to surgeons. Int. J. Prev. Med. 3, 749–63.
[8] IBDUK (2019) IBD Standards 2019: Homepage | IBD UK
[9] Mowat C, Cole A, Windsor A et al. (2011) Guidelines for the management of inflammatory bowel disease in adults. Gut, 60, 571-607.
[10] Crohn's and Colitis Foundation.(2020) Anaemia. https://www.crohnscolitisfoundation.org/sites/default/files/2020-03/anemia.pdf
[11] 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

	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.[12] Stigma and lack of wider understanding of the condition exacerbate the impact. Anxiety and depression are higher in people with IBD, with mood disorders at least in part a consequence of the IBD itself and its medical treatment (e.g., corticosteroid therapy), surgery, including specifically colectomy and stoma formation.[13] Additionally, most reports indicate that stress may be involved in triggering relapse. "*The last 9 months have been really quite horrible for me dealing with my UC and I went through a really low point in my life, feeling very anxious and depressed. I took 5 months off work and only recently started a new job. My UC really affected my social life and confidence especially with getting out of the house and carrying out simple tasks."* **Quote from a person living with Ulcerative Colitis.** "*The isolation I have felt has been overwhelming. I can't take my children to the park, for a walk or play date or any of the other simple things that I used to take for granted. I do not have any kind of social life myself as it is simply not possible for me to go out when I may need to open my bowels with no warning."* **Quote from a person living with Ulcerative Colitis.** *"When I am unwell, the constant anaemia makes everyday life feel like wading through treacle, the pain can be crippling. The very real concern of faecal incontinence gives me physical symptoms of stress as well as affecting me emotionally and mentally."* **Quote from a person living with Ulcerative Colitis.** The experience of caring for someone with IBD can be especially difficult given that it is to some degree an invisible condition and due to the unpredictable nature of the symptoms, which many also find extremely uncomfortable to talk about, and the effects of treatment. For parents of young people, there are challenges around providing support, while enabling independence and seeing lives and aspiration affected by the son or daughter's condition. "*He was struggling to maintain a healthy weight, was constantly feeling sick, rushing to the toilet and in pain and missing a great deal of his work at a stage in his career that was very important to him. He was unable to continue his sport and his social life was negligible*." **Quote from the parent of a person living with Ulcerative Colitis.** **Social functioning**

[12] Cosnes J, et al., (2011). Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology, 140 (6), 1785-94.
[13] 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.

	Social functioning can be impaired - leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. *"During the majority of my time living with UC and the ever-changing drugs, I had no quality of life. I was off sick from work for 8 months. I was unable to drive my children to or from school or make them their breakfast as this was the time, usually until about midday, that I could not leave the toilet. There was no fun time with my 3 wonderful children or my husband, I was always in bed, in pain or on the toilet. We did not cuddle or play, because if any of them touched my tummy, it would be so sore. This period of illness really affected my confidence. My friends gave up coming around as I was so poorly. My quality of work really dropped. I continuously made mistakes because of the side effects from all the drugs."* **Quote from a person living with Ulcerative Colitis.** Research shows that young people aged 16-25 with IBD who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. There is a clear associated "productivity loss" by health state, whereby the lowest score for health state (Visual Analogue Score 0-2.5) corresponds with a 71% productivity loss.[14]

Current treatment of the condition in the NHS

[14] Gay M et al. (2011) Crohn's, Colitis and Employment – from Career Aspirations to Reality. Crohn's and Colitis UK.

7. What do patients or carers think of current treatments and care available on the NHS?	The recent service audit and patient survey carried out by IBD UK revealed that around one-third of adult patients with IBD reported the quality of their care as 'fair' or 'poor'.[8] Over half of adults responding to the IBD Patient survey reported experiencing one or more flares in the past 12 months, and of these individuals, 45% reported experiencing three or more flares. Concerningly, roughly 1 in 6 adults reported experiencing more than five flares in the previous 12 months. While flares can occur for a variety of different reasons, for some this high volume in a single year might reflect poor care optimisation and/or adherence to treatment. This can be highly detrimental to the person's quality of life, as flares may reduce their ability to complete daily activities, such as attending school, college or work. Patients express dissatisfaction with many of the current treatment options. Many experience lack of response (primary or secondary) and/or adverse reactions. The effects of steroids are extremely unpleasant and long-term safety profile of other treatments, including biologics, are of some concern. "*I have suffered with UC for 13 years. It's always been moderate to severe. I have tried all drugs including all biologics. All failed after a while. The best was Infliximab, I had my first ever remission for 2 years. However, it came to an end in Aug 2017. I had 18 months of pain and blood, countless hospital admissions, yet I was still pushed to try yet another biologic, Vedolizumab then Golimumab. None of it worked. 6 weeks later I had an emergency op and my colon was removed. My recovery is slow as I was ill for quite some time before and I'm building up my stamina now."* **Quote from a person living with Ulcerative Colitis.** *"My 'moon face' from the constant use of prednisolone was depressing and because of my ill health my hair became really thin. Prednisolone also affected my mood. I was so angry and unhappy. This also kept me awake at night, so I took sleeping pills."* **Quote from a person living with Ulcerative Colitis.**
8. Is there an unmet need for patients with this condition?	The range of options available for treating Ulcerative Colitis remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies. There are significant short and long-term side effects with corticosteroids, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis. Their use is also limited to induction of remission. *"I was steroid dependent and all conventional UC therapies failed – including anti TNF (Infliximab). Long term steroid use resulted in osteoporosis at age 28. I was housebound for many years due to UC and was unable to work. Quality of life was zero."* **Quote from a person living with Ulcerative Colitis.** Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them. In the majority of patients who do respond, the benefits take three to six months to appear. Significant risks of thiopurines including non-Hodgkin's lymphoma (as high as 4-5-fold compared with unexposed IBD patients and further increased

	when used in combination with anti-TNFs). Other side effects include early hypersensitivity reactions such as fever and pancreatitis, bone marrow suppression and hepatotoxicity requiring frequent lab monitoring during treatment. Anti-TNFs are increasingly being used earlier in the treatment pathway and can have a significant and positive effect on quality of life for patients. However, up to 40% of patients treated with anti-TNF therapy do not respond to induction therapy. In the approximately one-third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time. Overall, there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with Ulcerative Colitis to resume their lives and restore their quality of life.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	One of the key advantages is that Guselkumab is a treatment option that can be taken at home. Furthermore, the value of an additional treatment option, which has a different mode of action, reduced likelihood of loss of response, and a convenient delivery method would result in an associated reduction in NHS costs due to reduced infusions. Patients most likely to benefit from this drug are those for whom currently available therapies are ineffective, contraindicative or they develop an intolerance. In this group, it is likely that individuals, without further choice, will return to treatment/s which have already been established to be inadequate. This may include highly undesirable long-term steroid use or unproven unconventional therapy. It is also likely that patients in this group who exhaust all other treatment options would be forced to have a colectomy, either elective or as an emergency.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Prescription costs faced people living with long-term and chronic conditions, including Ulcerative Colitis, in England, are shown to contribute to economic disadvantage, which can impact adherence and lead to complications and increased cancer risks and cost to the NHS. However, the disadvantage is not specific to Guselkumab, 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 Guselkumab, 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?	N/A

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, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships.[15] [16] • There is significant unmet need for people with moderate to severe Ulcerative Colitis. Current treatments remain far from optimal for patients, a substantial number of whom experience a lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety. • Guselkumab offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making).

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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

For more information about how we process your personal data please see our privacy notice.

[15] Crohn's and Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards
[16] IBD UK (2019) IBD Standards

EAG cost comparison report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 169597

Completed 13 May 2025

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]
Produced by:	Liverpool Reviews & Implementation Group (LRiG)
Authors:	Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LRiG, University of Liverpool Angela Stainthorpe, Senior Economic Modeller, LRiG, University of Liverpool Marty Chaplin, Research Associate (Medical Statistician), LRiG, University of Liverpool Vincy Huang, Research Associate, LRiG, University of Liverpool Yenal Dundar, Research Fellow (Clinical Effectiveness), LRiG, University of Liverpool Joanne McEntee, Advanced Medicines Advice Pharmacist, North West Medicines Information Centre, Liverpool Keith Bodger, Reader & Consultant Gastroenterologist (Honorary), Department of Health Data Science, Institute of Population Health, University of Liverpool
Correspondence to:	Nigel Fleeman, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB
Date completed:	13 May following factual accuracy check and confidential information check

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 169597.

Acknowledgements: The authors would like to thank Chris Probert (Professor of Gastroenterology, University of Liverpool), Janette Greenhalgh (Senior Research Fellow, LRiG) and James Mahon (Coldingham Analytical Services) who provided feedback on a draft version of the report, and Sam Bryning (Research Associate, LRiG) who provided feedback on the report economic sections and model validity checks.

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.

Declared competing interests of the authors/peer reviewers: Keith Bodger has received fees for speaking from Takeda UK Ltd. Chris Probert has received reimbursement for attending a symposium from Abbvie.

This report should be referenced as follows: Fleeman N, Stainthorpe A, Chaplin M, Huang V, Dundar Y, McEntee J, Bodger K. Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]: A Cost comparison Technology Appraisal. LRiG, University of Liverpool, 2025

Contributions of authors <To match the order above>:

Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
Angela Stainthorpe	Critical appraisal of the economic evidence
Marty Chaplin	Critical appraisal of the statistical evidence
Vincy Huang	Critical appraisal of the economic evidence
Yenal Dundar	Conduct of searches for the External Assessment Group
Jo McEntee	Critical appraisal of the company submission
Keith Bodger	Clinical advice and critical appraisal of the clinical evidence

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADT	advanced therapy
AE	adverse event
BSG	British Society of Gastroenterology
CrI	credible interval
CRP	C-reactive protein
EAG	External Assessment Group
CS	company submission
EQ-5D	EuroQol-5 Dimensions
FAS	full analysis set
FDA	Food and Drug Administration
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
IL-12	interleukin 12
IL-23	interleukin 23
IPD	individual patient data
IV	intravenous
JAKi	Janus kinase inhibitor
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
PAS	Patient Access Scheme
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
SC	subcutaneous
SLR	systematic literature review
SmPC	summary of product characteristics
TA	Technology Appraisal
TNFi	tumour necrosis factor alpha inhibitor
UC	ulcerative colitis
VAS	visual analogue scale

1 EXECUTIVE SUMMARY

This appraisal focuses on the use of guselkumab (Tremfya) for patients with moderately to severely active ulcerative colitis (UC). In the National Institute for Health and Care Excellence (NICE) final scope, the technology (guselkumab) was selected to be appraised as a cost comparison appraisal. Therefore, the company (Johnson & Johnson) sought to make a case that guselkumab offers similar or greater health benefits at similar or lower costs compared to relevant comparators.

1.1 Population

The company presented evidence for both induction treatment and maintenance treatment for patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to an advanced therapy (ADT). This population is referred to as the ADT-failure population by the company and in this External Assessment Group (EAG) report. First-line ADT usually consists of tumour necrosis factor alpha inhibitors (TNFi) but may also include other ADTs, typically where a TNFi is unsuitable. This is a narrower population than the expected marketing authorisation [redacted]

1.2 Intervention

Guselkumab is an interleukin 23 (IL-23) inhibitor, administered by intravenous (IV) infusion or subcutaneous (SC) injection. The QUASAR phase IIb and phase III induction trials examined the clinical efficacy and safety of the recommended induction dose of 200mg by IV infusion every 4 weeks (Q4W). The QUASAR phase III maintenance trial examined the recommended maintenance doses of 100mg SC injection every 8 weeks (Q8W) or 200mg SC injection Q4W. The ASTRO trial examined the recommended induction dose of 400mg by SC injection Q4W and recommended maintenance doses of 100mg SC injection Q8W or 200mg SC injection Q4W.

1.3 Comparators

The company has chosen vedolizumab and mirikizumab as relevant comparators. Vedolizumab is an integrin inhibitor and has the greatest market share following failure with a first-line ADT in the NHS. Mirikizumab has a similar mechanism of action to guselkumab (both are IL-23 inhibitors) and is also commonly used following failure with a first-line ADT. The company has presented evidence for guselkumab verses the licensed doses of these comparators.

1.4 Outcomes assumed to be similar in the cost comparison analysis

The only clinical outcomes included in the cost comparison analysis are clinical response (initial and delayed response) and all-cause discontinuation of treatment. No safety data are incorporated into the cost comparison analysis. Based on the results of outcomes analysed by network meta-analyses (NMAs), the company assumes that there are no differences in clinical response rates, discontinuation rates or safety between guselkumab, vedolizumab and mirikizumab.

1.5 Summary of clinical effectiveness evidence presented

1.5.1 Direct clinical evidence

The company has presented evidence from the QUASAR trial programme (consisting of the QUASAR phase IIb randomised controlled trial [RCT] of induction treatment, QUASAR phase III RCT of induction treatment and QUASAR phase III RCT of maintenance treatment) and the ASTRO phase III RCT. These RCTs compared guselkumab with placebo. Guselkumab was superior to placebo in the overall trial and ADT-failure populations for all the efficacy outcomes specified in the NICE scope which were reported. The company reports that the guselkumab safety results were consistent with the safety profile of guselkumab in its licensed indications of plaque psoriasis and psoriatic arthritis. Clinical advice to the EAG is that no unexpected adverse events (AEs) were observed from the safety data presented for guselkumab.

1.5.2 Network meta-analyses

As placebo is not a relevant comparator for this appraisal, the company conducted NMAs to compare guselkumab versus vedolizumab and versus mirikizumab. Evidence for the relevant comparators included in the NMAs was derived from placebo controlled RCTs. All trials employed a response re-randomised design in which patients who responded to induction treatment were re-randomised to maintenance treatment. Overall, the EAG considers that all trials were well-designed and well-conducted.

In all trials, the overall trial populations (mixed populations of patients with and without ADT-failure) had broadly similar eligibility criteria and the patients enrolled had characteristics that are generalisable to patients who would be treated in the NHS. However, differences in placebo response to efficacy outcomes across trials were observed (in both the induction and maintenance periods). These differences may result from:

- the trials conducted in different years
- outcomes evaluated at Week 6 (vedolizumab) or Week 12 or Week 24 (guselkumab and mirikizumab) in the induction period

- maintenance treatment outcomes were evaluated from 44 weeks from the start of maintenance treatment (Maintenance Week 44) or 52 weeks from the start of induction treatment (Overall Week 52)
- carry over effects from previous ADTs received prior to enrolment into the induction period
- carry over effects from active treatment received in the induction period for patients re-randomised to placebo in the maintenance period.

Differences in placebo response across trials tended to be less marked in the ADT-failure populations than in the overall trial populations.

The efficacy outcomes analysed and compared for guselkumab versus vedolizumab and versus mirikizumab were clinical response and clinical remission. Endoscopic healing, an efficacy outcome evaluated in both the recent appraisals of IL-23 inhibitors (TA925 [mirikizumab] and TA998 [risankizumab]), was not evaluated. The company considered that endoscopic healing may be correlated with clinical remission given this outcome includes an endoscopic component (mucosal appearance at endoscopy). Clinical advice to the EAG is that all three outcomes are relevant outcomes.

NMAs were conducted utilising efficacy data from the ADT-failure population, which is the relevant population for the current appraisal. Serious adverse events (SAEs) and discontinuation due to AEs were the safety outcomes analysed in the company NMAs and were only conducted for the induction period and in the overall trial safety populations (mixed populations of patients with and without ADT-failure).

The company highlights, and the EAG agrees, that performing NMAs of data from the response re-randomised trials would be limited by fundamental differences between patients receiving maintenance treatment with placebo across the trials. The company therefore 'normalised' the data utilised in the maintenance period NMAs so that they mimicked treat-through designs. The company NMAs also appeared to include QUASAR trial data that were measured using alternate definitions of clinical response and clinical remission to the primary definitions. Overall, the EAG considers this approach to be justified and all methods used by the company to conduct the NMAs to be appropriate. The company's methods rely heavily on data imputations and assumptions, but the EAG is not aware of an alternative approach that could have been used that would provide more robust results.

Results from the company NMAs showed the point estimate of the odds ratio favoured guselkumab versus relevant comparators in most instances. The exceptions in which the point estimate of the odds ratio favoured one of the comparators were:

- clinical remission following induction treatment (favoured vedolizumab 300mg IV)

- SAEs during induction (favoured vedolizumab 300mg IV)
- discontinuation due to AEs during induction (favoured mirikizumab 300mg IV Q4W)
- clinical remission following maintenance treatment (favoured mirikizumab 200mg SC Q4W).

All NMA results produced wide 95% credible intervals for all comparisons, and all included either a doubling or a halving (or both) of the odds of the event, indicating substantial uncertainty in the results. The company partially attributes the wide credible intervals to the loss of power resulting from re-randomisation of patients in the included trials. The EAG notes that substantial uncertainty was observed for both induction period results (which would be unaffected by re-randomisation) and maintenance period NMA results. The EAG considers it likely that some uncertainty in the results can also be attributed to the sparse nature of the evidence network, and the use of the random effects model (driven by the heterogeneity between trials) inherently leads to wider credible intervals (relative to the fixed effects model).

1.5.3 Additional support for similar or greater health benefits

The EAG conducted informal comparisons of individual trial results, i.e., an examination of similarities or differences across trials without using statistical methods. In summary:

- in the induction period, trial results suggest that the proportion of patients treated with guselkumab achieving clinical response and clinical remission was similar to that of patients treated with mirikizumab and greater than the proportion of patients treated with vedolizumab; the proportion of patients achieving endoscopic response was broadly similar for guselkumab, mirikizumab and vedolizumab
- in the maintenance period, trial results suggest that the proportion of patients treated with guselkumab maintaining clinical response and clinical remission was similar to that of patients treated with mirikizumab and likely greater than the proportion of patients treated with vedolizumab; the proportion of patients maintaining endoscopic response was broadly similar for guselkumab, mirikizumab and vedolizumab
- differences in placebo response to efficacy outcomes were observed across all trials in the induction and maintenance periods; differences in placebo response across trials tended to be less marked in the ADT-failure populations than in the overall trial populations.

No notable differences in the proportions of patients with the types of AEs measured in the trials were observed from the EAG's informal comparisons of individual trial results. This suggests the safety profiles may be broadly similar across the three treatments, although the safety data that could be compared across trials was limited to mixed populations of patients with and without ADT-failure.

A recent publication reporting NMAs for clinical response, clinical remission and endoscopic healing was identified by the EAG. This publication only reported results for guselkumab in the induction period. Guselkumab was found to be superior to vedolizumab in relation to

endoscopic healing. The point estimates of the relative risk in relation to the other outcomes for guselkumab versus vedolizumab or versus mirikizumab favoured guselkumab but were not statistically significantly different.

1.6 Economic evidence

The company developed a cost comparison model in Microsoft® Excel. The EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the company submission (CS) and in the original sources. The EAG has updated the model base case at the request of NICE so that guselkumab induction is administered 100% via IV infusion in accordance with the expected marketing authorisation (see Section 2.4). [redacted]. The EAG has made the following revisions to the company base case cost comparison analysis:

- guselkumab induction 100% IV (updated base case)
- guselkumab extended induction period included in induction costs (updated base case)
- adjusted probability of response after induction/extended induction (R1)
- adjusted long term discontinuation rate (R2)
- adjusted timing of dose escalation and reinduction (R3)
- increased proportion of patients receiving vedolizumab SC maintenance (R4).

1.7 Conclusions

1.7.1 Clinical effectiveness evidence conclusions

There are no data to directly demonstrate whether guselkumab is statistically equivalent to or non-inferior to vedolizumab and mirikizumab and only indirect evidence is available. Overall, there is some evidence (from NMAs and EAG informal comparisons) that guselkumab may be at least similar to vedolizumab and mirikizumab in terms of efficacy and safety. NMA evidence is considered more robust than informal comparisons of individual trial results. However, while the company NMAs were well conducted, the NMA results have wide 95% credible intervals, indicating considerable uncertainty in the relative efficacy and safety of guselkumab versus vedolizumab and mirikizumab. Given the lack of definitive evidence, it is not possible to rule out the existence of important differences in some treatment outcomes (efficacy and/or safety) for guselkumab versus vedolizumab or versus mirikizumab.

1.7.2 Economic evidence conclusions

The EAG considers that the company cost comparison methods were largely appropriate, and model results are robust. The only EAG revision with a large individual impact on the company results is the change from a constant to a declining discontinuation rate. All other EAG

revisions were minor and had comparatively small ([redacted]) individual effects on the company base case results.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal focuses on the use of guselkumab (Tremfya) for treating moderately to severely active ulcerative colitis (UC). The company has presented evidence for both induction treatment and maintenance treatment for patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to an advanced therapy (ADT), including biologics and small molecules such as Janus kinase inhibitor inhibitors (JAKi). **For brevity, this population is referred to as the ADT-failure population throughout this EAG report.** In the National Institute for Health and Care Excellence (NICE) final scope,[1] the technology (guselkumab) was selected to be appraised as a cost comparison appraisal.

The External Assessment Group (EAG) critique of the company submission document B (referred to as the CS) is presented in this report. Additional evidence was provided by the company in response to the clarification letter.

2.2 Background

UC is a chronic inflammatory condition of the gastrointestinal tract and is the most common form of inflammatory bowel disease (IBD).[2] It is reported in the CS (p17) that patients with UC experience a range of debilitating symptoms including rectal bleeding, bloody stools, diarrhoea, bowel urgency, increased stool frequency, faecal incontinence, mucus discharge, fatigue, abdominal pain and tenesmus.[3,4] Peak incidence of UC is between the ages of 15 and 25 years, with a second smaller peak occurring between 55 and 65 years.[5]

The company highlights (CS, p18) that the most sensitive and specific tool to establish a diagnosis of UC is endoscopy.[3] The most sensitive non-invasive test is the faecal calprotectin stool test.[6] Clinical advice to the EAG agrees with the company that the faecal calprotectin stool test is often used in clinical practice for both diagnosis and management.

A measure of disease severity recommended by the British Society of Gastroenterology (BSG) guidelines[7] is the total Mayo score (range 0 to 12). The total Mayo score considers stool frequency, rectal bleeding, endoscopy subscores and physician global assessment. Moderately active UC is defined by scores of 6 to 10 and severely active UC by scores of 11 to 12. An alternative measure of disease severity which has been used in clinical trials of guselkumab[8,9] is the modified Mayo score (range 0 to 9). This measure omits the physician global assessment and excludes scoring for friability in endoscopic findings. Therefore, patients with moderately to severely active UC have scores ranging from 5 to 9. Another

measure of disease severity is the partial Mayo score (range 0 to 9) which excludes endoscopic findings (CS, Appendix G.1.2, Table 28).

The company reports (CS, p19) that in the UK, the incidence of UC was estimated as 23.2 per 100,000 person years between 2000 and 2018.[10] It has been reported in previous NICE appraisals of UC (TA828[11] and TA956[12]) that 52% of patients have moderately or severely active disease. Clinical advice to the EAG agrees that at the time of original diagnosis, approximately 50% of patients may have moderate or severe disease. However, UC is an unpredictable fluctuating disease with spontaneous periods of remission and relapse or varying loss of response to existing treatments, thus the prevalence may be lower.

2.3 Company's overview of current service provision

The company highlights (CS, p21) that treatment options for UC are guided by the severity and the extent of the disease with the goal of relieving symptoms during flare-ups and maintaining remission.[3,5] The BSG guidelines[7] highlight that there is no fully agreed or validated definition of remission, many clinical and endoscopic parameters have been suggested. However, the guidelines[7] highlight a growing consensus that remission should be defined as symptomatic remission (absence of rectal bleeding and return to normal bowel habit) combined with endoscopic remission (Mayo endoscopic subscore of ≤1). The guidelines[7] therefore suggest that symptomatic remission combined with mucosal healing should be the target of medical therapy in UC.

The NICE guideline for UC (NG130[5]) and the BSG guidelines[7] recommend conventional therapy, such as aminosalicylate (5-ASA), as first-line therapy, or corticosteroids and immunomodulator for when 5-ASA is intolerable; ADTs are recommended for moderately to severely active UC as the standard of care where conventional treatments fail, are not tolerated or are contraindicated. Current ADT options with their NICE recommendations are summarised in Table 1.

Table 1 NICE recommended ADTs for moderately to severely active UC

Type*	ADT	TA	Year	NICE recommendation for treating moderately to severely active UC
TNFi (SC)	Infliximab Adalimumab Golimumab	TA329[13]	2015	Options for adults: (i) whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or (ii) who cannot tolerate, or have medical contraindications for, such therapies. Golimumab is recommended only if the company provides the 100mg dose of golimumab at the same cost as the 50mg dose, as agreed in the PAS.
Integrin inhibitor (IV_i, IV_m or SC_m)	Vedolizumab	TA342[14]	2015	An option for adults only if the company provides vedolizumab with the discount agreed in the PAS. Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.
JAKi (oral)	Tofacitinib	TA547[15]	2018	An option for adults: (i) when conventional therapy or a biological agent cannot be tolerated, or (ii) the disease has responded inadequately or lost response to treatment and (iii) if the company provides tofacitinib with the discount agreed in the commercial arrangement.
	Filgotinib	TA792[16]	2022	An option for adults: (i) when conventional or biological treatment cannot be tolerated, or (ii) if the disease has not responded well enough or has stopped responding to these treatments, and (iii) if the company provides filgotinib according to the commercial arrangement.
	Upadacitinib	TA856[17]	2023	An option for adults: (i) when conventional or biological treatment cannot be tolerated, or (ii) if the condition has not responded well enough or has stopped responding to these treatments, and (iii) if the company provides upadacitinib according to the commercial arrangement.
IL12/23 inhibitor (IV_i, SC_m)	Ustekinumab	TA633[18]	2020	An option for adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if: (i) a TNFi has failed (that is the disease has responded inadequately or has lost response to treatment) or (ii) a TNFi cannot be tolerated or is not suitable, and (iii) the company provides ustekinumab at the same price or lower than that agreed with the CMU.
S1PR modulator (oral)	Ozanimod	TA828[11]	2022	An option for adults, only if: (i) conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable, or (ii) biological treatment cannot be tolerated or is not working well enough, and (iii) the company provides it according to the commercial arrangement.

Type*	ADT	TA	Year	NICE recommendation for treating moderately to severely active UC
	Estrasimod	TA956[12]	2024	An option for people aged 16 years and over when: (i) conventional or biological treatments cannot be tolerated or (ii) the condition has not responded well enough, or lost response to treatment, and (iii) the company provides it according to the commercial arrangement.
IL-23 inhibitor (IV_i, SC_m)	Mirikizumab	TA925[19]	2024	An option for adults when conventional or biological treatment cannot be tolerated, or the condition has not responded well enough or lost response to treatment, only if: (i) a TNFi has not worked (that is the condition has not responded well enough or has lost response to treatment) or (ii) a TNFi cannot be tolerated or is not suitable and (iii) the company provides it according to the commercial arrangement.
	Risankizumab	TA998[20]	2024	An option for adults when conventional or biological treatment cannot be tolerated, or the condition has not responded well enough or has lost response to treatment, only if: (i) a TNFi has not worked (that is the condition has not responded well enough or has lost response to treatment), or (ii) a TNFi cannot be tolerated or is not suitable and (iii) the company provides it according to the commercial arrangement.

* Drug class and administration route
ADT=advanced therapy; CMU=Commercials Medicines Unit; IL=interleukin; IV=intravenous; IV_i=intravenous induction; IV_m=intravenous maintenance; JAKi=Janus kinase inhibitor; PAS=Patient Access Scheme; SC=subcutaneous; SC_i=subcutaneous induction; SC_m=subcutaneous maintenance; S1PR=sphingosine-1-phosphate receptor; TA=Technology Appraisal; TNFi=tumour necrosis factor alpha inhibitor; UC=ulcerative colitis

Clinical advice to the EAG agrees with the company (CS, p22) that tumour necrosis factor alpha inhibitors (TNFi) are the most commonly used 1L ADTs in the NHS. For patients with a non-response to ADT, clinical advice to the EAG is that often, patients will need to cycle through various ADTs with different mechanisms of action since:

- primary non-response [PNR] is ≥50% for induction with first-line (1L) TNFi as first-line agent
- PNR to a second-line or later (≥2L) ADT after TNFi failure would be no better
- secondary loss of response (i.e., a subsequent loss of response after having had an initial primary response to induction treatment) is also common during ongoing maintenance treatment occurring in maybe 25% to 50% of patients after one year and ≥50% after 5 years; most cases occur at 1-2 years.

Clinical advice to the EAG is that consideration of ≥2L ADT includes mechanism of action, patient preference regarding the route of administration (intravenous [IV] infusion, subcutaneous [SC] injection or orally) and cost. It is highlighted in the BSG guidelines[7] that: "It is important to note that surgery should always be discussed as an option in patients failing a therapeutic agent, particularly as there is generally a reduction in response to each successive immunosuppressive or biologic drug."

Market share data cited in the most recent technology appraisal (TA) for risankizumab (TA998[20]) suggested that where TNFi are considered unsuitable or where prior biological treatment is not tolerated or not working well enough, vedolizumab was the most used ADT (~49%) followed by ustekinumab (~29%). In the earlier TA for mirikizumab (TA925[19]), the EAG's clinical expert estimated that the market share of vedolizumab was ~40%, tofacitinib ~35% and ustekinumab ~20%. Clinical advice to the EAG is that the market shares of vedolizumab are probably ~30% to ~40%, JAKi are probably ~30% to ~40% and ustekinumab are probably ~20%.

2.4 Guselkumab

In the CS, the company has positioned guselkumab as 2L ADT for use in patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to an ADT, including biologics and small molecules such as a JAKi (CS, p22). The company also anticipates that guselkumab may be used in a small proportion of patients for whom TNFi are not suitable (i.e., as 1L ADT).

Guselkumab is an interleukin 23 (IL-23) inhibitor (more detail provided in CS, Table 2) and has a similar mechanism of action to mirikizumab and risankizumab, which are also IL-23 inhibitors.

The anticipated marketing authorisation for guselkumab is as follows (CS, Table 2): [redacted] This [redacted] to the marketing authorisations for mirikizumab[21] and risankizumab,[22] both of which are indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

Notably, it is proposed that induction treatment with guselkumab may be administered by IV infusion (similar to these IL-23 inhibitors [and vedolizumab, which along with mirikizumab, is a comparator in this cost comparison appraisal, see Section 3.3]) or SC injection (unlike these IL-23 inhibitors [and also unlike vedolizumab]). As highlighted in the CS (CS,Table 2), the licence application for IV induction and SC maintenance was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted] and the anticipated date of marketing authorisation is [redacted]. The application for MHRA filing for SC induction will be submitted in [redacted] and the anticipated date of marketing authorisation is [redacted].

The following information about contraindications is given in the CS (CS, Table 2):

- guselkumab is contraindicated in patients with serious hypersensitivity to the active substance or to any of the following excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose, water for injections
- guselkumab may increase the risk of infection and is contraindicated in patients with clinically important active infections (e.g. active tuberculosis).

These contraindications are common to all other ADTs for UC recommended by NICE[11-20] (albeit, the excipients differ for each drug). Other ADTs also have additional contraindications including moderate to severe heart failure (all TNFi[23-25] and both S1PR modulators[26,27]), severe hepatic impairment (JAKi [tofacitinib[28] and upadacitinib,[29] not filgotinib[30]] and both S1PR modulators[26,27]), pregnancy (all JAKi[28-30] and both S1PR modulators[26,27]). Additional contraindications are also listed for both S1PR modulators.[26,27]

As detailed in the CS (CS, Table 2), a Patient Access Scheme (PAS) representing a simple discount is currently in place for guselkumab.

2.5 Sources of clinical effectiveness evidence

The company reports evidence for guselkumab from the QUASAR phase IIb/III trial programme [8,31] and the ASTRO trial.[9] All trials were placebo-controlled randomised controlled trials (RCTs). Brief information is provided in Section 2.5.1 and Section 2.5.2. As all trials compared guselkumab versus placebo, rather than versus an active treatment, evidence for the relevant comparators was derived from trials identified by a systematic literature review (SLR) and network meta-analyses (NMAs) were conducted.

2.5.1 QUASAR trial programme

The QUASAR trials[8,31] are randomised withdrawal trials and enrolled patients with moderately to severely active UC who had demonstrated an inadequate response to or a failure to tolerate conventional therapy (6-mercaptopurine, azathioprine or corticosteroids) or ADT (TNFi, vedolizumab or tofacitinib). In brief:

- the QUASAR phase IIb trial[31] is a double-blind, dose-ranging RCT that examined the efficacy and safety of guselkumab versus placebo as IV induction treatment; this RCT is considered by the company to be supportive (results presented in CS, Appendix I.3, only)
- the QUASAR phase III trial[8] is a double-blind, multicentre RCT that examined the efficacy and safety of guselkumab versus placebo as IV induction treatment and SC maintenance treatment; patients responding to induction treatment were enrolled into the maintenance period as were patients responding to induction treatment in the QUASAR phase IIb trial.[31]

2.5.2 ASTRO trial

The ASTRO phase III trial[9] is an ongoing double-blind, multicentre treat-through RCT that enrolled patients with moderately to severely active UC who had demonstrated an inadequate response to or an intolerance to conventional therapy (6-mercaptopurine, azathioprine or corticosteroids) or ADT (TNFi, vedolizumab, ozanimod or an approved JAKi). The trial has evaluated the efficacy and safety of guselkumab versus placebo as SC induction treatment. The trial also includes a 72-week extended follow-up of maintenance treatment (results due October 2025).

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The key elements of the decision problem outlined in the NICE final scope[1] and addressed by the company are summarised in Table 2. More information regarding the key issues relating to the decision problem is provided in Sections 3.1 to 3.5.

Table 2 Summary of the decision problem

Parameter	NICE final scope	Decision problem addressed in the company submission	Rationale if different from the NICE final scope	EAG comment
Population	Adults with moderately to severely active UC that have had an inadequate response, lost response to, or were intolerant to conventional therapy and/or a biological treatment or a JAK inhibitor	Adults with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to an advanced therapy, including patients for whom TNFis are deemed unsuitable	Similar to the populations addressed in the comparator submissions (mirikizumab and vedolizumab) and the evidence base for guselkumab	The EAG agrees the population aligns with the population of the comparator submissions. **For brevity, this population is referred to as the ADT-failure population throughout this EAG report.** See Section 3.1 for further information about the population.
Intervention	Guselkumab	Guselkumab	Not applicable	As per scope. See Section 3.2 for further information about the intervention.
Comparator(s)	• TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • JAK inhibitors (such as tofacitinib, filgotinib or upadacitinib) • Vedolizumab • Ustekinumab • Ozanimod • Mirikizumab • Etrasimod • Risankizumab • Conventional therapies, without biological treatments	• Mirikizumab • Vedolizumab	Conventional therapy with aminosalicylates, oral corticosteroids and/or immunomodulators should not be considered as a comparator in the evaluation, as these are unlikely to be appropriate alternative options for the proposed population. This is also consistent with the mirikizumab appraisal (TA925).[19] Guselkumab is positioned as an alternative to mirikizumab 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 advanced therapy. The anticipated use of guselkumab in UK clinical practice is similar to the patient populations in which mirikizumab and vedolizumab are recommended by NICE. Mirikizumab and vedolizumab are considered relevant comparators in this appraisal for the following reasons:	Not all treatments used in clinical practice are required to be comparators for a cost comparison appraisal.[33] The EAG considers the comparators chosen by the company to be appropriate. See Section 3.3 for further information about the comparators.

Parameter	NICE final scope	Decision problem addressed in the company submission	Rationale if different from the NICE final scope	EAG comment
			• Both guselkumab and mirikizumab are IL-23 inhibitors and share a similar mechanism of action • In the NICE appraisal of mirikizumab (TA925),[19] vedolizumab was identified as a relevant comparator to mirikizumab. Therefore, by extension, vedolizumab is also considered a relevant comparator to guselkumab • In UK clinical practice, vedolizumab has a significant market share in the proposed population as discussed in recent UC NICE submissions[19,20] and a UK real-world evidence trial on patients with IBD.[32] • The outcomes of NMAs demonstrate that guselkumab has similar efficacy to mirikizumab and vedolizumab in the intended treatment population • It is anticipated that guselkumab would be considered by UK clinicians as an alternative treatment to mirikizumab and vedolizumab in the proposed treatment population	
Outcomes	• Rates of and duration of response, relapse and remission • Endoscopic healing • Endoscopic remission combined with histological improvement • Mortality • Measures of disease activity • Rates of hospitalisation (including readmission)	• Clinical remission and response • Endoscopic healing • Mucosal healing (histologic-endoscopic mucosal healing) • Measures of disease activity (symptomatic remission) • Rates of hospitalisation • Rates of surgical intervention	Data for mortality as an efficacy outcome were not collected during QUASAR[8] (similar to other trials conducted in this disease). However, it was reported as an adverse event. It is anticipated that mortality would not be a key driver within the cost comparison analysis. Relapse was not an efficacy outcome in QUASAR[8] and ASTRO[9]; however,	All outcomes in the decision problem addressed by the company were reported for the comparison of guselkumab versus placebo in the QUASAR phase III trial[8] and many were also reported in the ASTRO trial.[9] The only outcomes included in the NMAs comparing guselkumab versus

Parameter	NICE final scope	Decision problem addressed in the company submission	Rationale if different from the NICE final scope	EAG comment
	• Rates of surgical intervention • Corticosteroid-free remission • Medicine adherence • Adverse effects of treatment • HRQoL	• Corticosteroid-free remission • Maintenance of clinical remission • Fatigue response • Endoscopic normalisation • Adverse effects • HRQoL	clinical remission was the primary efficacy endpoint. Since relapse is defined as a loss of remission, clinical remission is indicative of relapse rates. Data on medicine adherence was not collected during the QUASAR[8] and ASTRO[9] trials.	mirikizumab and versus vedolizumab were: • Clinical response • Clinical remission The only clinical outcomes included in the cost comparison analysis are clinical response (initial and delayed response) and all-cause discontinuation of treatment. See Section 3.4 for further information about the outcomes.
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 PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken	A cost comparison analysis has been conducted to estimate the incremental costs of guselkumab versus mirikizumab 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 PSS perspective An existing PAS for guselkumab has been included as part of the analysis	Johnson & Johnson asserts that guselkumab is most appropriately assessed through the NICE cost comparison process due to similarities with mirikizumab and vedolizumab, in terms of both effectiveness and resource use. Therefore, a cost comparison has been submitted. The cost comparison compares the drug acquisition and administration costs for guselkumab versus mirikizumab and vedolizumab. A 10-year time horizon was adopted to sufficiently reflect all important differences in costs between the technologies being compared, as per the NICE health technology evaluations manual (PMG36).[34]	The company has presented cost comparison analysis results over a 10-year time period. Lack of definitive evidence to demonstrate that guselkumab provides similar or greater health benefits to other drugs in the ADT-failure setting means that it is not clear if a cost comparison analysis approach is appropriate. See Section 3.5 for further information about the economic analysis.

Parameter	NICE final scope	Decision problem addressed in the company submission	Rationale if different from the NICE final scope	EAG comment
	into account The availability and cost of biosimilar and generic products should be taken into account.			

CS=company submission; EAG=External Assessment Group; HRQoL=health-related quality of life; IBD=inflammatory bowel disease; IL=interleukin; JAK=Janus kinase; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; PAS=Patient Access Scheme; PSS=Personal Social Services; TNFi=tumour necrosis factor inhibitor; UC=ulcerative colitis

Source: NICE final scope[1] and CS, Table 1

3.1 Population

The QUASAR trial programme[8] and ASTRO trial[9] include adults with moderately to severely active UC who have an inadequate response, lost response to, or were intolerant to conventional therapy and/or a biological treatment or a JAKi. This population aligns with the population defined in the NICE final scope[1] [redacted]

The population that is the focus of the CS, and for whom the company are positioning guselkumab as a treatment option (see Section 2.4), is a narrower population, namely patients that have had an inadequate response, lost response to, or were intolerant to ADT (i.e., biological treatment or a JAKi). Subgroup analyses are presented in the CS for this population. **For brevity, this population is referred to as the ADT-failure population throughout this EAG report.**

The EAG considers the company has focussed on the most appropriate population since:

- it would be inappropriate to focus on the overall trial populations of the guselkumab trials[8,9] as they include patients who demonstrated an inadequate response or failure to tolerate conventional treatment but who were also ADT naïve; as highlighted in Section 2.3, patients who are ADT naïve typically receive treatment with a TNFi in the NHS
- as highlighted in Section 2.4, the company are positioning guselkumab as a 2L ADT for use in patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to an ADT
- this population is similar to that used to derive evidence for other IL-23 inhibitors in TA925[19] and TA998.[20]

3.2 Intervention

As highlighted in Section 2.4, guselkumab as induction treatment can be administered by IV infusion or SC injection. Evidence for the former is provided in the QUASAR trials[8,31] and evidence for the latter is provided in the ASTRO phase III trial.[9] Guselkumab is only administered by SC injection as maintenance treatment.

As described in CS, Table 2, as per the draft SmPC, the recommended induction dose is:

- guselkumab 200mg IV infusion at Week 0, Week 4, and Week 8; or
- guselkumab 400mg SC injection at Week 0, Week 4, and Week 8.

The recommended maintenance dose for those responding to induction treatment is:

- guselkumab 100mg SC injection at Week 16, followed by
- guselkumab 100mg SC injection every 8 weeks (Q8W) thereafter.

A different maintenance dose may be considered for patients who do not show adequate therapeutic benefit, according to clinical judgement, after completion of induction dosing, as follows:

- guselkumab 200mg SC injection at Week 12 and
- guselkumab 200mg SC injection every 4 weeks (Q4W) thereafter.

For patients who show no evidence of therapeutic benefit after 24 weeks of treatment, consideration should be given to discontinuing guselkumab.

While the recommended maintenance dose in clinical practice, as per the draft SmPC is 200mg for patients considered not to be achieving adequate therapeutic benefit, in the QUASAR phase III trial,[8] the 200mg dose was available to:

- patients who had adequate therapeutic benefit at Week 12, (patients responding at Week 12 in the induction trials,[8,31] were randomised to either this 200mg maintenance dose, the 100mg dose or placebo)
- patients who had not responded to induction treatment by Week 12 but had responded by Week 24 (all Week 24 responders received this 200mg maintenance dose).

3.3 Comparators

Not all treatments used in clinical practice are required to be comparators for a cost comparison appraisal.[33] The comparators for this cost comparison appraisal are vedolizumab and mirikizumab. Vedolizumab was chosen as a comparator since it has the greatest market share (where TNFi are deemed unsuitable or where prior biological treatment is not tolerated or not working well enough) and was also a comparator in the appraisal of mirikizumab (TA925).[19] The EAG notes that vedolizumab was also suggested as a comparator by the EAG in the more recent appraisal of risankizumab (TA998).[20] Vedolizumab is administered by IV infusion as induction treatment and IV infusion or SC injection as maintenance treatment. Mirikizumab was chosen as a comparator since it has the same mechanism of action as guselkumab. Mirikizumab is administered by IV infusion as induction treatment and SC injection as maintenance treatment.

Clinical advice to the EAG is that the choice of an ADT (following a TNFi) largely depends on clinical and patient preference and suggested that a JAKi may have been an additional relevant comparator. However, clinical advice to the EAG is that the company's rationale for choosing vedolizumab and mirikizumab as relevant comparators is appropriate.

Further information about the dosing regimens of the comparators is provided in Section 3.3.1 and Section 3.3.2.

3.3.1 Vedolizumab

Vedolizumab is available as 300mg powder for concentrate for solution for IV infusion, 108mg solution for SC injection in pre-filled pen and 108mg solution for SC injection in pre-filled syringe.[35] According to the summary of product characteristics (SmPC):[35]

- the recommended induction dose is vedolizumab 300mg IV infusion at Week 0, 2 and 6 and then Q8W thereafter
- some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to vedolizumab 300mg IV infusion Q4W

For patients who have shown no evidence of therapeutic benefit after 10 weeks of treatment, consideration should be given to discontinuing vedolizumab.[35]

As maintenance treatment, patients may continue on the IV dose (as above) or switch to SC injection.[35] According to the summary of product characteristics (SmPC):[35]

- the recommended dose regimen of SC vedolizumab as a maintenance treatment, following at least 2 IV infusions, is 108mg administered by SC injection once every 2 weeks (Q2W)
- the first subcutaneous dose should be administered in place of the next scheduled IV dose and Q2W thereafter.

It is stated in the SmPC[35] that there are insufficient data to determine if patients who experience a decrease in response on maintenance treatment with vedolizumab SC infusion would benefit from an increase in dosing frequency.

3.3.2 Mirikizumab

Mirikizumab is available as 300mg powder for concentrate for solution for IV infusion, 100mg solution for SC injection in pre-filled pen and 100mg solution for SC injection in pre-filled syringe.[21] According to the SmPC:[21]

- the induction dose is mirikizumab 300mg IV infusion for at least 30 minutes at Weeks 0, 4 and 8
- patients should be evaluated after Week 12 and if there is adequate therapeutic response, transition to maintenance dosing; the maintenance dose is mirikizumab 200mg SC injection Q4W after completion of induction dosing
- for patients who do not achieve adequate therapeutic benefit at Week 12 of induction dosing, mirikizumab 300mg IV infusion may be continued at Weeks 12, 16 and 20 (extended induction treatment); if therapeutic benefit is achieved with the additional IV infusions, patients may initiate mirikizumab 200mg SC maintenance dosing Q4W starting at week 24
- patients with loss of therapeutic response during maintenance treatment may receive mirikizumab 300mg IV infusion Q4W, for a total of 3 doses (reinduction); if clinical benefit is achieved with the additional IV infusions, patients may resume mirikizumab SC maintenance dosing Q4W (but it is noted that the efficacy and safety of repeated re-induction treatment have not been evaluated).

Mirikizumab should be discontinued in patients who do not show evidence of therapeutic benefit to extended induction treatment by Week 24.

3.4 Outcomes

The outcomes reported in the CS for the guselkumab trials[8,9,31] are listed in Table 3; these are all outcomes specified in the NICE final scope.[1] A hierarchical testing procedure for statistical significance was adopted for analysing outcomes in the QUASAR phase III trial[8] and ASTRO trial.[9]

Table 3 Outcomes reported in the CS from the guselkumab trials

QUASAR phase IIb trial (induction)[31] [a]	QUASAR phase III trial (induction)[8]	ASTRO phase III trial[9] (induction and maintenance) [b]	QUASAR phase III trial[8] (maintenance)
Primary outcome			
Clinical response	*Clinical remission*	*Clinical remission*	*Clinical remission*
Major secondary outcomes			
Clinical remission	*Symptomatic remission*	*Symptomatic remission*	*Symptomatic remission*
Symptomatic remission	*Endoscopic healing*	*Endoscopic improvement*	*Endoscopic healing*
Endoscopic improvement	*Clinical response*	*Clinical response*	*Corticosteroid-free clinical remission*
Histologic-endoscopic mucosal improvement	*Symptomatic remission at 4 weeks* [c]	*Histologic-endoscopic mucosal improvement*	*Maintenance of clinical response*
Endoscopic normalisation	*IBDQ remission*		*Histologic-endoscopic mucosal healing*
	Histologic-endoscopic mucosal healing		*IBDQ remission*
	Fatigue response [d]		*Fatigue response* [e]
	Symptomatic remission at 2 weeks [c]		*Maintenance of clinical remission* [e]
	Endoscopic normalisation [d]		*Endoscopic normalisation* [e]
	Symptomatic normalisation [d]		
Other outcomes			
Adverse events	Adverse events	Adverse events	Adverse events
HRQoL [f]	HRQoL [g]		HRQoL [g]
	Emergency department visits [d]		Emergency department visits [e]
	Hospitalisations [d]		Hospitalisations [e]
			Surgeries [e]
			Hospitalisations or surgeries [e]

All outcomes in italics were outcomes included in the hierarchical testing procedure for statistical significance (reported in order for which the testing was applied); for the ASTRO trial[8] the hierarchical testing procedure includes outcomes at Weeks 12 and 24 starting with clinical remission at Week 12 until clinical response at Week 12, then clinical remission at Week 24 to clinical response at Week 24, (histologic-endoscopic mucosal improvement was only included in the hierarchy at Week 12 following the testing of Week 24 outcomes)

[a] All outcomes reported in CS, Appendix I.3.2

[b] Week 44 data only available for adverse events (reported in CS, Appendix E2)

[c] Outcomes are part of the hierarchical testing procedure but results are not reported in the CS

[d] Reported in CS, Appendix I.1.4; not all outcomes reported in the published paper[8] but extracted by the company from CSR[36]

[e] Reported in CS, Appendix I.1.4; not all outcomes reported in the published paper[8] but extracted by the company from CSR[37]

[f] Reported in CS, Appendix I.3.2.2 as IBQD Total and domain scores and PROMIS-Fatigue SF-7a

[g] Reported in CS, Appendix I.1.4 as IBQD Total and domain scores and EQ-VAS scores, EQ-5D questionnaire dimensions and bowel urgency and abdominal pain through Week 12 and through Week 44; data extracted by company from CSR[37]
CS=company submission; CSR=clinical trial report EQ-5D= EuroQol-5 Dimensions; EQ-VAS= Euro-Quality of life visual analogue scale; HRQoL=health-related quality of life; IBDQ=Inflammatory Bowel Disease Questionnaire; PROMIS=Patient-Reported Outcomes Measurement Information System Short Form

Results from the analysis of the ASTRO trial[9] outcomes were only available at Week 12 and Week 24 for efficacy outcomes. Safety data were available at Week 12, Week 24 and Week 44 (but only limited safety data at Week 44).

The only clinical outcomes included in the cost comparison analysis are clinical response (initial and delayed response) and all-cause discontinuation of treatment. No safety data are incorporated into the cost comparison analysis. Based on the results of outcomes analysed by network meta-analyses (NMAs), the company assumes that there are no differences in clinical response rates or safety between guselkumab, vedolizumab and mirikizumab.

Clinical advice to the EAG is that the outcome measures chosen for the NMAs are relevant, but there is increasing recognition of the importance of objective outcome measures such as endoscopic healing and histological-endoscopic mucosal healing. Clinical advice to the EAG is that a comparison of adverse events (AEs) would also have been informative. The EAG notes that outcomes analysed in the NMAs conducted for the most recent cost comparison appraisal of risankizumab (TA998)[20] were clinical response, clinical remission, endoscopic healing, serious adverse events (SAEs) and serious infections. In the cost comparison appraisal of mirikizumab (TA925),[19] the NMA outcome measures were clinical response, clinical remission, endoscopic healing, all cause discontinuation and SAEs.

In response to clarification requests (clarification question A5), the company noted histological-endoscopic mucosal healing NMAs were not planned in the original NMA protocol. However, the company considered that endoscopic healing may be correlated with clinical remission given this outcome includes an endoscopic component (mucosal appearance at endoscopy). Also, in response to clarification requests (clarification question A5), the company provided safety NMAs with the following outcomes: SAEs and treatment discontinuation due to AEs. Informal comparisons of safety data were also reported (clarification question A8).

3.5 Economic analysis

The company has presented cost comparison analysis results over a 10-year time period and costs were considered from an NHS perspective. Guselkumab, vedolizumab and mirikizumab are available to the NHS at PAS prices. Only the confidential prices of guselkumab are known to the company. Results generated using the discounted prices for all drugs are presented in a confidential appendix. The EAG considers that a lack of definitive evidence to demonstrate that guselkumab provides similar or greater health benefits to vedolizumab or mirikizumab in

the ADT-failure setting means that it is not clear if a cost comparison analysis approach is appropriate.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant evidence of the effectiveness of guselkumab versus comparators are presented in the CS (Appendix D). The EAG considers that the company's SLR was conducted to a good standard; searches carried out by the EAG did not identify any relevant trials in addition to those identified by the company. An assessment of the extent to which the review was conducted in accordance with the LRiG in-house systematic review checklist is summarised in Table 4.

Table 4 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of PICOS?	Yes	See CS, Appendix D.1.4, Table 4. The review question was specified using the PICOS framework
Were appropriate sources searched?	Yes	See CS, Appendix D.1.3.1 and D.1.3.2. Electronic searches of Embase, MEDLINE, The Cochrane Library, and grey literature (i.e. ClinicalTrials.gov and hand searches of key clinical conferences published and published SLR bibliographies)
Was the timespan of the searches appropriate?	Yes	See CS, Appendix D.1.3.1 and response to clarification question A1. Although the company's SLR was conducted in July 2023, in response to clarification the company also conducted searches in March 2025. The company found no additional relevant trials, aside from the ASTRO trial[9] (to be included in future updates). The EAG also conducted its own searches and did not find any additional relevant trials.
Were appropriate search terms used?	Yes	See CS, Appendix D.1.3.1, Table 2. Search strings included medical subject headings and free text words
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D.1.4, Table 4. Eligibility criteria were wide (and therefore sufficient) to find trials relevant to the decision problem
Was trial selection applied by two or more reviewers independently?	Yes	See CS, Appendix D.1.5. All title/abstract and full-text publications were reviewed by two independent reviewers, with discrepancies resolved by consensus or by a third reviewer. Searches of the grey literature were conducted by a single reviewer and verified by a second reviewer. A third reviewer was consulted if the two reviewers did not reach agreement
Were data extracted by two or more reviewers independently?	Yes	See CS, Appendix D.1.6. Data extraction was performed by one reviewer and validated by a second independent reviewer with discrepancies resolved by consensus or by a third independent reviewer

Review process	EAG response	Note
Were appropriate criteria used to assess the risk of bias and/or quality of the primary trials?	Yes	See CS, Appendix D.1.7. The risk of bias assessment of included trials was performed using the NICE: Single Technology Appraisal Evidence Submission checklist for assessment of risk of bias in RCTs
Was the quality assessment conducted by two or more reviewers independently?	Yes	See CS, Appendix D.1.7. Assessments of risk of bias were performed by one reviewer and validated by a second independent reviewer with discrepancies resolved by consensus or by a third independent reviewer
Were attempts to synthesise evidence appropriate?	Yes	See CS, Section B.3.8 and response to clarification question A5. NMAs were performed for the induction and maintenance treatment phases separately. The outcomes chosen were clinical response, clinical remission, SAEs and treatment discontinuation due to AEs

AE= adverse event; CS=company submission; NMA=network meta-analysis; PICOS=population, interventions, comparators, outcomes and trial; RCT=randomised controlled trial; SAE=serious adverse event; SLR=systematic literature review

4.2 Included trials

The QUASAR trial programme[8,31] and the ASTRO trial[9] were the only trials that provide direct evidence for guselkumab in the treatment of moderately to severely active UC. The comparator in all these trials is placebo.

Studies identified by the company's SLR were included in the company's NMAs if they assessed the efficacy of guselkumab, vedolizumab or mirikizumab and reported outcomes of interest (clinical response and clinical remission) for patients with ADT-failure. The company's induction period NMAs included data from the QUASAR,[8,31] GEMINI[38] and LUCENT-1/2[39] trials, and the company's maintenance period NMAs included data from these trials and the VISIBLE-1 trial.[40]

Excluded from the SLR and CS was the VEGA trial[41] which was a phase II randomised, double-blind, controlled, proof-of-concept trial comparing combination therapy with guselkumab and golimumab versus guselkumab monotherapy and versus golimumab monotherapy. As golimumab is not considered to be a relevant comparator in this appraisal, the EAG considers the exclusion of this trial is justified.

4.3 Direct clinical effectiveness evidence

Information about the trial designs, eligibility criteria, statistical approach to analysing data and patient characteristics that provided direct clinical effectiveness evidence from the guselkumab trials[8,9,31] is reported in the CS, Section B.3.3, CS, Appendix I and response to clarification questions A9 to A16. Further information is also provided in Section 4.4.1 to Section 4.4.4 of this EAG report.

In addition to the NMAs which provide the most relevant results for this appraisal, the company provided extensive results from the trials[8,9,31] of guselkumab versus placebo for the primary outcomes, all major secondary outcomes and other outcomes specified in the NICE scope in the CS (efficacy: CS, Section B3.5, CS Appendices I.1.4, I.3.2 and I.3.3; safety: Section B3.9, Appendix E and Appendix I.3.4). The overall trial populations all include mixed populations of patients with and without ADT-failure. Therefore, the company provided efficacy results for both the overall trial (full analysis set [FAS]) and ADT-failure populations. Safety results were only available for the overall trial population (safety population). In summary, in all the guselkumab trials,[8,9,31] guselkumab was superior to placebo in the overall trial and ADT-failure populations for all the efficacy outcomes specified in the NICE scope which were reported. This was true for the induction period[8,9,31] and maintenance period.[8] The company reports (CS, p104) that the guselkumab safety results were consistent with the safety profile of guselkumab and clinical advice to the EAG is that no unexpected AEs were observed from the safety data presented for guselkumab which were similar to the AEs expected with IL-23 inhibitors. Further information is also provided in Appendix 1 (Section 10) of this EAG report.

Since the guselkumab 400mg IV infusion dose is not recommended for use as induction treatment in clinical practice, results for this dose in the QUASAR phase IIb trial[31] are presented for information only. As highlighted in the CS (pp44-45), as the results showed no apparent incremental benefit with the higher guselkumab induction dose, guselkumab 200mg IV was selected as the induction dose for the phase III trial.

4.4 Network meta-analyses and the ASTRO trial

To assess the relative clinical effectiveness of guselkumab, vedolizumab, and mirikizumab in patients with ADT-failure, the company conducted NMAs for both induction and maintenance periods, evaluating clinical response and clinical remission. In response to clarification question A5, the company also conducted NMAs for the outcomes of SAEs, and AEs leading to discontinuation (both in the induction period). The company did not explain why they did not conduct safety NMAs in the maintenance period. The safety NMAs were performed using the overall trial population of each of the included trials, as the relevant ADT-failure subgroup data for vedolizumab and mirikizumab is not currently in the public domain.

The ASTRO trial[9] was excluded from the company NMAs because relevant data were not available at the time the NMAs were conducted. However, further information about this trial and all trials included in the NMAs is presented in the remainder of this EAG report.

4.4.1 Included trials: trial designs

While all trials were RCTs, most trials included some patients who were not initially randomised to induction treatment (GEMINI-1 trial[42] and VISIBLE-1 trial[40]) or re-randomised to maintenance treatment (QUASAR phase III trial,[8] GEMINI-1 trial,[42] VISIBLE-1 trial[40] and LUCENT-1/2 trial[39]).

Four trials[8,9,39,42] evaluated the effects of both induction treatment and maintenance treatment. While the QUASAR phase IIb trial[31] only studied induction treatment, patients who responded to induction treatment were enrolled into the QUASAR phase III trial.[8] The VISIBLE-1 trial[40] only evaluated the effects of maintenance treatment in patients who had completed and responded to open-label induction treatment with vedolizumab

Further information about all the trials' study designs is provided below.

QUASAR phase IIb trial: study design

Patients (N=313) were randomly assigned (1:1:1) to receive guselkumab 200mg IV infusion or guselkumab 400mg IV infusion or placebo IV infusion at Weeks 0, 4, and 8. At Week 12:

- patients who responded to treatment in any of the three trial arms entered the QUASAR phase III trial (maintenance period)[8]
- patients randomised to guselkumab 200mg or 400mg IV infusions who did not achieve clinical response received guselkumab 200mg SC at Weeks 12, 16, and 20 and were re-evaluated for clinical response at Week 24
- patients randomised to placebo who did not achieve clinical response crossed over to receive guselkumab 200mg IV infusions at Weeks 12, 16, and 20 and were re-evaluated for clinical response at Week 24.

Matching IV or SC placebo was administered to all Week 12 non-responders to maintain blinding. Patients who responded to treatment by Week 24 entered the QUASAR phase III trial (maintenance period).[8] Patients who were not in clinical response at Week 24 did not receive further trial treatment but were followed-up for safety approximately 12 weeks after receiving their last dose of guselkumab.

QUASAR phase III trial: study design

Patients (N=701) were randomly assigned (3:2) to receive guselkumab 200mg IV or placebo IV administered at Weeks 0, 4 and 8. At Week 12:

- patients who were initially randomised to guselkumab or placebo and who responded to treatment entered the maintenance period
- patients who were initially randomised to guselkumab and who did not achieve clinical response at Week 12 received three doses of guselkumab 200mg SC at Weeks 12, 16 and 20 and were re-evaluated for clinical response at Week 24; patients who responded to treatment by Week 24 entered the maintenance period

- patients initially randomised to placebo who were not in clinical response crossed over to guselkumab, received three doses of guselkumab 200mg IV at Weeks 12, 16 and 20 and were re-evaluated for clinical response at Week 24; patients who responded to treatment by Week 24 entered the maintenance period.

The maintenance period included patients (N=805) who responded to treatment (guselkumab or placebo) by Week 12 or Week 24 in both the phase IIb trial[31] and phase III trial,[8] with some patients being re-randomised and others not re-randomised, as follows:

- patients who responded to treatment in the guselkumab arm at Week 12 and placebo arm crossover responders at Week 24, from both the phase IIb trial and phase III[8] trial (induction period), were randomised in a 1:1:1 ratio to one of three arms:
    - guselkumab 200mg SC Q4W
    - guselkumab 100mg SC Q8W
    - placebo SC Q4W
- patients who responded on placebo at Week 12, in both the phase IIb trial[31] and phase III trial (induction period)[8], were not re-randomised but continued to receive placebo SC Q4W
- patients who responded to guselkumab at Week 24, in both the phase IIb trial and phase III trial (induction period)[8], were not re-randomised but received guselkumab 200mg SC Q4W.

ASTRO trial: study design

To determine the efficacy of guselkumab SC (induction and maintenance) versus placebo in the ASTRO trial,[9] patients (N=418) were randomised in a 1:1:1 ratio to the following arms:

- guselkumab 400mg SC at Weeks 0, 4 and 8 followed by guselkumab 200mg SC Q4W (starting at Week 12) through Week 24
- guselkumab 400mg SC at Weeks 0, 4 and 8 followed by guselkumab 100mg SC Q8W (starting at Week 16) through Week 24
- placebo SC every Q4W from Week 0 through Week 24.

Rescue treatment was provided for patients who met rescue criteria at Week 16, defined as no improvement in Mayo endoscopy subscore at Week 12 and a <2-point improvement in partial Mayo score at Weeks 12 and 16, when compared with baseline. Rescue treatment consisted of:

- guselkumab 400mg SC at Weeks 16, 20 and 24 followed by guselkumab 100mg SC Q8W for patients in the placebo arm
- continuation of assigned guselkumab treatment regimen (200mg SC Q4W from Week 12 or 100mg SC Q8W from Week 16) and blinded sham rescue with matching placebo SC injections at Weeks 16, 20 and 24 for patients in either guselkumab arm.

All patients who benefited from treatment, in the opinion of the investigator, were eligible for the 72-week trial extension period with the same treatment regimen they received before Week 24 (either the treatment regimen assigned at randomisation, or the relevant rescue regimen).

Vedolizumab trial: study designs

The GEMINI-1 trial[42] included an induction period (6 weeks) and maintenance period (46 weeks). Patients (N=374) were initially randomly assigned, in a 3:2 ratio, to receive induction with vedolizumab 300mg IV or placebo IV on Days 1 and 15 (cohort 1). Additional patients (n=521) were enrolled in an open-label arm (cohort 2) to receive vedolizumab 300mg IV on Days 1 and 15. Patients from both cohorts who had a clinical response to vedolizumab at Week 6 (n=373) were randomly assigned (1:1:1) to receive vedolizumab 300mg IV Q4W, vedolizumab 300mg IV Q8W (with placebo administered every other visit to preserve blinding), or placebo Q4W. Patients who did not respond at Week 6 also received vedolizumab 300mg IV Q4W and were followed through to Week 52. However, they were not evaluated for efficacy, only safety.

In the VISIBLE-1 trial,[40] patients (N=383) were enrolled into an open-label trial to receive vedolizumab 300mg IV. At the end of Week 6, patients (n=218) who had responded to treatment were randomly assigned (2:1:1) to receive maintenance treatment with vedolizumab 108mg SC Q2W along with placebo IV Q8W, vedolizumab 300mg IV Q8W along with placebo SC Q2W, or placebo SC Q2W along with placebo IV Q8W. Patients were followed up for 52 weeks. Patients who had not achieved a clinical response at Week 6 received open-label vedolizumab 300mg IV at Week 6 and were re-assessed for clinical response at Week 14 and had the option to enrol into a separate open-label extension trial[43] if they had responded. Patients who did not respond to vedolizumab 300mg IV at Week 14 were discontinued.

Mirikizumab trial: study design

In the LUCENT-1/2 trials[39] patients (N=1281) were initially randomly assigned, in a 3:1 ratio to induction treatment with mirikizumab 300mg IV Q4W or placebo IV Q4W. At Week 12:

- patients who responded to treatment with mirikizumab were randomised to mirikizumab 200mg SC Q4W or placebo SC Q4W in the maintenance period
- patients who responded on placebo IV received placebo SC in the maintenance period
- patients in both the mirikizumab and placebo arms who did not have a response to induction received open-label extended induction with mirikizumab 300mg IV Q4W and were reassessed for clinical response at Week 24.

Patients who responded to induction treatment were followed up for 40 weeks in the maintenance period (52 weeks in total). Patients who had a loss of response at or after week 12 of the maintenance period discontinued mirikizumab 200mg SC Q4W or placebo SC Q4W and received rescue treatment with three doses of mirikizumab 300mg IV Q4W.

4.4.2 Included trials: eligibility criteria and patient characteristics

Clinical advice to the EAG is that, overall, the patients enrolled into the included trials are generally similar to patients who would be treated in the NHS.

Eligibility criteria

A summary of the trial eligibility criteria is presented in Table 5. The main differences between the trials related to the use of the total Mayo score or modified Mayo score to define severity and the type of ADTs previously used by patients in the ADT-failure populations. The trials of guselkumab[8,9,31] also included the Mayo rectal bleeding subscore as an eligibility criteria. The type of ADTs previously used reflected the type of ADTs used in clinical practice when the trials were conducted.

Clinical advice to the EAG is consistent with that received in the recent appraisal of risankizumab (TA998[20]) that results would not be expected to differ in patients who had prior exposure to only TNFi versus other advanced therapies such as JAKi or ozanimod. Clinical advice to the EAG is that, overall, the trial eligibility criteria were broadly similar for all trials. Clinical advice was that the eligibility criteria would likely result in patients being enrolled with similar characteristics to patients who would be treated in the NHS.

Table 5 Key eligibility criteria of included trials

Eligibility criteria	Trials of guselkumab		Trials of vedolizumab		Trials of mirikizumab
	QUASAR trials	ASTRO trial	GEMINI-1 trial	VISIBLE-1 trial	LUCENT-1/2 trial
Patients	Aged ≥18 years with documented diagnosis (histological and either endoscopic or radiographic) of moderately to severely active UC at least 3 months prior to screening	Aged ≥18 years with documented diagnosis (histological and either endoscopic or radiographic) of moderately to severely active UC at least 12 weeks prior to screening	Aged 18 to 80 years with moderately to severely active UC with a sigmoidoscopy subscore of ≥2, and disease that extended 15cm or more from the anal verge	Aged 18 to 80 years with moderately to severely active UC for >6 months, confirmed with histopathology	Aged 18 to 80 years with an established diagnosis of moderately to severely active UC at least 3 months prior to baseline (endoscopic evidence of UC and a histopathology report that supports a UC diagnosis)
Total Mayo Score	--	--	6 to 12	6 to 12	--
Modified Mayo score	4 to 9*	5 to 9	--	--	4 to 9
Mayo rectal bleeding subscore	≥1	≥1	--	--	--
Mayo endoscopic subscore	≥2	≥2	≥2	≥2	≥2
Extent of disease	≥20cm of involved colon	≥20cm of involved colon	≥15cm of involved colon	≥15cm of involved colon	Beyond rectum (rectosigmoid junction ~10 to ~15cm from the anal margin)
Prior failure category	Biologic/advanced or conventional therapy failure	Biologic/advanced or conventional therapy failure	Biologic/advanced or conventional therapy failure	Biologic/advanced or conventional therapy failure	Biologic/advanced or conventional therapy failure
Prior biologic/advanced therapy	TNFi, vedolizumab, or tofacitinib	TNFi, vedolizumab, ozanimod or approved JAK inhibitor (e.g., tofacitinib)	TNFi	TNFi	TNFi, anti-integrin (e.g., vedolizumab) or tofacitinib

*Patients with modified Mayo score 5-9 included in the overall trial full analysis set and safety analysis populations
JAKi=Janus kinase inhibitor; TNFi=tumour necrosis factor alpha inhibitor; UC=ulcerative colitis
Source: published papers[8,9,31,39,40,42]

Patient characteristics

Patient characteristics data for all six trials[8,9,31,39,40,42] were only available for the FAS populations (overall trial populations for efficacy). The EAG therefore compared baseline characteristics across the trials in the FAS populations. As baseline data were not available for all six trials,[8,9,31,39,40,42] the EAG compared the data between the FAS and ADT-failure population where the data were available.

FAS populations

A summary of the patient characteristics in each trial is presented in Table 6. Data are reported for all patients regardless of treatment arm since the EAG consider patient characteristics were well balanced between treatment arms in all six trials.[8,9,31,39,40,42] Data are presented for baseline at the induction period where available. However, it appears (but is not clear) that most data reported for the VISIBLE-1 trial[40] relate to when patients were randomised to maintenance treatment (Week 6). Where it is clear that data are reported for when patients entered the induction open-label study (baseline) in the VISIBLE-1 trial,[40] this is denoted by footnotes in the table.

The EAG considers that, from the data available, overall, patient characteristics were broadly similar across all trials, exceptions being:

- the proportion of patients with colitis limited to left side ranged from 37.9% in the GEMINI-1 trial[42] to 63.0% in the LUCENT-1/2 trial[8]
- median faecal calprotectin levels were notably lower in the GEMINI-1 trial[42] than in the other trials[8,9,31,39,40]
- the proportions of patients with severe disease (measured by total Mayo score) varied from 18.0% in the QUASAR phase III trial[8] to 61.6% in the VISIBLE-1 trial.[40]

Clinical advice to the EAG is that these differences are not likely to be important. While differences in disease extent across studies (i.e., colitis limited to left side) are noted, they are probably not important given that the cases are otherwise well-matched for severity on most of the traditional clinical parameters. While there appears to be a relatively lower proportion of patients categorised as having severe disease in the QUASAR trials,[8,31] the mean/median scores for traditional activity indices and biomarkers (C-reactive protein [CRP], calprotectin) were broadly comparable across the trials and the magnitude of any differences do not seem to be important.

Table 6 Patient characteristics of included trials [a]

	Trials of guselkumab [b]			Trials of vedolizumab [b]		Trials of mirikizumab [b]
Characteristic	**QUASAR phase IIb trial**	**QUASAR phase III trial**	**ASTRO trial**	**GEMINI-1 trial**	**VISIBLE-1 trial**	**LUCENT-1/2 trials**
Number of patients	313	701	418	895	216	1162
Number of treatment arms	3	2	2	3	3	2
Mean age, years	41.6	40.5	41.7	40.3	39.3	42.5
Male, %	59.1	56.9	61.2	58.7	60.2	59.8
Mean total Mayo Score	9.2	9.1	9.0	8.6	9.0 [c]	--
Severe (total Mayo score >10), % [d]	[redacted]	18.0	--	--	68.5 [d]	35.2 [d]
Mean modified Mayo score	7.0	6.9	6.7	--	--	--
Severe (modified Mayo score >6), %	69.6	[redacted]	62.1	--	--	53.2
Endoscopy subscore=3	70.0	67.9	56.0	--	--	66.7
Mean disease duration, years	7.6	7.5	7.6	6.9	7.9	7.1
UC limited to left side of colon, %	[redacted]	52.2	46.4	37.9	42.1	63.0
Median faecal calprotectin, ug/g *Lowest median value (any arm)* *Highest median value (any arm)*	1564 *1457* *1667*	1641 *1606* *1651*	1566 *1494.5* *1749*	899 *868* *1006*	-- [e] *1554* *1735*	-- [e] *1471.5* *1559*
Median CRP,mg/L	4.6	4.2	4.1	--	--	≥4.1 [e]
Concomitant therapies						
Immunomodulators, %	22.0	[redacted]	[redacted]	17.8 [f]	--	24.1 [f]
Corticosteroids, %	39.9	[redacted]	[redacted]	37.1 [g]	41.7	39.9
Aminosalicylates, %	77.3	[redacted]	[redacted]	--	--	74.3

[a] All data reported for baseline characteristics in the induction period, except for the VISIBLE-1 trial[40] where it seems most data were only available for the maintenance period (Week6) baseline characteristics (data are presented for the induction period where available)
[b] Baseline characteristics data are for the total population, i.e., pooled across all trial arms
[c] Data known to be baseline data, data also reported at Week 6 (not reported here); mean score not presented, median score is reported in the table
[d] Severe defined as total Mayo score of 9-12 in the VISIBLE-1 trial[40] and 10-12 in the LUCENT-1/2 trial[39]
[e] Data available for individual trial arms only
[f] Data were reported for patients with only concomitant immunomodulator therapy.
[g] Data were reported for patients with only concomitant corticosteroids.
BMI=Body-Mass Index; CRP=C-reactive protein; UC=ulcerative colitis.
Source: company NMA report[44] Table 3.4, guselkumab trials clinical study reports[9,36,37] and published papers[8,31,39,40,42]

In addition, the company presented the characteristics of patients when they entered the QUASAR phase III trial (maintenance period) (CS, Section B.3.3.1.3.2, Table 12). These characteristics were similar to those reported at induction baseline, with the exception of characteristics that would be expected to be impacted by treatment, i.e., measure of total Mayo score, modified Mayo score, partial Mayo score, CRP and faecal calprotectin.

ADT-failure populations

The company provided baseline characteristics for the ADT-failure populations of the QUASAR phase IIb trial,[31] QUASAR phase III trial[8] and ASTRO trial[9] (response to clarification question A12, CS, Section I.1.2 and response to clarification question A14, respectively). Baseline characteristics for the ADT-failure population were also available for the GEMINI-1 trial[42] ADT-failure population but not the other two comparator trials.[39,40]

The EAG considers that in the trials of guselkumab,[8,9,31] the baseline characteristics of the ADT-failure populations were similar to those of their respective FAS populations, with the following exceptions (related to the disease severity):

- the proportions of patients with left-sided colitis in the ASTRO trial[9] (FAS: 46.4%, ADT-failure: 35.7%)
- the proportions of patients with Mayo endoscopy subscore=3 in both the QUASAR phase III trial[8] (FAS: 67.9%, ADT-failure: [redacted]%) and ASTRO trial[9] (FAS: 56.0%, ADT-failure: 70.2%)
- median CRP (FAS: 4.1ug/g; ADT-failure: 5.1ug/g) and the proportion of patients with abnormal CRP (FAS: 57.5%, ADT-failure: 72.6%) in the ASTRO trial.[9]

The characteristics were also similar across the QUASAR trials[8,31] and ASTRO trial[9] ADT-failure populations with the exception of the proportion of patients with left-sided colitis. The proportion of patients with left-sided colitis was 35.7% in the ASTRO trial[9] ADT-failure population compared with 53.5% in the QUASAR phase III trial[8] ADT-failure population.

In the GEMINI-1 trial,[42] there were large variations in mean faecal calprotectin across the treatment arms in the ADT-failure population, from 1306ug/g in vedolizumab cohort 2 to 3008ug/g in vedolizumab cohort 1. These levels were higher than the overall GEMINI-1 trial[42] population but were lower than in the ADT-failure populations of the trials of guselkumab[8,9] In addition, fewer patients (31.3%) had left-sided colitis in the GEMINI-1 trial[42] ADT-failure population than in the QUASAR phase III trial[8] ADT-failure population (53.5%). Clinical advice to the EAG is that calprotectin levels vary considerably and although they are broadly correlated with severity of inflammation, values of 1306ug/g or 3008ug/g are both markedly raised and consistent with moderate to severe disease.

Clinical advice to the EAG is that, overall, patient characteristics were broadly similar to the ADT-failure population that would be seen in the NHS.

4.4.3 Statistical approach adopted for the analysis of results from the included trials

The EAG considers that the statistical approaches employed for each trial are appropriate. A summary of the key features of the statistical approach adopted for the analysis of results is provided below.

Trials of guselkumab

In all the QUASAR trials,[8,31] the primary efficacy populations (FAS) included all randomised and treated patients with a baseline modified Mayo score of ≥5 and ≤9 (even though the QUASAR trials[8,31] also included patients with a modified Mayo score of 4) who received ≥1 dose of trial treatment, analysed according to the assigned treatment. The primary safety population included all randomised and treated patients with a baseline modified Mayo score of ≥5 and ≤9 who received ≥1 dose of trial treatment, analysed according to the treatment they actually received. The ADT-failure populations were pre-defined subgroups in both trials.[8,31]

In the ASTRO trial,[9] both the FAS and safety populations included all randomised participants who received at least one dose of study intervention. The ADT-failure population (which was described as “inadequate response to or intolerance of advanced therapy” [ADT-IR]) was a pre-defined subgroup.

Comparator trials: vedolizumab

In the GEMINI-1 trial,[42] the primary outcome for induction treatment was clinical response at Week 6. The primary outcome for maintenance treatment was clinical remission at Overall Week 52. Efficacy analyses for both the induction and maintenance periods were performed according to the intention-to-treat principle. The safety population was defined as all patients who received at least one dose of the study drug. Analyses of data for the ADT-failure population were post-hoc analyses.[38]

In the VISIBLE-1 trial,[40] the primary efficacy outcome was clinical remission at Overall Week 52. Efficacy data were analysed in the FAS (all randomised patients who received ≥1 dose of study drug) according to treatment allocation. AEs were analysed in the safety analysis set (all randomised patients who received ≥1 dose of study drug according to actual treatment received). Pre-specified subgroup analyses were conducted for the ADT-failure population

Comparator trials: mirikizumab

In the LUCENT-1/2 trial,[39] the primary outcome in the induction trial was clinical remission at

Week 12. The primary outcome in the maintenance period was clinical remission at Week 40 (i.e., 52 weeks of follow-up). Efficacy analyses were performed in the modified intention-to-treat populations (all randomised patients who received ≥1 dose of trial treatment) for both the induction and maintenance studies. This modified intention-to-treat population included all patients who underwent randomisation and received any amount of mirikizumab or placebo but excluded patients affected by an electronic clinical-outcomes assessment transcription error that occurred in Poland and Turkey. The safety population in both studies included all patients who had undergone randomisation and received any amount of mirikizumab or placebo, including those who were affected by the electronic clinical-outcomes assessment transcription error. Pre-specified subgroup analyses were conducted for the five defined ADT-failure populations (biologic or tofacitinib failure [the ADT-failure population used for the company NMAs], biologic failure excluding tofacitinib, TNFi failure, TNFi and vedolizumab or tofacitinib failure, vedolizumab failure).

4.4.4 Key outcome definitions

All trials of guselkumab[8,9,31] and all comparator trials[39,40,42] included either clinical response or clinical remission as a primary or major secondary outcome. These were the two efficacy outcomes used for the company NMAs. A comparison of how these efficacy outcomes were defined and measured in the trials is presented in Table 7 and Table 8.

Table 7 Definition of clinical response used in included trials

Trials	Definition	Timepoint
Guselkumab: • QUASAR phase IIb trial [a] • QUASAR phase III trial [a] • ASTRO trial	• Decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a • ≥1-point decrease from baseline in the rectal bleeding subscore, or • absolute rectal bleeding subscore of 0 or 1	Induction: Week 12 Week 24 [b] Maintenance after induction: Week 44
Vedolizumab: • GEMINI-1 trial [c]	• Decrease from baseline in the total Mayo score by ≥30% and ≥3 points, with • ≥1-point decrease from baseline in the rectal bleeding subscore, or • absolute rectal bleeding subscore of 0 or 1	Induction: Week 6 Overall: Week 52
Mirikizumab: • LUCENT-1/2 trial	• Decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a • ≥1-point decrease from baseline in the rectal bleeding subscore, or • absolute rectal bleeding subscore of 0 or 1	Induction: Week 12 Week 24 [b] Overall: Week 52

[a] A different definition of response appears to have been used for the QUASAR trials[8,31] in the company network meta-analysis, i.e., identical to the definition used in the GEMINI-1 trial[42]
[b] Non-responders at Week 12
[c] Clinical response not measured in the VISIBLE-1 trial[40]
Source: CS, Table 7 and Table 13 and published papers[8,31,39,40,42]

Table 8 Definition of clinical remission used in included trials

Trials	Definition [a]	Timepoint
Guselkumab: • QUASAR phase IIb trial [a] • QUASAR phase III trial [a] • ASTRO trial	• Mayo stool frequency subscore of 0 or 1 which has not increased from induction baseline, with • Rectal bleeding subscore of 0, and • Endoscopy subscore of 0 or 1 with no friability present on the endoscopy	Induction: Week 12 Week 24 [b] Maintenance after induction: Week 44
Vedolizumab: • GEMINI-1 trial • VISIBLE-1 trial	• Total Mayo score of ≤2 and no subscore higher than 1 • Total Mayo score of ≤2 and no subscore higher than 1	Induction: Week 6 Overall: Week 52
Mirikizumab: • LUCENT-1/2 trial [c]	• Modified Mayo stool-frequency subscore of 0, or stool-frequency subscore of 1, with decrease of ≥1 point from baseline, and • rectal bleeding subscore of 0, and • endoscopy subscore of 0 or 1 with no friability present on the endoscopy	Induction: Week 12 Week 24 [b] Overall: Week 52

[a] A different definition of remission was used for the QUASAR trials[8,31] in the company network meta-analysis which was the same as that used in the GEMINI-1[42] and VISIBLE-1 trial[40]
[b] Non-responders at Week 12
[c] The LUCENT-1/2 trial also evaluated clinical remission using an alternate definition; this alternate definition is identical to that used in the trials of guselkumab and is the definition preferred by the US Food and Drug Administration [45]
Source: CS, Table 7 and Table 13 and published papers[8,31,39,40,42]

It is noticeable that in defining clinical response, the trials of guselkumab and mirikizumab used modified Mayo scores whereas the vedolizumab trials used total Mayo scores. It is also noticeable that the primary analyses had different timepoints for measuring efficacy of induction treatment: Week 12 for the analysis of guselkumab and mirikizumab and Week 6 for the analysis of vedolizumab. Furthermore, the timepoint for analysis of maintenance treatment also varied: 44 weeks from the start of maintenance (Maintenance Week 44) for the analysis of guselkumab (i.e., 56 weeks in total for responders at Week 12 and 68 weeks in total for responders at Week 24) and Overall Week 52 for the analysis of vedolizumab and mirikizumab.

The EAG highlights that a recent publication by Sandborn 2024[46] re-analysed and reported the post-hoc findings for vedolizumab versus placebo at Overall Week 52, using data from the GEMINI-1 trial[42] and VISIBLE-1 trial,[40] according to 4 different definitions (A to D) for clinical remission (all based on modified Mayo scores). The results from the analyses using these different definitions were then compared with the original GEMINI-1 trial[42] and VISIBLE-1 trial[40] results using the original definitions (based on total Mayo scores). The definitions tested included definitions that matched those used in the trials of guselkumab[8,9,31] (definition D) and the LUCENT-1/2 trial[39] (definition C with an alternate definition also used which matches definition D). Definitions C and D are described by Sandborn 2024[46] as the two definitions

most similar to those recommended by the United States Food and Drug Administration (FDA)[45] and the authors of the LUCENT-1/2 trial[39] consider definition D to be the most similar definition recommended by the FDA.[45] The results from the post hoc re-analyses found that of the four definitions tested, definitions C and D produced results that were most similar to the results from the original analyses originally reported in the GEMINI-1 trial[42] and VISIBLE-1 trial.[40] Sandborn 2024[46] concluded that comparisons of clinical remission outcomes can be made between trials that used the total Mayo score and trials using modified Mayo score-based outcome definitions.

Nonetheless, in the company NMAs, the company appear to have used data from the QUASAR trials[8,31] measured using alternate definitions of clinical response and clinical remission (based on total Mayo scores) to the primary definitions described in Table 7 and Table 8. These definitions were the same as those originally used in the GEMINI-1 trial[42] for clinical response and the GEMINI-1 trial[42] and VISIBLE-1 trial[40] for clinical remission. The rationale for using alternate definitions for the QUASAR trials[8,31] appears to be because the company's original NMAs (i.e., those included in the NMA report[44]) included additional trials of additional comparators, most of which used outcome definitions similar to the alternate definitions.

4.4.5 Quality assessment of the included trials

The company conducted quality assessments of the trials[8,31,38-40,42] included in the NMAs and the ASTRO trial[9] (see Table 9) using criteria recommended in the NICE Guide to the Methods of Technology Appraisal;[47] these methods are consistent with the methods recommended by the Centre for Reviews and Dissemination (CRD).[48]

Table 9 Company quality assessment for the phase III trials of guselkumab

Quality assessment item	Company assessment				
	QUASAR trials[8,31]	ASTRO trial[9]	GEMINI-1 trials,[38,42]	VISIBLE-1 trial[40]	LUCENT-1/2 trials[39]
a. Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes
b. Was concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes
c. Were the groups similar at the outset of the trial in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes
d. Were the care providers, participants, and the outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Yes
e. Were there any unexpected imbalances in dropouts between groups?	No	No	No [a]	Yes [a]	No
f. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No
g. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No [b]	No [c]	Yes	Yes [d]	Yes [d]

[a] There were large variations in dropout rates in the VISIBLE-1 trial[40] which randomised patients at the maintenance period. However, the EAG highlights similar imbalances were also found for patients re-randomised to maintenance treatment in the GEMINI-1 trial[42]; the EAG considers both trials have the same risk of bias for this item and in both instances the response should be 'No' since there was no unexpected loss to follow-up in either trial.
[b] The EAG disagrees with the company's assessment; the primary efficacy population was based on a modified intention-to-treat principle and included all randomised and treated patients with a baseline modified Mayo score of ≥ 5 and ≤ 9 who received ≥ 1 dose of study treatment analysed according to the assigned treatment (i.e., a modified intention-to-treat analysis). Hence the response to this item should be 'Yes'.
[c] The EAG disagrees with the company's assessment; the primary efficacy population included all randomised participants who received at least one dose of study intervention (i.e., a modified intention-to-treat analysis). Hence the response to this item should be 'Yes'.
[d] Modified intention-to-treat analysis.
Source: CS, Appendix D.3, Table 11

The EAG agrees that where randomisation was conducted, this appears to have been carried out appropriately. However, the EAG highlights that not all patients were randomised (or re-randomised) to treatment in the trials (see also Section 4.4.1 for more detail):

- no patient was randomised to induction treatment with vedolizumab in the VISIBLE-1 trial;[40] all but 5 patients who responded to induction treatment were randomised to subsequent maintenance treatment (which is the focus of the VISIBLE-1 trial[40])
- a high proportion of patients were not randomised to induction treatment with vedolizumab in the GEMINI-1 trial,[42] although patients who responded entered the maintenance period and were randomised to subsequent maintenance treatment
- not all patients in the maintenance period of the QUASAR trials[8,31] and LUCENT-1/2 trial[39] had been randomised to their allocated treatment, although most were.

The other potential risk of bias identified by the company relates to whether an intention-to-treat analysis was employed in the QUASAR trials[8,31] and ASTRO trial.[9] The EAG considers

modified intention-to-treat analyses were employed in these trials, as was the case in the LUCENT-1/2 trial[39] (the GEMINI-1 trial[42] and VISIBLE-1 trial[40] employed an intention-to-treat analysis). Therefore, the risk of bias for this item is the same across all trials.

Overall, the EAG considers that all trials are well-designed (given the challenges in evaluating induction and maintenance treatment within the same overall trial design) and all trials were well-conducted.

4.4.6 Sources of heterogeneity across trials

While the trial and patient characteristics were broadly similar across all trials, the EAG identified the following sources of heterogeneity:

- trials were conducted in different years; the earliest trial was the GEMINI-1 trial[42] (conducted between 2008 and 2012 when there were fewer treatment options) and the most recent trial is the ASTRO trial[9] (ongoing)
- induction treatment outcomes were evaluated at Week 6 (vedolizumab) or Week 12 or Week 24 (guselkumab and mirikizumab)
- maintenance treatment outcomes were evaluated at maintenance Week 44 (guselkumab) or Overall Week 52 (vedolizumab and mirikizumab)
- carry over effects from previous ADTs received prior to enrolment into the induction period
- carry over effects from active treatment received in the induction period for patients re-randomised to placebo in the maintenance period.

4.4.7 NMA methodology

Network diagrams for the company's NMAs are provided in the CS, Figure 5 (efficacy outcomes), and company's response to clarification question A5 (Figure 2 [SAEs] and Figure 3 [discontinuation due to AEs]).

As described in Section 4.4.6 of this EAG report, the time points of assessments for trials included in the NMAs varied for both the induction period and the maintenance period (from the start of maintenance treatment). The company made no adjustments to account for these different assessment time points.

The company conducted both fixed-effects and random-effects Bayesian NMAs, stating that random-effects models "were preferred a priori given differences in trial designs" (CS, p90). The EAG highlights that this preference was not pre-specified in the NMA protocol,[44] with the company instead stating that the relative fit between fixed-effects and random-effects models would be compared with deviance information criteria (DIC); a difference of 3-5 points would provide justification to prefer one model over another. For the company's NMAs for efficacy outcomes, model fit statistics did not provide any evidence to prefer either the random-effects

model or the fixed-effects model.[44] Considering some differences between the trials[8,31,39,40,42] included in the NMAs (noted in Section 4.4.6), the EAG agrees with the company that results from random-effects models are most appropriate for decision-making purposes. The company did not provide model fit statistics for the safety outcome NMAs, so the EAG is unable to assess the suitability of fixed-effects versus random-effects models.

'Normalisation' of trial designs in the maintenance period

In UC treatment research, trials that include a maintenance period adopt either a treat-through design, or a response re-randomised design. In treat-through trials, patients are randomised at baseline and outcomes are measured at the end of an induction period and at the end of a maintenance period. In response re-randomised trials, patients who achieve clinical response during an induction period (randomised or single-arm) are randomised to either placebo or to the maintenance dose of the intervention. Outcomes are then measured for these induction-phase responders at the end of the maintenance period. The company identified two variations of the treat-through trial design (Type 1 and Type 2), and two variations of the response re-randomised trial design (Type 3 and Type 4). These trial designs are described in Table 10.

Table 10 Treat-through and response re-randomised trial designs

Trial design	Description
Type 1	Treat–through. Continuation in the trial is not conditional on achieving response at a pre-defined time point; patients who elect to remain in the trial may have a delayed response to treatment
Type 2	Treat-through. Continuation in the trial is conditional on achieving response at a pre-defined time point
Type 3	Response re-randomised. Patients receiving active therapy who respond by an initial time point are re-randomised to continue active therapy or placebo
Type 4	Response re-randomised. Same as Type 3, but patients who do not initially respond to active treatment are provided with additional induction treatment to allow for delayed response. Outcome data for these delayed responders may be available (although these delayed responders are not typically included in the primary efficacy estimate)

Source: CS, Appendix D, pp34-35

In the mirikizumab appraisal (TA925[19]), the RCTs included in the company's NMAs included a mix of these trial designs. The company in TA925[19] attempted to account for differences between trial designs by converting data from treat-through trials to mimic re-randomised trials. All trials included in the company's NMAs for this appraisal employed a type 4 response re-randomised design. However, the company highlights, and the EAG agrees, that performing NMAs of data from the response re-randomised trials would be subject to important limitations. Namely, maintenance period placebo arms of these trials are fundamentally different; some of the maintenance period placebo arm patients had received and responded to placebo induction, whereas other maintenance period placebo arm patients had received and responded to active treatment induction (see Section 4.4.1 for more information). Different active treatments may have different carry-over effects. This may explain differences in

placebo response noted across trials (see Section 4.4.6). The EAG notes that in TA925,[19] the company converted data from treat-through trials to mimic re-randomised trials, and considers that these NMAs would be limited by fundamental differences between patients in the maintenance period placebo arms of the trials.

To overcome this limitation, the company 'normalised' data from each response re-randomised trial to mimic a Type 1 trial design as closely as possible; this approach was also used in the appraisal of ustekinumab (TA633).[18] The company proposes that the most relevant design for clinical decision making is the Type 1 treat-through design, stating that "rigid timelines for response assessment are not realistic in practice owing to realities of clinical scheduling and the decision for continued treatment being a shared one between individual patients and clinicians" (CS, Appendix D, p35). Clinical advice to the EAG is that patients may continue receiving active treatment in clinical practice if they experience some treatment benefit, even if they have not achieved a clinical response as defined in clinical trials. Therefore, the EAG considers that the Type 1 trial design is likely to generate estimates of treatment effectiveness that are reflective of clinical practice. The company's base-case maintenance period NMAs are hereafter referred to as the "maintenance period NMAs (with delayed responders)".

The company also conducted sensitivity analyses, which 'normalised' data from each trial to replicate a Type 2 treat-through trial design as closely as possible. These sensitivity analyses do not allow for delayed response; all patients who do not initially respond at induction are assumed not to achieve clinical response or remission at the maintenance time point.

In response to clarification question C4, the company provided the full NMA report.[44] The company used methods first proposed by Thorlund 2014[49] to 'normalise' data from the response re-randomised trials. To approximate the proportion of patients who would have responded to active treatment at the maintenance time point if no re-randomisation had occurred after induction, the company had to ensure that the proportions of active induction treatment responders and non-responders was the same at the maintenance time point as at the induction time point. The company therefore diluted the number of active treatment non-responders from the induction period, using a dilution factor that varies by trial and corresponds to the proportion of active induction treatment responders who were randomised to receive active maintenance treatment. The number of induction non-responders achieving clinical response, clinical remission and experiencing AEs were diluted in the same way. The company also made various assumptions and imputations to estimate maintenance outcomes for patients treated with placebo, and for patients who did not respond to active treatment.

If the required data were only available for a mixed ADT failure and ADT non-failure population, the company's approach varied:

- if subgroup data were not available for maintenance response/remission among active induction treatment responders, these data were not included in the analysis (i.e., no conversion from mixed was done)
- otherwise, i.e., for induction response (at initial or delayed time point), maintenance response/remission among placebo induction responders, and maintenance response/remission among induction non-responders, the company converted this mixed population to subgroup data following a procedure that is outlined in CS, Appendix D.

Full details of the calculations performed are provided in Appendix L to the NMA report.[44] With the exception of values obtained from individual patient data (IPD) for the ACT-1,[50] PURSUIT,[51] QUASAR,[8,31] and UNIFI[52] trials, the EAG was able to verify most data inputs used in the NMAs (see Section 4.4.9). Although the ACT-1,[50] PURSUIT[51] and UNIFI[52] trials were not included in the company's NMAs, IPD from these studies were used to impute maintenance outcomes for patients in the placebo arms of the "hypothetical" treat-through trials.

4.4.8 NMA results

Induction treatment NMA results

A summary of induction period NMA results is provided in Table 11.

Table 11 Induction period NMA results (random-effects model), guselkumab 200mg IV Q4W versus comparators

Outcome	OR (95% CrI) for guselkumab 200mg IV Q4W vs			
	Guselkumab 400mg IV Q4W	Vedolizumab 300mg IV [a]	Mirikizumab 300mg IV Q4W	Placebo
ADT-failure population				
Clinical response	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission	[redacted]	[redacted]	[redacted]	[redacted]
Mixed population				
SAEs	-- [b]	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs	-- [b]	-- [c]	[redacted]	[redacted]

[a] Administered on Day 1 and Day 15
[b] Guselkumab 400mg IV Q4W was not included as a comparator in the safety NMAs
[c] Discontinuation due to AEs data not available from the GEMINI-1 trial
Green shading indicates that the point estimate of the odds ratio favours guselkumab 200mg IV Q4W; red shading indicates that the point estimate of the odds ratio favours the comparator
ADT=advanced therapy; AE=adverse event; CrI=credible interval; IV=intravenous; OR=odds ratio; Q4W=every 4 weeks; SAE=serious adverse event
Source: CS, Figure 6 and Figure 7

For the comparison between guselkumab 200mg IV Q4W and vedolizumab 300mg IV, the odds ratio (OR) point estimate numerically favoured guselkumab 200mg IV Q4W for clinical

response, and favoured vedolizumab 300mg IV for clinical remission. The OR point estimate suggested little difference between the two treatments for the outcome of SAEs.

For the comparison between guselkumab 200mg IV Q4W and mirikizumab 300mg IV Q4W, OR point estimates numerically favoured guselkumab 200mg IV Q4W for clinical response, clinical remission, and SAEs. However, the OR point estimate numerically favoured mirikizumab 300mg IV Q4W in comparison to guselkumab 200mg IV Q4W for AEs leading to discontinuation.

In their response to clarification question A5, the company highlighted that the safety NMAs were limited by low event numbers. Indeed, for all comparisons and all outcomes, wide 95% credible intervals (CrIs) indicated a high level of uncertainty in the company NMA results. The EAG notes that fixed-effects NMA generated similar ORs to those from the random-effects model, although 95% CrIs were narrower (NMA report[44] and company response to clarification question A5, Figure 5 and Figure 7).

Maintenance treatment NMA results

A summary of maintenance period NMA (with delayed responders) results is provided in Table 12 (guselkumab 100mg SC Q8W versus comparators) and Table 13 (guselkumab 200mg SC Q4W versus comparators).

The EAG notes that three different regimens of vedolizumab were included as comparators in the company's maintenance period NMA: vedolizumab 108mg SC Q2W, vedolizumab 300mg IV Q8W and vedolizumab 300mg IV Q4W:

- the EAG considers that vedolizumab 108mg SC Q2W and vedolizumab 300mg IV Q8W are the most relevant vedolizumab regimens versus guselkumab 100mg SC Q8W
- as the vedolizumab 300mg IV Q4W regimen is an option for patients who have experienced a decrease in their response,[35] the EAG considers that this regimen is the most relevant comparator for vedolizumab versus guselkumab 200mg SC Q4W; these regimens are recommended for patients who do not show adequate therapeutic benefit, according to clinical judgement (Section 3.2 and 3.3.1).

Table 12 Maintenance period NMA (with delayed responders) results (ADT-failure population, random-effects model, guselkumab 100mg SC Q8W versus comparators)

Outcome	OR (95% CrI) for guselkumab 100mg SC Q8W vs					
	Guselkumab 200mg SC Q4W	Vedolizumab 108mg SC Q2W	Vedolizumab 300mg IV Q8W	Vedolizumab 300mg IV Q4W	Mirikizumab 200mg SC Q4W	Placebo
Clinical response	[redacted]	--*	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The VISIBLE-1 trial[40] does not report clinical response data by ADT-failure status, and so was not included in the NMA for this outcome
Green shading indicates that the point estimate of the odds ratio favours guselkumab 100mg SC Q8W; red shading indicates that the point estimate of the odds ratio favours the comparator
ADT-advanced therapy; CrI=credible interval; IV=intravenous; OR=odds ratio; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SC=subcutaneous
Source: CS, Figure 8 and Figure 9

Table 13 Maintenance period NMA (with delayed responders) results (ADT-failure population, random-effects model, guselkumab 200mg SC Q4W versus comparators)

Outcome	OR (95% CrI) for guselkumab 200mg SC Q4W vs					
	Guselkumab 100mg SC Q8W	Vedolizumab 108mg SC Q2W	Vedolizumab 300mg IV Q8W	Vedolizumab 300mg IV Q4W	Mirikizumab 200mg SC Q4W	Placebo
Clinical response	[redacted]	--*	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The VISIBLE-1 trial[40] does not report clinical response data by ADT-failure status, and so was not included in the NMA for this outcome
Green shading indicates that the point estimate of the odds ratio favours guselkumab 200mg SC Q4W; red shading indicates that the point estimate of the odds ratio favours the comparator
CrI=credible interval; IV=intravenous; OR=odds ratio; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W= every 8 weeks; SC=subcutaneous
Source: CS, Figure 8 and Figure 9

Maintenance period NMA (with delayed responders) results favoured guselkumab 100mg SC Q8W over vedolizumab 108mg SC Q2W (only clinical remission data is available for vedolizumab 108 SC Q2W in the public domain) and vedolizumab 300mg IV Q8W (clinical response and clinical remission).

The ORs numerically favoured guselkumab 100mg SC Q8W over mirikizumab 200mg SC Q4W for clinical response, but the point estimate suggested little difference between the treatments in terms of clinical remission.

For the comparison between guselkumab 200mg SC Q4W and vedolizumab 300mg IV Q4W, point estimates of ORs numerically favoured guselkumab 200mg SC Q4W for both clinical response and clinical remission.

For the comparison between guselkumab 200mg SC Q4W and mirikizumab 200mg SC Q4W, the OR point estimate numerically favoured guselkumab 200mg SC Q4W for clinical response, and favoured mirikizumab 200mg SC Q4W for clinical remission.

The results from all maintenance period (with delayed responders) NMAs were highly uncertain, as demonstrated by wide 95% CrIs. The EAG notes that fixed-effects NMAs generated similar odds ratios to those from the random-effects model, although 95% credible intervals were narrower.[44] Results from sensitivity analyses, which did not allow for delayed response to induction, were similar to those from the base-case NMAs (CS, Appendix I, pp122-123).

4.4.9 EAG comment on company NMAs: key issues

The EAG considers that the methods used by the company to conduct the NMAs were generally appropriate. The company's methods rely heavily on data imputations and assumptions, but the EAG is not aware of an alternative approach that could have been used that would provide more robust results.

With the exception of values obtained from IPD for trials conducted by the company,[8,31] the EAG was able to verify most data inputs used in the NMAs. The EAG notes that the numbers of patients achieving clinical response and clinical remission at week 12 in the QUASAR trials[8,31] (reported in Appendix O to the NMA report[44]) do not match values reported in the CS (CS, Table 17, Table 20 and CS, Appendix H, Figure 13B). The EAG considers that the clinical remission data may differ as the company used an alternative definition of clinical remission (based on total Mayo Score) in the NMAs to the definition used in the QUASAR trials[8,31] (based on modified Mayo Score, CS, p89). Considering information provided in Appendix K to the NMA report,[44] the EAG assumes that the company used an alternative definition of clinical response in the NMAs (based on total Mayo Score) to the definition used in the QUASAR trials[8,31] (based on modified Mayo Score). Nevertheless, differences between the data inputs used in the NMAs and the data values reported in the CS are minor, and the EAG considers that they are unlikely to have an important impact on conclusions that can be drawn from the company's NMAs.

The EAG notes that data on delayed response at an intermediate time point (week 24) were available from the QUASAR[8,31] and LUCENT-1/2[39] trials but not the GEMINI-1[38] or VISIBLE-1[40] trials. This is a source of heterogeneity in the company's maintenance period NMAs (with delayed responders). Results from the company's sensitivity analyses, which did not allow for delayed response to induction, provide reassurance that including intermediate time point delayed responder data from the QUASAR[8,31] and LUCENT-1/2[39] trials but not the GEMINI-

1[38] or VISIBLE-1[40] trials has not had an important impact on the NMA treatment efficacy estimates.

All NMA results produced wide 95% credible intervals for all comparisons. The company partially attributes the wide credible intervals to the loss of power resulting from re-randomisation of patients in the included trials. The EAG notes that substantial uncertainty was observed for both induction period results (which would be unaffected by re-randomisation) and maintenance period NMA results. Therefore, the EAG considers it is likely that some uncertainty in the results can also be attributed to the sparse nature of the evidence network, and notes that heterogeneity between trials made the random effects model the most appropriate analysis method, which inherently leads to wider credible intervals (than the fixed effects model).

The EAG highlights that uncertainty in the estimates of treatment effect from the maintenance period NMAs has been underestimated. This is because the company's maintenance period NMAs rely heavily on data imputation, particularly for the estimation of maintenance outcomes among those who did not respond at induction to either placebo or active treatment. The company replaced missing response and remission rates for these patients with single, predicted values (i.e. single imputation). The company's NMA methodology treats the imputed values as if they were observed data, ignoring the fact that these values were imputed with uncertainty. If the company had accounted for imputation uncertainty, 95% CrIs would have been even wider.

To demonstrate that guselkumab offers similar or greater health benefits to a comparator treatment, the EAG considers that 95% CrIs for the ORs (for all outcomes) ought to exclude the possibility of a clinically important treatment effect in favour of a relevant comparator treatment. However, the EAG highlights that the reported 95% CrIs (for all relevant comparators, all outcomes, base-case and sensitivity NMAs) that indicate a clinically important treatment effect in favour of the intervention also include ORs that indicate a clinically important treatment effect in favour of the comparator treatment. Indeed, all 95% credible intervals included either a doubling or a halving (or both) of the odds of the event. Furthermore, if the company had accounted for imputation uncertainty, the 95% CrIs would have been wider, including even greater clinically important treatment effects in favour of the relevant comparators. Therefore, the EAG considers that the company's NMAs alone do not demonstrate that guselkumab offers similar or greater health benefits to the relevant comparator treatments.

4.5 Additional support for similar or greater health benefits

As the NMA results cannot be considered to be definitive, the EAG sought additional evidence to support the assumption of whether guselkumab could be considered to have similar or greater health benefits than vedolizumab and mirikizumab:

- the EAG conducted informal comparisons of the individual trial results, i.e., an examination of similarities or differences across trials without using statistical methods
- the EAG sought evidence from published NMAs.

4.5.1 Individual trial results

The results of the EAG's informal comparisons are presented in Appendix 1 (Section 10).

In summary, in the induction period, trial results suggest that the proportion of patients treated with guselkumab achieving clinical response and clinical remission was similar to that of patients treated with mirikizumab and greater than the proportion of patients treated with vedolizumab; the proportion of patients achieving endoscopic response was broadly similar for guselkumab, mirikizumab and vedolizumab. In the maintenance period, trial results suggest that the proportion of patients treated with guselkumab maintaining clinical response and clinical remission was similar to that of patients treated with mirikizumab and likely greater than the proportion of patients treated with vedolizumab; the proportion of patients maintaining endoscopic response was broadly similar for guselkumab, mirikizumab and vedolizumab. Differences in placebo response to efficacy outcomes were observed across all trials in the induction and maintenance periods. Differences in placebo response across trials tended to be less marked in the ADT-failure populations than in the FAS populations.

No notable differences in the proportions of patients with the types of AEs measured in the trials were observed from the EAG's informal comparisons of individual trial results. This suggests the safety profiles may be broadly similar although the safety data that could be compared across trials was limited to mixed populations of patients with and without ADT-failure.

4.5.2 Published network meta-analysis results

The EAG identified three published NMAs[53-55] that compared the efficacy and safety of guselkumab versus alternative treatment options. Only one of these NMAs (Ananthakrishnan 2024[53]) carried out NMAs including only patients who had previously been treated with an ADT. Not all patients had necessarily failed treatment with an ADT; the proportion of patients who failed treatment with an ADT is unknown.

In relation to the comparators of interest to this appraisal, Ananthakrishnan 2024[53] included the QUASAR phase IIb trial,[8] QUASAR phase III trial,[8] GEMINI-1 trial,[38] and LUCENT-1/2

trial.[39] Additional evidence for vedolizumab was included from a phase III placebo-controlled RCT which only included Japanese patients[56] and the phase IIIb VARSITY trial[57] comparing vedolizumab versus adalimumab. Additional evidence for mirikizumab was included from the AMAC phase II RCT.[58] NMAs were conducted using the frequentist approach. The key results relating to induction treatment of relevance to this appraisal were:

- compared with placebo, there was moderate-certainty evidence that guselkumab and mirikizumab (relative risk [RR] 2.86; 95% CI: 1.39 to 5.88 and RR 2.83; 95% CI: 1.30 to 4.16, respectively) were associated with a higher likelihood of achieving clinical remission whereas there was low-certainty evidence with vedolizumab (RR 1.64; 95% CI: 0.82 to 3.36)
- compared with vedolizumab, there was low certainty evidence that guselkumab and mirikizumab were associated with a higher likelihood of achieving clinical remission (RR 1.73; 95% CI: 0.64 to 4.71 and RR 1.41; 95% CI: 0.57 to 3.49, respectively)
- compared with mirikizumab, there was very low certainty evidence that guselkumab was associated with a higher likelihood of achieving clinical remission (RR 1.23; 95% CI: 0.49 to 3.10)
- compared with vedolizumab, guselkumab and mirikizumab led to statistically significantly higher likelihood of endoscopic improvement (RR 2.57; 95% CI: 1.24 to 5.31 and 1.94; 95% CI: 1.08 to 3.51, respectively); there was no statistically significant difference between guselkumab and mirikizumab (RR 1.32; 95% CI: 0.62 to 2.82).

Guselkumab was not included in the maintenance NMAs.

4.6 Summary of the clinical effectiveness section

In the absence of any trials directly comparing guselkumab versus vedolizumab or versus mirikizumab, the company's evidence for the comparability of guselkumab is derived from NMAs. Although the NMAs were well conducted and, in most instances, results showed the point estimate of the odds ratio favoured guselkumab versus the comparators, the point estimates were accompanied by wide 95% credible intervals, indicating considerable uncertainty.

Informal comparisons of individual trial results conducted by the EAG suggest the proportion of patients treated with guselkumab achieving and/or maintaining defined clinical outcomes tend to be at least similar to the proportions reported for patients treated with mirikizumab or vedolizumab (induction and maintenance). The safety profiles were also broadly similar. However, this informal comparison cannot be considered to be as robust as NMAs because differences for baseline risk across trials cannot be accounted for. Furthermore, differences in placebo response to efficacy outcomes were observed across trials.

The EAG also summarised results from NMAs conducted by Ananthakrishnan 2024.[53] While guselkumab was found to be superior to vedolizumab in relation to endoscopic healing as induction treatment, there was no statistically significant difference between guselkumab and

mirikizumab. The results did not find guselkumab to be statistically superior to vedolizumab or mirikizumab in relation to clinical remission. NMAs were not conducted for safety outcomes and data were not reported for guselkumab in the maintenance period.

Overall, the EAG considers there is some evidence that guselkumab may have at least similar clinical efficacy and safety to vedolizumab and mirikizumab, but the evidence is not definitive.

5 EAG CRITIQUE OF COMPANY COST COMPARISON EVIDENCE

5.1 Company approach to cost comparison analysis

The company submitted an economic model, developed in Microsoft® Excel, to generate cost comparison results for guselkumab versus vedolizumab and for guselkumab versus mirikizumab for treating moderately to severely active UC. The EAG considers that a lack of definitive evidence to demonstrate that guselkumab provides similar or greater health benefits to other vedolizumab or mirikizumab in the ADT-failure setting means that it is not clear if a cost comparison analysis approach is appropriate.

The EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the CS and in the original sources. A summary of the EAG's review of the company cost comparison analysis is presented in Table 14.

Table 14 Summary of EAG's review of company cost comparison analysis

Parameter	Company base case	EAG comment
Time horizon	10 years	Appropriate
Cycle length	2 weeks	Appropriate
Discount rate (costs)	0%	Appropriate
Age	42.6 years	Appropriate
Proportion M:F	59.4%:40.6%	Appropriate
Dose escalation	Vedolizumab: Yes Mirikizumab: Yes Guselkumab: No	Dose escalation occurs earlier in the company model than is reported in the literature (Section 5.2.3)
Extended induction/delayed responders	Vedolizumab: Yes Mirikizumab: Yes Guselkumab: Yes	Appropriate
Administration: induction	Vedolizumab: IV 100% Mirikizumab: IV 100% Guselkumab: IV 20%/SC 80%	[redacted] (Section 5.2)
Administration: maintenance	Vedolizumab: IV 50%/SC 50% Mirikizumab: SC 100% Guselkumab: SC 100%	A lower proportion of patients in the company model switch to vedolizumab SC maintenance than is reported in the literature (Section 5.2.4)
AEs	Not included	Appropriate
Probability of response after 1st induction	[redacted] (derived from company NMA)	EAG prefers to use absolute probabilities directly from QUASAR trials[8,31] (Section 5.2.1)
Probability of response after extended induction	46.5% (NICE TA633 [Ustekinumab])	
Discontinuation	Constant rate across model time horizon (11.1% at 44 weeks [QUASAR trial[8]])	Clinical advice and evidence from the literature suggests that discontinuation rates decline over time (Section 5.2.2)

AE=adverse events; EAG=External Assessment Group;; F=female; M=male; NMA=network meta-analysis; SC=subcutaneous

5.2 EAG correction and revisions

The EAG made four revisions to the company model (see Section 5.2.1 to Section 5.2.4). The EAG has also updated the model base case at the request of NICE so that guselkumab induction is administered 100% via IV in accordance with the expected marketing authorisation (see Section 2.4). [redacted] The EAG has also reorganised the disaggregated results for guselkumab so that total induction costs include delayed responders. The EAG has calculated extended delayed responder costs for guselkumab in the same way that extended induction costs are calculated for vedolizumab and mirikizumab. This change makes a minor ([redacted]) difference to total treatment costs.

5.2.1 Probability of response after induction

The company calculated the probability of initial response after induction (assessed at Week 12 for guselkumab and mirikizumab, and at Week 6 for vedolizumab) using the absolute probability of placebo response ([redacted]) and the OR for guselkumab versus placebo from the company's random effects NMA. There is considerable uncertainty around the OR of primary response after induction for guselkumab versus placebo [redacted], CS, Figure 6), which translates into considerable uncertainty in the probability of initial response to induction ([redacted]), assuming the probability of placebo response remains fixed at [redacted]. The company has assumed that 46.5% of people receiving extended induction (assessed at Week 24 for guselkumab and mirikizumab, and at Week 14 for vedolizumab) will achieve a delayed response and move to maintenance treatment. This value is from TA633[18] and represents overall delayed response for patients treated with ustekinumab in the bio failure subgroup in the UNIFI trial.[52]

The EAG's preference, is that, where possible, these two estimates of clinical response should be a) derived from the same patient group for consistency and b) relate to either the intervention or comparators. The absolute probability of initial response after induction and of delayed response after extended induction for guselkumab are both available from the QUASAR trials[8,31] (Table 15). The EAG has used the average Week 12 response rate across the QUASAR trials[8,31] (52.0%) to represent probability of initial response and the average Week 24 response rate ([redacted]) to represent probability of delayed response to extended induction for all three treatments in the economic model.

Table 15 Clinical response at Week 12 and Week 24 in the guselkumab QUASAR trials

Regimen	Trial	Response rate % (n/N)
Clinical response at Week 12 in the guselkumab trials (ADT-failure population)		
GUS 200mg IV Q4W W12	QUASAR phase IIb trial	54.3% (25/46)
	QUASAR phase III trial	51.4% (107/208)
	IV trials average	**52.0% (132/254)**
GUS 400mg SC Q4W W12	ASTRO trial	57.1% (64/112)
All	**Overall trials average (IV and SC)**	**53.6% (196/366)**
Clinical response at Week 24 in the guselkumab trials (ADT-failure population)		
GUS 200mg IV Q4W W12 to GUS 200mg SC Q4W	QUASAR phase IIb trial	50.0% (10/20)
	QUASAR phase III trial	[redacted]
	IV trials average	[redacted]

GUS=guselkumab; IV=intravenous; n=number of events; N=number of patients; SC=subcutaneous; W12=Week 12
Source: CS, Table 20, CS, Table 24, CS, Table 35 and published papers[8,31,39]

5.2.2 Long term discontinuation rate

The company used the QUASAR phase III trial[8] guselkumab 200mg Q4W discontinuation rate at 44 weeks to calculate the cycle discontinuation rate for all treatments in the company model. The cycle discontinuation rate is applied as a constant probability of discontinuation throughout the model time horizon. The discontinuation rate is one of the most influential variables in the company model (CS, Table 57 and CS Table 58).

Clinical advice to the EAG is that treatment discontinuation following initial primary response is most common in the first two years after beginning treatment. In a recent retrospective, observational, cohort study,[59] 21.7% (63/290) of patients discontinued vedolizumab due to secondary non-response after initial primary response. Of these, the majority discontinued within two years of beginning induction therapy (14%; [8+33]/290) with discontinuation dropping year on year thereafter (year 3=4.5%; year 4=1.7%; and year 5=1.4%). The EAG has presented a scenario that illustrates the impact of reducing discontinuation rates from two years after beginning treatment. In the scenario, discontinuation rates in the maintenance period are set to halve each year from year two onwards.

Table 16 Percentage of patients discontinuing annually during maintenance period*

Scenario	Years from beginning maintenance treatment				
	1	2	3	5	10
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Declining annual discontinuation rate after 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* The proportion of people discontinuing treatment is on top of background mortality included elsewhere in the company model
Source: company model

5.2.3 Dose escalation and reinduction

The SmPC[21,35] for the comparators recommends that dose escalation (vedolizumab) and reinduction (mirikizumab) may be offered to patients with loss of therapeutic benefit during

maintenance treatment. The company assumed that 30% of patients who receive maintenance treatment with either vedolizumab IV or mirikizumab will be prescribed an escalated dosing regimen or reinduction, as appropriate. The company has assumed that dose escalation or reinduction occurs at the beginning of the maintenance period (vedolizumab=Week 14, mirikizumab=Week 12) in the base case (Table 17).

Table 17 Base case dose escalation and reinduction

Treatment	Standard maintenance regimen	Escalated/reinduction		
		Regimen	Proportion receiving	Duration
Vedolizumab	300mg IV Q8W or 108mg SC Q2W	300mg IV Q4W	30% of responders receiving IV maintenance. Not available for patients using SC maintenance	From start of maintenance (Week 14) until end of model
Mirikizumab	200mg SC Q4W	300mg IV Q4W	30% of all responders (after induction and extended induction)	From start of maintenance (Week 12) for 12 weeks
Guselkumab	100mg SC Q8W	n/a	n/a	n/a

IV=intravenous; n/a=not applicable; Q4|W=every 4 weeks; Q8W=every 8 weeks; SC=subcutaneous
Source: EAG extraction from company model

The results of a 2021 retrospective cohort study[60] showed that median time to dose escalation for vedolizumab was 46 weeks (interquartile range 25–72). The EAG has revised the company model so that dose escalation and reinduction are implemented in line with the published value. Dose escalation and reinduction were implemented from Week 48 onwards instead of Week 46, due to the model dosing structure.

5.2.4 Vedolizumab maintenance administration method

The company assumed that, following IV induction therapy, 50% of patients treated with vedolizumab will switch to SC administration for maintenance therapy. There is no difference in the total vedolizumab drug cost of IV 300mg Q8W and SC 108mg Q2W when considered per eight-week treatment cycle. However, since dose escalation is only permitted for those patients receiving the drug via IV administration, a higher proportion of patients receiving IV vedolizumab will lead to more dose escalations (increasing frequency of doses from Q8W to Q4W) and therefore higher costs for vedolizumab. In the 2021 TRAVELESS study,[61] 70% (124/178) of UK patients offered the opportunity to switch from IV to SC vedolizumab agreed to transition. No clinically significant differences were noted between those who transitioned and those who did not 12 weeks after switching. The EAG has increased the proportion of patients receiving vedolizumab SC maintenance to 70% to reflect the findings of the TRAVELESS study.[61]

6 COMPANY AND EAG COST COMPARISON ANALYSIS RESULTS

6.1 EAG cost comparison analysis conclusions

The EAG has made the following revisions to the company base case cost comparison analysis:

- guselkumab induction 100% IV (updated base case)
- guselkumab extended induction period included in induction costs (updated base case)
- adjusted probability of response after induction/extended induction (R1)
- adjusted long term discontinuation rate (R2)
- adjusted timing of dose escalation and reinduction (R3)
- increased proportion of patients receiving vedolizumab SC maintenance (R4).

Details of the EAG revisions to the company model are presented in Appendix 2 (Section 11). The EAG cost comparison analysis results (guselkumab PAS price) are presented in Table 19 and Table 20. Cost comparison results using the PAS prices for guselkumab, vedolizumab and mirikizumab are provided in a confidential appendix. The sources of the prices used in the confidential appendix are presented in Table 18.

Table 18 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Guselkumab	Simple PAS discount
Vedolizumab	Simple PAS discount
Mirikizumab	Simple PAS discount

PAS=Patient Access Scheme
Source: Price tracker (February 2025)

The EAG considers that the company cost comparison model generates robust results. The only EAG revision with a major individual impact on incremental costs was the change from constant to declining discontinuation rates, which reduced incremental costs by increasing the cost of the comparators proportionately more than the cost of guselkumab. All other EAG revisions only had comparatively small ([redacted]) individual effects on the company's base case results.

Table 19 Company base case and EAG cost comparison results: guselkumab 100% IV induction versus vedolizumab (guselkumab PAS price)

Scenario/EAG revision	Guselkumab			Vedolizumab			Incremental costs	Change from (A2) base case
	Induction costs	Maintenance costs	Total treatment costs	Induction costs	Maintenance costs	Total treatment costs		
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A2. Update company base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1. Adjusted probability of response after induction/extended induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2. Adjusted long term discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3. Adjusted timing of dose escalation and reinduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4. Increased proportion of patients receiving vedolizumab SC maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG combined revisions (A2+R1 to R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Includes guselkumab induction 100% IV and guselkumab extended induction period included in induction costs
EAG=Evidence Assessment Group; IV=intravenous; PAS=Patient Access Scheme

Table 20 Company base case and EAG cost comparison results: guselkumab 100% IV induction versus mirikizumab (guselkumab PAS price)

Scenario/EAG revision	Guselkumab			Mirikizumab			Incremental costs	Change from (A2) base case
	Induction costs	Maintenance costs	Total treatment costs	Induction costs	Maintenance costs	Total treatment costs		
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A2. Update company base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1. Adjusted probability of response after induction/extended induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2. Adjusted long term discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3. Adjusted timing of dose escalation and reinduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1. EAG combined revisions (A2+R1 to R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Includes guselkumab induction 100% IV and guselkumab extended induction period included in induction costs
EAG=Evidence Assessment Group; IV=intravenous; PAS=Patient Access Scheme

7 EQUALITIES AND INNOVATION

In the CS (Section B.1.4), the company highlights that IBD is often called an “invisible disability”. The company argues that an effective treatment can help people living with UC to live “a more normal life”, giving them the same chances at work or education and helping them maintain emotional and physical relationships just like people without IBD.

Guselkumab and mirikizumab are similar treatments in terms of mechanism of action. Other IL-23 inhibitors (mirikizumab and risankizumab) are recommended by NICE as a treatment option for moderately to severely active ulcerative colitis (TA925[19] and TA998,[20] respectively) and, therefore, guselkumab cannot be considered an innovative treatment.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Clinical effectiveness evidence

The EAG considers that the most robust evidence to show guselkumab has similar or greater health benefits versus vedolizumab or mirikizumab would be derived from direct evidence, ideally from a non-inferiority or equivalence RCT. However, there is no direct RCT evidence for guselkumab versus these comparators.

Given the lack of direct evidence, the company conducted NMAs for two key efficacy outcomes (clinical response and clinical remission) for the induction and maintenance periods. The company also conducted NMAs of SAEs and AEs leading to discontinuation during the induction period.

The EAG considers that all trials[8,31,39,40,42] included in the NMAs are well-designed and well-conducted. In all trials[8,31,39,40,42] included in the NMAs, the overall trial populations (mixed populations of patients with and without ADT-failure) had broadly similar eligibility criteria and patients enrolled had characteristics that are generalisable to patients who would be treated in the NHS. However, differences in placebo response to efficacy outcomes across trials were observed (in both the induction and maintenance periods). These differences may result from:

- trials conducted in different years
- outcomes evaluated at different time points (induction and maintenance periods)
- carry over effects from previous ADTs received prior to enrolment into the induction period
- carry over effects from active treatment received in the induction period for patients re-randomised to placebo in the maintenance period.

Differences in placebo response across trials tended to be less marked in the ADT-failure populations than in the overall trial populations.

The company considered, and the EAG agrees, that performing NMAs of treat-through trials overcomes the problem of fundamental differences between maintenance period placebo arm patients that affect NMAs of response re-randomised trials. Therefore, the company 'normalised' the data so that they mimicked treat-through designs.

Results from the company NMAs showed that the point estimate of the odds ratio favours guselkumab versus relevant comparators in most instances. However, all NMA results produced wide 95% CrIs for all comparisons, indicating substantial uncertainty in the results.

The EAG informal comparisons of individual trial results suggesting that guselkumab offers similar or greater health benefits to vedolizumab and mirikizumab (as measured by efficacy and safety outcomes) provide less robust evidence. This is because differences for baseline risk across trials cannot be accounted for and differences in placebo response to efficacy outcomes were observed across trials.

Induction period NMAs conducted by Ananthakrishnan 2024[53] did not show guselkumab to be statistically superior to vedolizumab or mirikizumab for efficacy outcomes apart from versus vedolizumab for endoscopic healing.

Overall, the EAG considers there is some evidence that guselkumab may have at least similar efficacy and safety to vedolizumab and mirikizumab, but the evidence is not definitive. Given the lack of definitive evidence, it is not possible to rule out there being important differences in some treatment outcomes (efficacy and/or safety) for guselkumab versus vedolizumab or versus mirikizumab.

8.2 Cost effectiveness evidence

The EAG considers that company cost comparison methods were largely appropriate, and model results are robust. The only EAG revision with a large individual impact on the company results is the change from a constant to a declining discontinuation rate. All other EAG revisions were minor and had comparatively small ([redacted]) individual effects on the company base case results.

9 REFERENCES

1. National Institute for Health and Care Excellence. [ID6237] Guselkumab for moderately to severely active ulcerative colitis: final scope. Available from: https://www.nice.org.uk/guidance/gid-ta11247/documents/final-scope. Accessed 22 April 2025.
2. National Institute for Health and Care Excellence. Clinical Knowledge Summary: Ulcerative colitis. Last revised in March 2024. Available from: https://cks.nice.org.uk/topics/ulcerative-colitis/]. Accessed 22 April 2025.
3. Le Berre C HS, Peyrin-Biroulet L. Ulcerative colitis. Lancet. 2023; 402.
4. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017; 389:1756-70.
5. National Institute for Health and Care Excellence. [NG130] Ulcerative colitis: management. Published: 03 May 2019. Available from: https://www.nice.org.uk/guidance/ng130]. Accessed 22 April 2025.
6. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V*, et al.* ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019; 13:144-64.
7. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK*, et al.* British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019; 68:s1-s106.
8. Rubin DT, Allegretti JR, Panés J, Shipitofsky N, Yarandi SS, Huang K-HG*, et al.* Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR): phase 3 double-blind, randomised, placebo-controlled induction and maintenance studies. Lancet. 2025; 405:33-49.
9. Johnson & Johnson. [Data on file] ASTRO clinical study report (Week 24). RF-4513332025.
10. King D RR, Thomas T, Chandan JS, Thayakaran R, Subramanian A, Gokhale K, Bhala N, Nirantharakumar K, Adderley NJ, Trudgill N. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. Aliment Pharmacol Ther 2020; 51:922-34.
11. National Institute for Health and Care Excellence. [TA828] Ozanimod for treating moderately to severely active ulcerative colitis. Published: 05 October 2022. Available from: https://www.nice.org.uk/guidance/ta828]. Accessed 22 April 2025.
12. National Institute for Health and Care Excellence. [TA956] Etrasimod for treating moderately to severely active ulcerative colitis in people aged 16 and over. Published: 11 March 2024. Available from: https://www.nice.org.uk/guidance/ta956]. Accessed 22 April 2025.
13. National Institute for Health and Care Excellence. [TA329] Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. Published: 25 February 2015. Available from: https://www.nice.org.uk/guidance/ta329]. Accessed 22 April 2025.
14. National Institute for Health and Care Excellence. [TA342] Vedolizumab for treating moderately to severely active ulcerative colitis. Published: 05 June 2015. Available from: https://www.nice.org.uk/guidance/ta342]. Accessed 22 April 2025.
15. National Institute for Health and Care Excellence. [TA547] Tofacitinib for moderately to severely active ulcerative colitis. Published: 28 November 2018. Available from: https://www.nice.org.uk/guidance/TA547]. Accessed 22 April 2025.
16. National Institute for Health and Care Excellence. [TA792] Filgotinib for treating moderately to severely active ulcerative colitis. Published: 01 June 2022. Available from: https://www.nice.org.uk/guidance/ta792]. Accessed 22 April 2025.
17. National Institute for Health and Care Excellence. [TA856] Upadacitinib for treating moderately to severely active ulcerative colitis. Published: 04 January 2023. Available from: https://www.nice.org.uk/guidance/ta856]. Accessed 22 April 2025.

18. National Institute for Health and Care Excellence. [TA633] Ustekinumab for treating moderately to severely active ulcerative colitis. Published: 17 June 2020. Available from: https://www.nice.org.uk/guidance/TA633]. Accessed 22 April 2025.
19. National Institute for Health and Care Excellence. [TA925] Mirikizumab for treating moderately to severely active ulcerative colitis. Published: 25 October 2023. Available from: https://www.nice.org.uk/guidance/ta925]. Accessed 22 April 2025.
20. National Institute for Health and Care Excellence. [TA998] Risankizumab for treating moderately to severely active ulcerative colitis. Published: 22 August 2024. Available from: https://www.nice.org.uk/guidance/ta998]. Accessed 22 April 2025.
21. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Mirikizumab. Available from: https://products.mhra.gov.uk/search/?search=mirikizumab&page=1&doc=Spc&rerouteType=0. Accessed 13 March 2025.
22. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Risankizumab. Available from: https://products.mhra.gov.uk/search/?search=risankizumab&page=1&doc=Spc&rerouteType=0. Accessed 13 March 2025.
23. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Infliximab. Available from: https://products.mhra.gov.uk/search/?search=Infliximab&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
24. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Adalimumab. Available from: https://products.mhra.gov.uk/search/?search=Adalimumab&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
25. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Golimumab. Available from: https://products.mhra.gov.uk/search/?search=Golimumab&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
26. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Ozanimod. Available from: https://products.mhra.gov.uk/search/?search=Ozanimod&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
27. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Estrasimod. Available from: https://products.mhra.gov.uk/search/?search=Estrasimod&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
28. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Tofacitinib. Available from: https://products.mhra.gov.uk/search/?search=Tofacitinib&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
29. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Upadacitinib. Available from: https://products.mhra.gov.uk/search/?search=Upadacitinib&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
30. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Filgotinib. Available from: https://products.mhra.gov.uk/search/?search=Filgotinib&page=1&doc=Spc&ter=UK&rerouteType=0. Accessed 22 April 2025.
31. Peyrin-Biroulet L, Allegretti JR, Rubin DT, Bressler B, Germinaro M, Huang K-H*, et al.* Guselkumab in patients with moderately to severely active ulcerative colitis: QUASAR phase 2b induction study. Gastroenterology. 2023; 165:1443-57.
32. Kapizioni C, Desoki R, Lam D, Balendran K, Al-Sulais E, Subramanian S*, et al.* Biologic therapy for inflammatory bowel disease: Real-world comparative

effectiveness and impact of drug sequencing in 13 222 patients within the UK IBD BioResource. J Crohns Colitis. 2024; 18:790-800.
33. National Institute for Health and Care Excellence. [PMG32] User guide for the cost comparison company evidence submission template. Published: 01 April 2017. Available from: https://www.nice.org.uk/process/pmg32/chapter/instructions-for-companies]. Accessed 22 April 2025.
34. National Institute for Health and Care Excellence. [PMG36] NICE health technology evaluations: the manual. NICE process and methods. Published: 31 January 2022. Last updated: 31 October 2023. Available from: https://www.nice.org.uk/process/pmg36. Accessed 22 April 2025.
35. Medicines and Healthcare products Regulatory Agency (MHRA). Summary of Product Characteristics: Vedolizumab. Available from: https://products.mhra.gov.uk/search/?search=vedolizumab&page=1&doc=Spc&ter=GB. Accessed 13 March 2025.
36. Janssen Research and Development. [Data on file] Clinical Study Report: QUASAR (Induction Study 2)- A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis. 2024.
37. Janssen Research and Development. [Data on file] Clinical Study Report: QUASAR (Maintenance Study) - A Phase 2b/3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Ulcerative Colitis 2024.
38. Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S*, et al.* Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clin Gastroenterol Hepatol. 2017; 15:229-39 e5.
39. D'Haens G, Dubinsky M, Kobayashi T, Irving PM, Howaldt S, Pokrotnieks J*, et al.* Mirikizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2023; 388:2444-55.
40. Sandborn WJ, Baert F, Danese S, Krznaric Z, Kobayashi T, Yao X*, et al.* Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology. 2020; 158:562-72 e12.
41. Feagan BG, Sands BE, Sandborn WJ, Germinaro M, Vetter M, Shao J*, et al.* Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol. 2023; 8:307-20.
42. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ*, et al.* Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013; 369:699-710.
43. Takeda Development Centre Europe. A Phase 3b Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab Subcutaneous in Subjects with Ulcerative Colitis and Crohn's Disease. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000482-31/HU. Accessed 22 April 2025.
44. Johnson & Johnson. [Data on file] Efficacy of guselkumab versus available biologic therapies for the maintenance treatment of moderate to severe ulcerative colitis: A systematic review and meta-analysis 2025.
45. US Food and Drug Administration. Ulcerative colitis: developing drugs for treatment guidance for industry. 2022; Available from: https://www.fda.gov/media/158016/download Accessed 11 April 2025.
46. Sandborn WJ, Sands BE, Uddin S, Qasim Khan RM, Sagar Mukherjee R. Clinical trial design in ulcerative colitis: interpreting evolving endpoints based on post hoc

analyses of the vedolizumab phase 3 trials GEMINI 1 and VISIBLE 1. Crohn's & Colitis 360. 2024; 6:otad076.
47. National Institute for Health and Care Excellence (NICE). [PMG9] Guide to the methods of technology appraisal 2013. NICE process and methods [PMG9]. Published: 04 April 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed 22 April 2025.
48. University of York. Systematic Reviews CRD's guidance for undertaking reviews in health care. 2008; 1-294]. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 22 April 2025.
49. Thorlund K, Druyts E, Toor K, Jansen JP, Mills EJ. Incorporating alternative design clinical trials in network meta-analyses. Clin Epidemiol. 2014:29-35.
50. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J*, et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005; 353:2462-76.
51. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J*, et al.* Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014; 146:96-109 e1.
52. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J*, et al.* Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019; 381:1201-14.
53. Ananthakrishnan AN, Murad MH, Scott FI, Agrawal M, Haydek JP, Limketkai BN*, et al.* Comparative efficacy of advanced therapies for management of moderate-to-severe ulcerative colitis: 2024 American Gastroenterological Association evidence synthesis. Gastroenterology. 2024; 167:1460-82.
54. Chu X, Biao Y, Zhang Y, Liu C, Ma JZ, Guo Y, Gu Y. Network meta-analysis on efficacy and safety of different biologics for ulcerative colitis. BMC Gastroentero. 2023; 23(1) (no pagination).
55. Estevinho M, Sousa-Pinto B, Moreira P, Solitano V, Mesquita P, Costa C*, et al.* Network meta-analysis: histologic and histo-endoscopic improvement and remission with advanced therapy in ulcerative colitis. Aliment Pharmacol Ther. 2024; 60(10):1276-92.
56. Motoya S, Watanabe K, Ogata H, Kanai T, Matsui T, Suzuki Y*, et al.* Vedolizumab in Japanese patients with ulcerative colitis: A phase 3, randomized, double-blind, placebo-controlled study. PLoS One. 2019; 14:e0212989.
57. Sands BE, Peyrin-Biroulet L, Loftus EV, Jr., Danese S, Colombel JF, Törüner M*, et al.* Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med. 2019; 381:1215-26.
58. Sandborn WJ, Ferrante M, Bhandari BR, Berliba E, Feagan BG, Hibi T*, et al.* Efficacy and safety of mirikizumab in a randomized phase 2 study of patients with ulcerative colitis. Gastroenterology. 2020; 158:537-49.e10.
59. Gros B, Ross H, Nwabueze M, Constantine-Cooke N, Derikx L, Lyons M*, et al.* Long-term outcomes and predictors of vedolizumab persistence in ulcerative colitis. Therap Adv Gastroenterol. 2024; 17:17562848241258372.
60. Attauabi M, Vind I, Pedersen G, Bendtsen F, Seidelin JB, Burisch J. Short and long-term effectiveness and safety of vedolizumab in treatment-refractory patients with ulcerative colitis and Crohn's disease - a real-world two-center cohort study. Eur J Gastroenterol Hepatol. 2021; 33:e709-e18.
61. Ventress E, Young D, Rahmany S, Harris C, Bettey M, Smith T*, et al.* Transitioning from Intravenous to Subcutaneous Vedolizumab in Patients with Inflammatory Bowel Disease [TRAVELESS]. J Crohns Colitis. 2022; 16:911-21.
62. Sands BE, Feagan BG, Hunter Gibble T, Traxler KA, Morris N, Eastman WJ*, et al.* Mirikizumab improves quality of life in patients with moderately-to-severely active ulcerative colitis: Results from the phase 3 LUCENT-1 induction and LUCENT-2 maintenance studies. Crohns Colitis 360. 2023; 5:otad070.

10 APPENDIX 1: INDIVIDUAL TRIAL RESULTS

10.1 Induction: clinical response

Clinical response was either a primary outcome or a major secondary outcome in all trials.

The individual trial results for clinical response are summarised in Table 21. All results in the FAS populations and ADT-failure populations favoured guselkumab/vedolizumab/mirikizumab versus placebo; all results in the FAS populations were statistically significantly different. ADT-failure outcomes cannot be described as statistically significant since they were not part of the hierarchical statistical testing procedure (except for clinical response in the ADT-failure population in the LUCENT-1/2 trial[39] which showed a statistically significant difference).

The EAG notes that the clinical response rates reported in the trials of guselkumab[8,9,31] and LUCENT-1/2 trial[39] were similar for patients treated with the licensed doses of guselkumab and mirikizumab (FAS: 61.4% to 65.6%; ADT-failure: 51.4% to 57.1%); these rates were noticeably higher than reported for vedolizumab (FAS: 47.1%; ADT-failure: 39.0%). However, response was measured 6 weeks earlier for patients treated with vedolizumab.[38,42] It was also noticeable that placebo response varied across the trials, particularly in the FAS populations (FAS: 25.5% to 42.2%; ADT-failure: 19.9% to 29.7%).

Table 21 Clinical response at Week 6 or Week 12 in the trials

	GUS 200mg IV Q4W W12	GUS 400mg IV Q4W W12	GUS 400mg SC Q4W W12	VDZ 300mg IV* W6	MIRI 300mg IV Q4W W12	Placebo
FAS population						
QUASAR phase IIb trial (n/N)	61.4% (62/101)	60.7% (65/107)	--	--	--	27.6% (29/105)
QUASAR phase III trial (n/N)	61.5% (259/421)	--	--	--	--	27.9% (78/280)
ASTRO trial (n/N)	--	--	65.6% (183/279)	--	--	34.5% (48/139)
GEMINI-1 trial (n/N)	--	--	--	47.1% (106/225)	--	25.5% (38/149)
LUCENT-1/2 trial (n/N)	--	--	--	--	63.5% (551/868)	42.2% (124/294)
ADT-failure population						
QUASAR phase IIb trial (n/N)	54.3% (25/46)	47.1% (24/51)	--	--	--	25.5% (13/51)
QUASAR phase III trial (n/N)	51.4% (107/208)	--	--	--	--	19.9% (27/136)
ASTRO trial (n/N)	--	--	57.1% (64/112)	--	--	25.0% (14/56)
GEMINI-1 trial (n/N)	--	--	--	39.0% (32/82)	--	20.6% (13/63)
LUCENT-1/2 trial (n/N)	--	--	--	--	54.6% (197/361)	29.7% (35/118)

* Administered on Day 1 and Day 15
ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q4W=every 4 weeks; SC=subcutaneous; VDZ=vedolizumab; W6=Week 6; W12=Week 12
Source: CS, Table 20, CS, Table 35, CS, Appendix H, Figure 13B and published papers[8,31,38,39,42]

10.2 Induction: clinical remission

Clinical remission was either a primary outcome or a major secondary outcome in all trials.

The individual trial results for clinical remission are summarised in Table 22. All results in the FAS populations and ADT-failure populations favoured guselkumab/vedolizumab/mirikizumab versus placebo; all results in the FAS populations were statistically significantly different. ADT-failure outcomes cannot be described as statistically significant since they were not part of the hierarchical statistical testing procedure.

The EAG notes that the proportion of patients achieving clinical remission reported in the trials of guselkumab[8,9,31] and LUCENT-1/2 trial[39] were similar for patients treated with the licensed doses of guselkumab and mirikizumab (FAS: 22.6% to 27.6%; ADT-failure: 12.5% to 17.4%); these rates were higher than reported for vedolizumab (FAS: 16.9%; ADT-failure: 9.8%). However, response was measured 6 weeks earlier for patients treated with vedolizumab.[38,42] It was noticeable that placebo response varied across the trials in the FAS populations (5.4%

to 13.3%); placebo response was reasonably similar across trials in the ADT-failure populations (3.2% to 8.5%).

The authors of the LUCENT-1/2 trial[39] also evaluated clinical remission using an alternate definition (FAS population only). This alternate definition matched the definition used in the trials of guselkumab.[8,9,31] The LUCENT-1/2 trial[39] authors report that results using the alternate definition of clinical remission (25.6% in the mirikizumab arm versus 14.6% in the placebo arm) were similar to the results using the primary definition (24.2% in the mirikizumab arm versus 13.3% in the placebo arm).

Table 22 Clinical remission at Week 6 or Week 12 in the trials

	GUS 200mg IV Q4W W12	GUS 400mg IV Q4W W12	GUS 400mg SC Q4W W12	VDZ 300mg IV* W6	MIRI 300mg IV Q4W W12	Placebo
FAS population						
QUASAR phase IIb trial (n/N)	25.7% (26/101)	25.2% (27/107)	--	--	--	9.5% (10/105)
QUASAR phase III trial (n/N)	22.6% (95/421)	--	--	--	--	7.9% (22/280)
ASTRO trial (n/N)	--	--	27.6% (77/279)	--	--	6.5% (9/139)
GEMINI-1 trial (n/N)	--	--	--	16.9% (38/225)	--	5.4% (8/149)
LUCENT-1/2 trial (n/N)	--	--	--	--	24.2% (210/868)	13.3% (39/294)
ADT-failure population						
QUASAR phase IIb trial (n/N)	17.4% (8/46)	17.6% (9/51)	--	--	--	7.8% (4/51)
QUASAR phase III trial (n/N)	12.5% (26/208)	--	--	--	--	3.7% (5/136)
ASTRO trial (n/N)	--	--	16.1% (18/112)	--	--	3.6% (2/56)
GEMINI-1 trial (n/N)	--	--	--	9.8% (8/82)	--	3.2% (2/63)
LUCENT-1/2 trial (n/N)	--	--	--	--	15.2% (55/361)	8.5% (10/118)

*Administered on Day 1 and Day 15
ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q4W=every 4 weeks; SC=subcutaneous; VDZ=vedolizumab; W6=Week 6; W12=Week 12
Source: CS, Table 17, CS, Table 32, CS, Appendix H, Figure 13B and published papers[8,31,38,39,42]

10.3 Induction: other major secondary outcomes (other than clinical response or clinical remission)

The major secondary outcomes in the trials of guselkumab[8,9,31] at Week 12 included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal healing, Inflammatory Bowel Disease Questionnaire (IBDQ) remission, fatigue response, endoscopic

normalisation and symptomatic normalisation. All results favoured guselkumab versus placebo in the FAS and ADT-failure populations (as reported in CS Section B.3.5 and CS, Appendix I.1.4.1 and CS, Appendix I.3.2.1).

The only major secondary outcome (other than clinical remission) in the GEMINI-1 trial[42] was endoscopic healing. Major secondary outcomes (other than clinical remission) in the LUCENT-1/2 trial[39] included endoscopic healing, symptomatic remission, an improvement in bowel movement urgency and histo-endoscopic mucosal improvement. All results were statistically significantly in favour of vedolizumab or mirikizumab versus placebo ($p<0.01$) in the FAS populations.[39,42] All results in the ADT-failure population also favoured vedolizumab or mirikizumab versus placebo.[38,39]

Further information on results for endoscopic healing are summarised below since this was an outcome measured in the appraisal of mirikizumab (TA925)[19]

10.3.1 Endoscopic healing

This outcome was measured across all the trials (described as mucosal healing in the GEMINI-1 trial[42] and endoscopic remission in the LUCENT-1/2 trial[39]). The results are summarised in Table 23. The proportion of patients achieving this outcome was broadly similar in all four trials[8,31,39,42] in the FAS populations and in three trials[31,38,39] of the ADT-failure populations; the proportion achieving this outcome was lower in the QUASAR phase III trial[8] ADT-failure population. The proportion of patients achieving this outcome in the FAS and ADT-failure populations was highest for patients treated with vedolizumab in the GEMINI-1 trial,[38,42] which had a less stringent outcome definition than the other trials[8,31,39] (defined as an endoscopy subscore of 0 or 1; the other trials[8,31,39] also required there to be no friability present on the endoscopy). There was large variation in the placebo response across trials (FAS: 11.1% to 24.8%; ADT-failure: 5.1% to 20.6%).

Table 23 Endoscopic healing at Week 6 or Week 12 in the trials

	GUS 200mg IV Q4W W12	GUS 400mg IV Q4W W12	GUS 400mg SC Q4W W12	VDZ 300mg IV* W6	MIRI 300mg IV Q4W W12	Placebo
FAS population						
QUASAR phase IIb trial	30.7% (31/101)	30.8% (33/107)	--	--	--	12.4% (13/105)
QUASAR phase III trial	26.8% (113/421)	--	--	--	--	11.1% (31/280)
ASTRO trial	--	--	37.3% (104/279)	--	--	12.9% (18/139)
GEMINI-1 trial	--	--	--	40.9% (92/225)	--	24.8% (37/149)
LUCENT-1/2 trial	--	--	--	--	36.3% (315/868)	21.1% (62/294)
ADT-failure population						
QUASAR phase IIb trial	23.9% (11/46)	21.6% (11/51)	--	--	--	9.8% (5/51)
QUASAR phase III trial	14.9% (31/208)	--	--	--	--	5.1% (7/136)
ASTRO trial	--	--	24.1% (27/112)	--	--	7.1% (4/56)
GEMINI-1 trial	--	--	--	30.5% (25/82)	--	20.6% (13/63)
LUCENT-1/2 trial	--	--	--	--	23.5% (85/361)	10.2% (12/118)

*Administered on Day 1 and Day 15
ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q4W=every 4 weeks; SC=subcutaneous; VDZ=vedolizumab; W6=Week 6; W12=Week 12
Source: CS Table 19 and Table 34 and published papers [8,31,38,39,42]

10.4 Induction: other reported outcomes

In the overall QUASAR phase IIb trial[31] population, a greater proportion of patients in the guselkumab 200mg IV arm had improvement in HRQoL at Week 12 versus placebo, as assessed by IBDQ measures (IBDQ remission, IBDQ clinically meaningful improvement and >20 point IBDQ improvement) and Patient-Reported Outcomes Measurement Information System - Short Form v1.0 - Fatigue 7a (CS, Appendix I.3.2).

In the overall QUASAR phase III trial[36] population, patients in the guselkumab 200mg IV arm had greater improvements in each IBDQ domain score at Week 12 when compared with the placebo arm (CS, Appendix I.1.4.3.2). At Week 12, the mean change from baseline in EuroQol-5 Dimensions (EQ-5D) visual analogue scale (VAS) score was greater in the guselkumab 200mg IV group compared with the placebo arm (CS, Appendix I.1.4.3.3). At Week 12, compared with the placebo arm, a greater proportion of patients in the guselkumab 200mg IV arm had no bowel urgency as assessed by IBDQ items 24 and 16 and no abdominal pain as assessed by IBDQ item 13 (CS, Appendix I.1.4.3.4). The number of events of UC-

related medical utilisation (emergency department visits, hospitalisations or surgeries) at Week 12 were infrequent in the guselkumab and placebo arms in the QUASAR phase III trial[36] (CS, Appendix I.1.4.1.3).

In the overall GEMINI-1 trial[42] population, HRQoL measures at Week 6 were shown to have improved in all arms in terms of mean IBDQ score, mean Short Form (SF)-36 physical component summary (PCS) score, mean SF-36 mental component summary score (MCS), mean EQ-5D VAS score and mean EQ-5D utility score.

In the overall LUCENT-1/2 trial[62] population, compared with placebo, HRQoL was improved for patients in the mirikizumab arm at Week 12 for a large number of different measures. These included: IBDQ total and domain scores, IBDQ response, IBDQ remission, SF36 PCS, MCS, and domain scores, EQ-5D VAS scores, Work Productivity and Activity Impairment Questionnaire UC scores (WPAI-UC), Patient Global Rating of Severity scores and Patient Global Rating of Change scores.

Other outcomes specified in the NICE final scope,[1] (including HRQoL) were not reported in the ASTRO trial.[9] Subgroup analyses for the above outcomes were not reported for the ADT-failure population in any of the trials.

10.5 Individual trial efficacy results: Week 24

Week 24 results were only applicable to patients who had not responded to treatment at Week 12 in the QUASAR trials[8,31] and LUCENT-1/2 trial.[39] In the ASTRO trial,[9] Week 24 results were applicable to both responders and non-responders at Week 12. Week 24 results were not measured in the GEMINI-1 trial.[42]

Results at Week 24 in the QUASAR phase IIb trial were presented in the published paper[31] and results for the QUASAR phase III trial[8] were presented in the CS (Section B.3.5.1.7) for non-responders by the trial arm they were originally randomised to. Results for patients at Week 24 in the LUCENT-1/2 trial were presented for all patients who had received extended induction (i.e., non-responders to mirikizumab).

Results at Week 24 in the ASTRO trial[9] were presented in the CS (Sections B.3.5.3.5 to B.3.5.3.9) for patients by the arm they were re-randomised to.

10.6 Clinical response at Week 24 for delayed responders

A high proportion of patients who were non-responders at Week 12 in the trials[8,31,39] responded to treatment by Week 24, as shown in Table 24. Response rates for patients receiving guselkumab 200mg SC Q4W and mirikizumab 300mg IV Q4W at Week 24 were not too

dissimilar to response rates with guselkumab IV or mirikizumab IV at Week 12 in both the FAS populations and ADT-populations (Week 12 data shown in Table 21). Overall, in the FAS and ADT-failure populations in the trials, the proportion of Week 12 non-responders responding to guselkumab 200mg SC at Week 24 in the QUASAR trials[8,31] was slightly higher than the proportion of non-responders at Week 12 responding to mirikizumab 300mg extended induction at Week 24 in the LUCENT-1/2 trial.[39]

Table 24 Clinical response at Week 24 for Week 12 non-responders in the trials

	Prior treatment to receiving GUS 200mg SC				**Prior treatment to receiving MIRI 300mg IV at W12**
	GUS 200mg IV Q4W	**GUS 400mg IV Q4W**	**Placebo IV Q4W**	**Any arm IV Q4W**	**MIRI 300mg IV Q4W**
FAS population					
QUASAR phase IIb trial (n/N)	54.3% (19/35)	50.0% (19/38)	65.2% (43/66)	58.3% (81/139)	--
QUASAR phase III trial (n/N)	[redacted]	--	69.7% (115/165)	[redacted]	--
LUCENT-1/2 trial (n/N)	--	--	--	--	53.7% (146/272)
ADT-failure population					
QUASAR phase IIb trial (n/N)	50.0% (10/20)	44.0% (11/25)	--	--	--
QUASAR phase III trial (n/N)	[redacted]	--	[redacted]	[redacted]	--
LUCENT-1/2 trial (n/N)	--	--	--	--	46.3% (--)

ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q4W=every 4 weeks; SC=subcutaneous
Source: CS, Section B.3.5.1.7 and published papers[8,31,39]

10.7 Clinical remission at Week 24 for patients who were non-responders at Week 12

The proportions of non-responders at Week 12 who achieved clinical remission by Week 24 in the trials[8,31,39] are shown in Table 24. The proportion of patients in clinical remission tended to be lower with guselkumab SC at Week 24 than with guselkumab IV at Week 12 in the FAS populations and ADT-populations (Week 12 data shown in Table 22). The proportion of patients achieving clinical remission with mirikizumab at Week 24 was also lower than at Week 12 in the FAS population. Data were not available for the ADT-failure population in the QUASAR phase IIb trial[31] or LUCENT-1/2 trial.[39]

Table 25 Clinical remission at Week 24 for Week 12 non-responders in the trials

	Prior treatment to receiving GUS 200mg SC at W12				Prior treatment to receiving MIRI 300mg IV at W12
	GUS 200mg IV Q4W	GUS 400mg IV Q4W	Placebo IV Q4W	Any arm IV Q4W	MIRI 300mg IV Q4W
FAS population					
QUASAR phase IIb trial (n/N)	[redacted]	[redacted]	22.7% (15/66)	[redacted]	--
QUASAR phase III trial (n/N)	[redacted]	--	[redacted]	[redacted]	--
LUCENT-1/2 trial (n/N)	--	--	--	--	11.4% (31/272)
ADT-failure population					
QUASAR phase IIb trial (n/N)	--	--	--	--	--
QUASAR phase III trial (n/N)	[redacted]	--	[redacted]	[redacted]	--
LUCENT-1/2 trial (n/N)	--	--	--	--	--

ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q4W=every 4 weeks; SC=subcutaneous
Source: CS, Section B.3.5.1.7, QUASAR phase IIb induction study clinical study report (TEFCREM318) and published papers[8,31,39]

Other major secondary outcomes (other than clinical response or clinical remission) reported for non-responders at Week 12

Week 24 data for major secondary outcomes in the QUASAR phase IIb trial[31] were only available for patients in the FAS population originally randomised to receive placebo and who switched to guselkumab 200mg SC at Week 12. The proportions of patients achieving major secondary outcomes at Week 24 were similar to those achieved by patients at Week 12 in both of the guselkumab IV arms.

Data were available for the FAS populations and ADT populations in QUASAR phase III trial[8] by patients originally randomised to guselkumab 200mg IV and patients originally randomised to placebo. The proportions of patients achieving major secondary outcomes at Week 24 who were originally randomised to the placebo arm were similar to those achieved by patients at Week 12 in the guselkumab 200mg IV arm, an exception being histologic-endoscopic mucosal healing in the ADT population ([redacted] at Week 24 compared with 13.5% at Week 12). Generally, the proportion of patients originally randomised to the guselkumab 200mg IV arm who achieved a major secondary outcome at Week 24 was lower than the proportion of patients in this arm that achieved these outcomes at Week 12.

Results were not available for any major secondary outcomes other than clinical response (reported above) at Week 24 in the LUCENT-1/2 trial.[39]

10.8 Week 24 for patients in the ASTRO trial

It is unclear if Week 24 results in the ASTRO trial[8] include patients who required rescue treatment. As shown in CS Appendix D.2.3 (Figure 4), a total of [redacted] patients met the rescue criteria: [redacted] who received placebo induction and [redacted] who received guselkumab induction ([redacted] who then received 200mg SC Q4W and [redacted] who then received 100mg SC Q8W). Week 24 results are reported by the regimen received from Week 12 to Week 24.

10.8.1 Clinical response

At Week 24, a greater proportion of patients in the guselkumab 200mg arm and guselkumab 100mg arm responded to treatment compared with patients in the placebo arm in the FAS population ([redacted] and [redacted] versus [redacted]) and ADT-failure population ([redacted] and [redacted] versus [redacted]). Differences were reported to be statistically significant (p<0.01).

10.8.2 Clinical remission

At Week 24, a greater proportion of patients in the guselkumab 200mg arm and 100mg arm achieved clinical remission compared with patients in the placebo arm in the FAS population ([redacted] and [redacted] versus [redacted]) and ADT-failure population ([redacted] and [redacted] versus [redacted]). Differences were reported to be statistically significant (p<0.01).

10.8.3 Other major secondary outcomes

At Week 24, a greater proportion of patients in the guselkumab 200mg arm and 100mg arm achieved endoscopic healing compared with patients in the placebo arm in the FAS population ([redacted] and [redacted] versus [redacted]) and ADT-failure population ([redacted] and [redacted] versus [redacted]). Differences were reported to be statistically significant (p<0.01).

At Week 24, a greater proportion of patients in the guselkumab 200mg arm and 100mg arm achieved symptomatic remission compared with patients in the placebo arm in the FAS population ([redacted] and [redacted] versus [redacted]) and ADT-failure population ([redacted] and [redacted] versus [redacted]). Differences were reported to be statistically significant (p<0.01)..

No other data were available for major secondary outcomes at Week 24.

10.9 Maintenance: clinical response

The individual trial results for clinical response are summarised in Table 26. All results in the FAS populations and ADT-failure populations favoured guselkumab/vedolizumab/mirikizumab versus placebo; all results in the FAS populations were statistically significantly different. ADT-failure outcomes cannot be described as statistically significant since they were not part of the hierarchical statistical testing procedure.

The EAG notes that the clinical response rates reported in the trials of guselkumab[8,9,31] and LUCENT-1/2 trial[39] were similar for patients treated with the guselkumab and mirikizumab (FAS: 74.7% to 79.8%; ADT-failure: 67.0% to 71.1%). Data for vedolizumab varied across trials and was only available for the ADT-failure population from combined doses in the GEMINI-1 trial[42] where the proportion with durable clinical response was 44.6%. It was also noticeable that placebo response varied considerably across the trials (FAS: 23.8% to 49.4%; ADT-failure: 15.8% to 40.6%).

Table 26 Clinical response at Maintenance Week 44 (QUASAR trial) or Overall Week 52 (all other trials)

	GUS 100mg SC Q8W W44	GUS 200mg SC Q4W W44	VDZ 108mg SC Q2W W52	VDZ 300mg IV Q8W W52	VDZ 300mg IV Q4W W52	MIRI 200mg SC Q4W W52	Placebo
FAS population							
QUASAR phase III trial (n/N)	77.7% (146/188)	74.7% (142/190)	--	--	--	--	43.2% (82/190)
GEMINI-1 trial (n/N)	--	--	--	56.6% (69/122)	52.0% (65/125)	--	23.8% (30/126)
VISIBLE-1 trial (n/N)	--	--	64.2% (68/106)	72.2% (39/54)	--	--	28.6% (16/56)
LUCENT-1/2 trial (n/N)	--	--	--	--	--	79.8% [a] (285/357)	49.4% [a] (88/178)
ADT-failure population							
QUASAR phase III trial (n/N)	70.1% (54/77)	67.0% (59/88)	--	--	--	--	28.0% (21/75)
GEMINI-1 trial (n/N)	--	--	--	44.6% [b] (37/83)		--	15.8% (6/38)
VISIBLE-1 trial (n/N)	--	--	-- [c]	-- [c]	--	--	-- [c]
LUCENT-1/2 trial (n/N)	--	--	--	--	--	71.1% (91/128)	40.6% (26/64)

[a] Data not reported for FAS population; data reported by the addition of events/patients in the biologic/tofacitinib-failure and biologic/tofacitinib-naïve subgroups (thus, excludes data for 8 patients treated in the mirikizumab arm and 1 patient in the placebo arm)
[b] Data not reported by individual trial arm for patients receiving vedolizumab
[c] Data not reported for ADT-failure subgroup
ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SC=subcutaneous; VDZ=vedolizumab; W44=Week 44: W52=Week 52
Source: CS, Table 29 and published papers[8,31,38-40,42]

10.10 Maintenance: clinical remission

The individual trial results for clinical remission are summarised in Table 27. All results in the FAS populations and ADT-failure populations favoured guselkumab/vedolizumab/mirikizumab versus placebo; all results in the FAS populations were statistically significantly different. ADT-failure outcomes cannot be described as statistically significant since they were not part of the hierarchical statistical testing procedure.

The EAG notes that the proportion of patients achieving clinical remission reported in the trials of guselkumab[8,9,31] and LUCENT-1/2 trial[39] were similar for patients treated with guselkumab and mirikizumab (FAS: 45.2% to 50.0%%; ADT-failure: 39.8% to 46.1%); these rates were marginally higher than reported for vedolizumab in the FAS population (41.8% to 46.2) and notably higher than in the ADT-failure population (27.3% to 33.3%). Placebo response varied from 14.3% to 25.1% in the FAS population and 5.3% to 15.6% in the ADT-failure population.

The authors of the LUCENT-1/2 trial[39] also evaluated clinical remission using an alternate definition (FAS population only). This alternate definition matched the definition used in the trials of guselkumab.[8,9,31] The LUCENT-1/2 trial[39] authors report results using the alternate definition of clinical remission (54.9% in the mirikizumab arm versus 27.0% in the placebo arm) were similar to the results using the primary definition (49.9% in the mirikizumab arm versus 25.1% in the placebo arm).

Table 27 Clinical remission at Maintenance Week 44 (QUASAR trial) or Overall Week 52 (all other trials)

	GUS 100mg SC Q8W W44	GUS 200mg SC Q4W W44	VDZ 108mg SC Q2W W52	VDZ 300mg IV Q8W W52	VDZ 300mg IV Q4W W52	MIRI 200mg SC Q4W W52	Placebo
FAS population							
QUASAR phase III trial (n/N)	45.2% (85/188)	50.0% (95/190)	--	--	--	--	18.9% (36/190)
GEMINI-1 trial (n/N)	--	--	--	41.8% (51/122)	44.8% (56/125)	--	15.9% (20/126)
VISIBLE-1 trial (n/N)	--	--	46.2% (49/106)	42.6% (23/54)	--	--	14.3% (8/56)
LUCENT-1/2 trial (n/N)	--	--	--	--	--	49.9% (182/365)	25.1% (45/179)
ADT-failure population							
QUASAR phase III trial (n/N)	40.3% (31/77)	39.8% (35/88)	--	--	--	--	8.0% (6/75)
GEMINI-1 trial (n/N)	--	--	--	37.2% 16/43	35.0% 14/40	--	5.3% (2/38)
VISIBLE-1 trial (n/N)	--	--	33.3% (13/39)	27.3% (6/23)	--	--	5.3% (1/19)
LUCENT-1/2 trial (n/N)	--	--	--	--	--	46.1% (59/128)	15.6% (10/64)

ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SC=subcutaneous; VDZ=vedolizumab; W44=Week 44: W52=Week 52
Source: CS, Table 25 and published papers[8,31,38-40,42]

10.11 Maintenance: other major secondary outcomes

The major secondary outcomes in the trials of guselkumab[8,9,31] at Maintenance Week 44 included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal healing,

IBDQ remission, fatigue response, endoscopic normalisation, maintenance of clinical remission, maintenance of clinical response and corticosteroid-free clinical remission. All results favoured guselkumab versus placebo in the FAS and ADT-failure populations (as reported in CS Section B.3.5 and CS, Appendix I.1.4.1 and CS, Appendix I.3.2.1).

Major secondary outcomes in the GEMINI-1 trial[42] were mucosal healing, glucocorticoid-free remission and maintenance of clinical remission. Major secondary outcomes in the LUCENT-1/2 trial[39] included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal healing, IBDQ remission, endoscopic remission, maintenance of clinical remission and bowel urgency remission. Major secondary outcomes in the VISIBLE-1 trial[40] were patients with endoscopic improvement (termed mucosal healing in the study protocol), durable clinical response, durable clinical remission and corticosteroid-free remission. All results were statistically significantly in favour of vedolizumab or mirikizumab versus placebo ($p<0.01$) in the FAS populations. All results in the ADT-failure population also favoured vedolizumab or mirikizumab versus placebo.

Further information on results for endoscopic healing are summarised below since this was an outcome measured in the appraisal of mirikizumab (TA925)[19].

10.11.1 Endoscopic healing

This outcome was measured across all four trials[8,39,40,42] (described as mucosal healing in the GEMINI-1 trial,[42] endoscopic improvement in the VISIBLE-1 trial[40] and endoscopic remission in the LUCENT-1/2 trial[39]). The results are summarised in Table 23. The proportion of patients achieving this outcome was broadly similar with guselkumab, mirikizumab and vedolizumab in all trials.[8,39,40,42]

Table 28 Endoscopic healing at Maintenance Week 44 (QUASAR trial) or Overall Week 52 (all other trials)

	GUS 100mg SC Q8W W44	GUS 200mg SC Q4W W44	VDZ 108mg SC Q2W W52	VDZ 300mg IV Q8W W52	VDZ 300mg IV Q4W W52	MIRI 200mg SC Q4W W52	Placebo
FAS population							
QUASAR phase III trial (n/N)	49.5% (93/188)	51.6% (98/190)	--	--	--	--	18.9% (36/190)
GEMINI-1 trial (n/N)	--	--	--	51.6% (63/122)	56.0% (70/125)	--	19.8% (25/126)
VISIBLE1 trial (n/N)	--	--	56.6% (60/106)	53.7% (29/54)	--	--	21.4% (12/56)
LUCENT-1/2 trial (n/N)	--	--	--	--	--	58.6% (214/365)	29.1% (52/179)
ADT-failure population							
QUASAR phase III trial (n/N)	45.5% (35/77)	42.0% (37/88)	--	--	--	--	8.0% (6/75)
GEMINI-1 trial (n/N)	--	--	--	44.6% [a] (37/83)		--	7.9% (3/38)
VISIBLE1 trial (n/N)	--	--	-- [b]	-- [b]	--	--	-- [b]
LUCENT-1/2 trial (n/N)	--	--	--	--	--	50.8% (65/128)	20.3% (13/64)

[a] Data not reported for the separate vedolizumab arms
[b] Data not reported for ADT-failure subgroup
ADT=advanced therapy; FAS=full analysis set; GUS=guselkumab; IV=intravenous; MIRI=mirikizumab; n=number of events; N=number of patients; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SC=subcutaneous; VDZ=vedolizumab; W44=Week 44: W52=Week 52
Source: CS, Table 27 and published papers[8,31,38-40,42]

10.12 Maintenance: other reported outcomes

In the overall QUASAR phase III trial[8] population, improvements in the IBDQ total scores and individual dimensions reported at the end of induction were sustained at Maintenance Week 44 in the guselkumab 100mg SC arm and guselkumab 200mg SC arm (CS, Appendix I.1.4.3.2). Improvements assessed with the IBDQ diminished in the placebo arm over time. Improvements in the EQ-5D VAS score reported at the end of induction in the QUASAR phase III trial[36] were sustained in the guselkumab 100mg SC arm and guselkumab 200mg SC arm at Maintenance Week 44 whereas the EQ-5D VAS score worsened in the placebo arm (CS, Appendix I.1.4.3.3). By Maintenance Week 44, compared with the placebo arm, a greater proportion of patients in the guselkumab 100mg SC arm and guselkumab 200mg SC arm had

no bowel urgency and no abdominal pain (CS, Appendix I.1.4.3.4). The number of events of UC-related medical utilisation (emergency department visits, hospitalisations) at Maintenance Week 44 were infrequent in the guselkumab 100mg SC arm and guselkumab 200mg SC arm and comparable to the placebo arm. There were no surgeries in any of the arms (CS, Appendix I.1.4.2.4).

HRQoL with vedolizumab was evaluated at Overall Week 52 in both the GEMINI-1 trial[42] and VISIBLE-1 trial.[40] In the overall GEMINI-1 trial[42] population, greater proportions of patients met minimal clinically important difference thresholds for IBDQ, EQ-5D VAS, EQ-5D utility and SF-36 PCS in the vedolizumab arms (300mg IV Q8W and 300mg IV Q4W) than in the placebo arm. Results from the subgroup analyses found that the benefits versus placebo were greater in the TNFi-naïve subgroup than in the TNFi-failure subgroup population. In the overall VISIBLE-1 trial[40] population, mean IBDQ, mean EQ-5D VAS and mean WPAI-UC scores were improved from baseline with both vedolizumab regimens (108mg SC Q2W and 300mg IV Q8W) compared with placebo. Improvements in the IBDQ, EQ-5D VAS and WPAI-UC scores reported at the end of induction at Week 6 were sustained in both vedolizumab arms at Overall Week 52 whereas the IBDQ and EQ-5D VAS scores worsened in the placebo arm.

Improvements in HRQoL at Week 12 for patients treated with mirikizumab were sustained at Overall Week 52 in the overall LUCENT-1/2 trial[62] population. Compared with placebo, HRQoL was improved for patients in terms of IBDQ total and domain scores, IBDQ response, IBDQ remission, SF36 PCS, MCS, and domain scores, EQ-5D VAS scores, WPAI-UC scores, Patient Global Rating of Severity scores and Patient Global Rating of Change scores.

Subgroup analyses for the above outcomes were not reported for the ADT-failure population in any of the trials, with the exception of the GEMINI-1 trial,[42] as summarised above.

10.13 Individual trial safety results

In the CS (Sections B3.9, Appendix E and Appendix I.3.4), the company provided safety results for:

- QUASAR phase IIb trial
- QUASAR phase III trial at Week 12
- QUASAR phase III trial at Week 24
- QUASAR phase III trial at Maintenance Week 44
- ASTRO trial at Week 12
- ASTRO trial at Week 24
- ASTRO trial at Week 44 (limited to treatment-emergent AEs leading to treatment discontinuation).

In summary, the company reports (CS, p104) that the guselkumab safety results were consistent with the safety profile of guselkumab in its approved indications for plaque psoriasis and psoriatic arthritis.

No safety data were presented by the company for the comparator trials. However, in the company response to clarification question A8, the company considered that the overall rates of AEs, SAEs and serious infections were similar across the QUASAR trials,[8,31] GEMINI-1 trial[42] and LUCENT-1 trial.[39] The company highlighted that the most frequently reported AEs (>5%) across trials were found to be worsening symptoms of UC, anaemia, upper respiratory tract infection, headache, arthralgia and nasopharyngitis. Safety data up to Week 12 of induction and in the maintenance period, are summarised in Table 29 and Table 30, respectively.

Clinical advice to the EAG is that no unexpected AEs were observed from the safety data presented for guselkumab which were similar to the AEs expected with IL-23 inhibitors. Clinical advice was that while some uncommon SAEs such as serious infections/sepsis may occur with any of the ADTs (by virtue of their immunological actions), these SAEs are usually manageable and amenable to treatment.

Table 29 Adverse events up to Week 12 of the induction period

Characteristic	QUASAR phase IIb trial			QUASAR phase III trial		ASTRO trial		GEMINI-1 trial		LUCENT-1/2 trial	
	GUS 200mg IV Q4W (n=101)	GUS 400mg IV Q4W (n=107)	Placebo IV Q4W (n=105)	GUS 200mg IV Q4W (n=421)	Placebo IV Q4W (n=280)	GUS 400mg SC Q4W (n=279)	Placebo SC Q4W (n=139)	VDZ 300mg IV* (n=746)	Placebo IV* (n=149)	MIRI 300mg IV Q4W (n=958)	Placebo IV Q4W (n=321)
	Week 12	Week 12	Week 12	Week 12	Week 12	Week 12	Week 12	Week 6	Week 6	Week 12	Week 12
Deaths	0	0	0	0.2%	0.7%	0	0.7%	--	--	0	0
Any AE	44.6%	49.5%	56.2%	49.4%	49.3%	39.4%	52.5%	45.2%	46.3%	44.5%	46.1%
Any SAE	1.0%	2.8%	5.7%	2.9%	7.1%	2.5%	7.9%	3.4%	6.7%	2.8%	5.3%
Discontinuation	1.0%	0	2.9%	1.7%	3.9%	1.1%	5.8%	--	--	1.6%	7.2%
Serious infections	0	0	1.9%	0.7%	0.4%	0.7%	0%	0.5%	2.0%	0.7%	0.6%
Types of AEs**											
Anaemia	6.9%	7.5%	9.5%	5.0%	6.8%	[redacted]	[redacted]	--	--	3.3%	5.9%
COVID-19	5.9%	1.9%	3.8%	5.0%	4.3%	--	--	--	--	--	--
Headache	3.0%	5.6%	6.7%	3.1%	2.9%	[redacted]	[redacted]	7.6%	4.7%	3.3%	2.8%
Colitis ulcerative	1.0%	3.7%	5.7%	2.4%	8.2%	[redacted]	[redacted]	2.7%	5.4%	1.8%	7.5%
Arthralgia	2.0%	3.7%	1.9%	--	--	[redacted]	[redacted]	--	--	2.1%	1.2%
Abdominal pain	4.0%	2.8%	1.9%	--	--	--	--	--	--	--	--
Diarrhoea	3.0%	0.9%	1.9%	--	--	--	--	--	--	--	--
Lymphopenia	1.0%	1.9%	4.8%	--	--	--	--	--	--	--	--
Pyrexia	2.0%	0.9%	3.8%	--	--	--	--	--	--	1.5%	0.9%
Upper respiratory tract infection	--	--	--	--	--	[redacted]	[redacted]	--	--	--	--
Nasopharyngitis	--	--	--	--	--	[redacted]	[redacted]	--	--	4.1%	3.1%
Alopecia	--	--	--	--	--	[redacted]	[redacted]	--	--	--	--
Rash	--	--	--	--	--	--	--	--	--	0.5%	0.6%

* Administered on Day 1 and Day 15
** ≥3% in any treatment arm in trials of guselkumab and mirikizumab, ≥5% in trial of vedolizumab
AE=adverse event; IV=intravenous; Q4W=every 4 weeks; SAE=serious adverse event; TEAE=treatment-emergent adverse event
Source: CS Table 42, Appendix E1 (Table 12); CS, Table 44, published papers[8,31,38-40,42]

Table 30 Adverse events in the maintenance period

Characteristic	QUASAR phase III			GEMINI-1		VISIBLE-1			LUCENT-1/2	
	Guselkumab 100mg SC Q8W (n=186)	Guselkumab 200mg SC Q4W (n=190)	Placebo SC Q4W (n=192)	VDZ 300mg IV combined Q4W/Q8W (n=620)	Placebo IV Q4W/Q8W (n=275)	VDZ 108mg SC Q2W (n=106)	VDZ 300mg IV Q8W (n=54)	Placebo SC Q2W + Placebo IV Q8W (n=56)	MIRI 200mg SC Q4W (n=389)	Placebo SC Q4W (n=192)
	Maintenance Week 44	Maintenance Week 44	Maintenance Week 44	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52
Deaths	0	0	0	0.2%	0	0	0	0	0	0.5%
Any AE	64.5%	70.0%	68.2%	80.2%	80.0%	65.1%	75.9%	76.8%	64.5%	68.8%
Any SAE	2.7%	6.3%	0.5%	12.4%	13.5%	9.4%	13.0%	10.7%	3.3%	7.8%
Discontinuation	3.8%	2.6%	6.8%	--	--	4.7%	3.7%	8.9%	1.5%	8.3%
Serious infections	0.5%	1.1%	0	1.9%	2.9%	--	--	--	0.8%	1.6%
Types of AEs*										
Colitis ulcerative	9.1%	13.2%	29.7%	15.6%	21.1%	14.2%	11.1%	32.1%	6.7%	20.8%
COVID-19	12.9%	9.5%	14.1%	--	--	--	--	--	--	--
Arthralgia	4.3%	7.9%	6.8%	9.0%	9.1%	5.7%	7.4%	1.8%	6.7%	4.2%
Upper respiratory tract infection	3.2%	6.8%	4.2%	8.4%	7.6%	9.4%	3.7%	1.8%		
Headache	3.8%	4.2%	6.3%	12.9%	10.2%	8.5%	0	10.7%	4.1%	1.0%
Pyrexia	3.8%	4.7%	2.6%	--	--	--	--	--	3.3%	2.6%
Nasopharyngitis	4.3%	3.7%	4.7%	12.9%	9.5%	10.4%	18.5%	19.6%	7.2%	5.7%
Anaemia	2.2%	3.2%	2.6%	5.6%	5.8%	5.7%%	9.3	3.6%	2.1%	4.7%
Abdominal pain	2.7%	3.7%	2.1%	5.6%	3.6%	--	--	--	--	--
Back pain	4.3%	1.1%	2.6%	--	--	--	--	--	--	--
Injection site reaction	0	3.7%	0	--	--	--	--	--	4.4%	3.1%
Infusion reaction	--	--	--	7.9%	1.1%	--	--	--	--	--
Nausea	--	--	--	6.1%	6.9%	--	--	--	--	--
Investigations	--	--	--	--	--	1.9%	9.3%	1.8%	--	--
Alanine aminotransferase increased	--	--	--	--	--	0.9%	5.6%	0	--	--
Blood creatine	--	--	--	--	--	0.9%	5.6%	1.8%	--	--

Characteristic	QUASAR phase III			GEMINI-1		VISIBLE-1			LUCENT-1/2	
	Guselkumab 100mg SC Q8W (n=186)	Guselkumab 200mg SC Q4W (n=190)	Placebo SC Q4W (n=192)	VDZ 300mg IV combined Q4W/Q8W (n=620)	Placebo IV Q4W/Q8W (n=275)	VDZ 108mg SC Q2W (n=106)	VDZ 300mg IV Q8W (n=54)	Placebo SC Q2W + Placebo IV Q8W (n=56)	MIRI 200mg SC Q4W (n=389)	Placebo SC Q4W (n=192)
	Maintenance Week 44	Maintenance Week 44	Maintenance Week 44	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52	Overall Week 52
phosphokinase increased										
Musculoskeletal and connective tissue disorders	--	--	--	--	--	5.7%	7.4%	1.8%	--	--
Nervous system disorders	--	--	--	--	--	8.5%	0	10.7%	--	--
Psychiatric disorders	--	--	--	--	--	0.9%	5.6%	0	--	--
Insomnia	--	--	--	--	--	0.9%	5.6%	0	--	--
Skin and subcutaneous tissue disorders	--	--	--	--	--	0.9%	5.6%	1.8%	--	--
Rash	--	--	--	--	--	0.9%	5.6%	1.8%	3.6%	0
Fatigue	--	--	--	5.3%	3.6%	--	--	--	--	--
Influenza	--	--	--	4.8%	2.2%	--	--	--	--	--
Cough	--	--	--	5.8%	4.7%	--	--	--	--	--
Bronchitis	--	--	--	3.9%	4.4%	--	--	--	--	--
Sinusitis	--	--	--	2.4%	2.9%	0.9%	0	5.4%	--	--
Gastroenteritis	--	--	--	3.1%	1.8%	--	--	--	--	--
GI disorders	--	--	--	--	--	14.2%	11.1%	32.1%	--	--
Urinary tract infection	--	--	--	2.3%	4.0%	0	7.4%	3.6%	--	--
Blood and lymphatic system disorders	--	--	--	--	--	5.7%	9.3%	3.6%	--	--
Any cancer	--	--	--	0.2%	1.1%	--	--	--	0.3%	0.5%

* ≥3% in any treatment arm in trials of guselkumab and mirikizumab, ≥5% in any treatment arm in trials vedolizumab
AE=adverse event; GI=gastrointestinal; IV=intravenous; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SAE=serious adverse event; SC=subcutaneous
Source: CS Table 42, Appendix E1 (Table 13) and published papers[8,39,40,42]

11 APPENDIX 2: EAG REVISIONS TO THE COMPANY MODEL

This appendix contains details of the changes that the EAG made to the company model.

<table>
<tr><th>EAG revisions</th><th>Implementation instructions</th></tr>
<tr><td>Set up: EAG revision switches</td><td>
In sheet ‘Base case results’

Paste the following table into cells I8:M14
<table>
<tr><th>Name</th><th>Switch</th><th>Description</th><th colspan="2">EAG inputs</th></tr>
<tr><td>EAGrev1</td><td>0</td><td>Add guselkumab extended maintenance to induction sum</td><td></td><td></td></tr>
<tr><td>EAGrev2</td><td>0</td><td>100% IV gus induction</td><td></td><td></td></tr>
<tr><td>EAGrev3</td><td>0</td><td>Adjust probability of response after induction (a. initial and b. extended)</td><td>52%</td><td>51%</td></tr>
<tr><td>EAGrev4</td><td>0</td><td>Reduce discontinuation rate by half annually from year:</td><td>2</td><td></td></tr>
<tr><td>EAGrev5</td><td>0</td><td>Change start for dose escalation/reinduction to week:</td><td>48</td><td></td></tr>
<tr><td>EAGrev6</td><td>0</td><td>Adjust vedolizumab SC maintenance %</td><td>70%</td><td></td></tr>
</table>

Use names in ‘Name’ column to name the cells in the ‘Switch’ column

Set name of cell L11 to EAG_initialInductionResponse
Set name of cell M11 to EAG_extendedInductionResponse
Set name of cell L12 to EAG_disconStart
Set name of cell L13 to EAG_escalStart
Set name of cell L14 to EAG_pVedoSCmaintenance
</td></tr>
<tr><td>Update company base case: Guselkumab extended induction period included in induction costs and Guselkumab induction 100% IV administration</td><td>
In sheet ‘Calc GUS’

Insert 4 blank columns Q, R, S, T

Copy formulas, labels and formatting from cells Z19:AB31
Paste formulas, labels and formatting into cells R19:T31

Set formula in cell S25 = IF(EAGrev1=0,0,1-V21)

Paste the following range values into cells Q33:Q45
<table>
<tr><th>Dosing code</th></tr>
<tr><td>0</td></tr>
<tr><td>0</td></tr>
<tr><td>0</td></tr>
<tr><td>0</td></tr>
<tr><td>0</td></tr>
<tr><td>0</td></tr>
<tr><td>1</td></tr>
<tr><td>0</td></tr>
<tr><td>1</td></tr>
<tr><td>0</td></tr>
<tr><td>1</td></tr>
<tr><td>0</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>EAG revisions</th><th>Implementation instructions</th></tr>
<tr><td></td><td>
Paste the following range formulas into cells R33:T34
<table>
<tr><th>On extended induction</th><th>SC Drug costs</th><th>SC Admin costs</th></tr>
<tr><td>=IF($D34<$D$24,0, IF($D34<($D$24+$AG$25),$S$25, $AF$25*$S$25))</td><td>=Q34*R34*$S$21*H34*F34</td><td>=(IF(D34<$D$24,0, IF(D34=$D$24, p_c_Admin_SC_first*R34*F34*(1-p_Ind_GUS_SC_proportion), IF(MOD(D34-$D$24,$T$25)=0, p_c_Admin_SC_subsequent*R34*F34, 0))))*H34</td></tr>
</table>
Drag formulas from cells R34:T34 to R45:T45

Set formula in cell AE34 = IF(EAGrev1=0, CHOOSE(match_extended_induction,(IF($D34<$D$24,0,(IF($D34<($D$24+$AG$25), 1-$V$21,$AF$25*(1-$V$21)))))*(1-INDEX(EAG_rDiscontinuation,C34+1))^((D34-($D$24))/2)*H34,0), IF($D34<($D$24+$AG$25),0,$AF$25*(1-$V$21)*(1-INDEX(EAG_rDiscontinuation,C34+1))^((D34-($D$24))/2)*H34))

NOTE: name EAG_rDiscontinuation will be defined in R2

Drag formula into cells AE34:AE555

Set formula in cell D11 =K31*K25+N31*N25+IF(EAGrev1=0,0,S31)

Set formula in cell J11 = SUM(K31)*$K$25+SUM(N31)*$N$25+(SUM(W31)*$W$25+SUM(AA31)*$AA$25+SUM(AF31))+IF(EAGrev1=0,0,S31)

Set formula in cell K11 = SUM(L31)*$K$25+SUM(O31)*$N$25+(SUM(X31)*$W$25+SUM(AB31)*$AA$25+SUM(AG31))+IF(EAGrev1=0,0,T31)

Set formula in cell D12 = L31*K25+O31*N25+IF(EAGrev1=0,0,T31)

In sheet ‘Settings’

Set formula in cell H51 = IF(EAGrev2=0,I51,0)
</td></tr>
<tr><td>R1) Adjust probability of response after induction/extended induction</td><td>
In sheet ‘Clinical inputs’

Set formula in cell D9 = IF(EAGrev3=0,D33, EAG_initialInductionResponse)

Set formula in cell D21 = IF(EAGrev3=0,C42, EAG_extendedInductionResponse)
</td></tr>
<tr><td>R2) Adjust long term discontinuation rate</td><td>
In sheet ‘Life table’

Set value in cell W11 = “Base case discontinuation rate per cycle”
Set formula in cell X11 = -LN(1-'Clinical inputs'!D14)/(1/(1/((p_clin_discon_timepoint*7)/(misc_cycle_length*7))*1))

Set value in cell X14 to ‘Live discontinuation rate’
</td></tr>
</table>

EAG revisions	Implementation instructions
	Set formula in cell X15 = IFS(EAGrev4=0,$X$11, AND(EAGrev4=1,K15<= EAG_disconStart),$X$11, AND(EAGrev4=1,K15> EAG_disconStart),$X$11/2^(ROUNDDOWN(K15-1,0))) Drag formula into cells X15:X547 Set value in cell Y14 to 'Live discontinuation %' Set formula in cell Y15 = 1-EXP(-X15) Drag formula into cells Y15:Y547 Set name of range Y15:Y547 to EAG_rDiscontinuation <u>In sheet 'Calc GUS'</u> Set formula in cell V34 =(IF($D34<$D$23,0,$V$21*(1-INDEX(EAG_rDiscontinuation,C34+1))^((D34-$D$23)/2)*H34)) Drag formula into cells V34:V555 Set formula in cell Z34 =(IF($D34<$D$24,0,$V$21*(1-INDEX(EAG_rDiscontinuation,C34+1))^((D34-$D$24)/2)*H34)) Drag formula into cells Z34:Z555 **Note: Functionality for changing discontinuation for cells AE34:AE555 is included in the formula for the edited calculation of extended induction** <u>In sheet 'Calc VDZ'</u> Set formula in cell N34 =(IF($D34<$D$23,0, $N$21*(1-INDEX(EAG_rDiscontinuation,C34+1))^(($D34-$D$23)/2)))*$H34 Drag formula into cells N34:N555 Set formula in cell U34 =(IF($D34<$D$24,0, $N$21*(1-INDEX(EAG_rDiscontinuation,C34+1))^(($D34-$D$24)/2)))*$H34 Drag formula into cells U34:U555 Set formula in cell Y34 =(IF($D34<($D$23+$AA$25),0, ($Z$25*(1-$N$21))*(1-INDEX(EAG_rDiscontinuation,C34+1))^(($D34-$D$23)/2)))*$H34 Drag formula into cells Y34:Y555 Set formula in cell AF34 =(IF($D34<($D$24+$AA$25),0, ($Z$25*(1-$N$21))*(1-INDEX(EAG_rDiscontinuation,C34+1))^(($D34-($D$24+$AA$25))/2)))*$H34 Drag formula into cells AF34:AF555 <u>In sheet 'Calc_MIRI'</u> Set formula in cell N34 =(IF($D34<$D$23,0, $N$21*(1-INDEX(EAG_rDiscontinuation,C34+1))^(($D34-$D$23)/2)))*$H34 Drag formula into cells N34:N555 Set formula in cell U34 =(IF($D34<($D$23+$W$25),0, ($V$25*(1-$N$21))*(1-INDEX(EAG_rDiscontinuation,C34+1))^(($D34-($D$23+$W$25))/2)))*$H34 Drag formula into cells U34:U555

EAG revisions	Implementation instructions
R3) Adjust timing of dose escalation and reinduction	In sheet 'Calc_VDZ' Set formula in cell D26 =EAG_escalStart Set formula in cell R34 = (IF($D34<$D$23,0, IF(MOD($D34-$D$23, S$25)=0,$O$21*N34*$F34, 0)))*IF(EAGrev5=0,1,0)+ (IF($D34<$D$26,0, IF(MOD($D34-$D$26,S$25)=0,$O$21*N34*$F34, 0)))*IF(EAGrev5=1,1,0) Drag formula into cells R34:R555 Set formula in cell S34 = (IF($D34<$D$23,0, IF(MOD($D34-$D$23,$S$25)=0, p_c_Admin_IV*N34*$F34,0)))*IF(EAGrev5=0,1,0)+ (IF($D34<$D$26,0, IF(MOD($D34-$D$26,S$25)=0,p_c_Admin_IV*N34*$F34, 0)))*IF(EAGrev5=1,1,0) Drag formula into cells S34:S555 Set formula in cell AC34 = (IF($D34<($D$23+$AA$25),0, IF(MOD($D34-($D$23+$AA$25),S$25)=0,$O$21*Y34*$F34, 0)))*IF(EAGrev5=0,1,0)+ (IF($D34<($D$26+$AA$25),0, IF(MOD($D34-($D$26+$AA$25), S$25)=0, $O$21*Y34*$F34, 0)))*IF(EAGrev5=1,1,0) Drag formula into cells AC34:AC555 Set formula in cell AD34 = (IF($D34<($D$23+$AA$25),0, IF(MOD($D34-($D$23+$AA$25),$S$25)=0, p_c_Admin_IV*Y34*$F34,0)))*IF(EAGrev5=0,1,0)+ (IF($D34<($D$26+$AA$25),0, IF(MOD($D34-($D$26+$AA$25), S$25)=0, p_c_Admin_IV*Y34*$F34, 0)))*IF(EAGrev5=1,1,0) Drag formula into cells AD34:AD555 In sheet 'Calc MIRI' Set formula in cell D25 =EAG_escalStart Set formula in cell S26 = IF(EAGrev5=0,D23,D25)+p_IND_LastDose_MIRI+S25 Set formula in cell S34 =IF(EAGrev5=0,(IF($D34<$D$23,0, IF($D34<$S$26,IF(MOD($D34-$D$23,S$25)=0,p_c_Admin_IV*N34*$F34,0), IF(D34=$S$26,p_c_Admin_SC_first*N34*F34, IF(MOD(D34-$S$26,$P$25)=0,p_c_Admin_SC_subsequent*N34*F34,0))))), IF(D34<$D$23,0, IF(D34=$D$23,p_c_Admin_SC_first*N34*F34, IF(AND(D34>$D$23,D34<$D$25),0, IF(AND(D34>=$D$25,D34<$S$26,MOD($D34-$D$25,S$25)=0),p_c_Admin_IV*N34*$F34, IF(D34>=$S$26,0,0)))))) Drag formula into cells S34:S555
R4) Increased proportion of patients receiving vedolizumab SC maintenance	In sheet 'Settings' Set formula in cell H59 = IF(EAGrev6=0,I59,EAG_pVedoSCmaintenance)

Single Technology Appraisal

Guselkumab for treating moderately to severely active ulcerative colitis [ID6237]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 2 May 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

EAG response, 13 May 2025

Issue 1 Identified Factual Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1, page 8, states: This is a narrower population than the expected marketing authorisation ([redacted].	Please amend as follows: This is a narrower population than the expected marketing authorisation (which is expected to also include patients who have had [redacted]	Wording aligned with the expected marketing authorisation	This statement was intended to make clear exactly what the key difference is, but the EAG agrees that the company's suggestion reflects the actual wording of the marketing authorisation and so is preferable. Text amended in the EAG report for clarity, as suggested.
Section 1.2, page 8, states: The QUASAR phase IIb and phase III trials examined the clinical efficacy and safety of the recommended induction dose of 200mg by IV infusion every 4 weeks (Q4W)	Please amend as follows: The QUASAR phase IIb and phase III **induction** trials examined the clinical efficacy and safety of the recommended induction dose of 200mg by IV infusion every 4 weeks (Q4W).	As per the QUASAR trial protocol, the guselkumab 200mg IV dose was evaluated in the QUASAR phase IIb and phase III induction trials only. It is important to highlight this as the QUASAR phase III maintenance study did not include this dosing regimen.	Text amended in the EAG report for clarity, as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.2, page 8, states: The QUASAR phase III trial examined the recommended maintenance doses of 100mg SC injection every 8 weeks (Q8W) or 200mg SC injection Q4W.	Please amend as follows: The QUASAR phase III **maintenance** trial examined the recommended maintenance doses of 100mg SC injection every 8 weeks (Q8W) or 200mg SC injection Q4W.	As per the QUASAR trial protocol, the guselkumab 100mg SC Q8W and 200mg SC Q4W doses were evaluated in the QUASAR phase III maintenance trial only. It is important to highlight this as the QUASAR phase IIb and phase III induction studies did not include these dose regimens.	Text amended in the EAG report for clarity, as suggested.
Section 1.4, page 9, states: The company assumes that there are no differences in clinical response rates, discontinuation rates or safety between guselkumab, vedolizumab and mirikizumab.	Please amend as follows: The company assumes that **as similar or greater efficacy and safety has been demonstrated in the NMA outcomes, there are unlikely to be any consequential differences** in clinical response rates, discontinuation rates or safety between guselkumab, vedolizumab and mirikizumab.	Although the current wording states the assumptions that Johnson & Johnson have made, the rationale of these assumptions has not been provided, i.e., based on the outcomes of the NMAs conducted. The current wording implies that these assumptions were made in the absence of supporting evidence.	Text amended in the EAG report to highlight the rationale of these assumptions is based on the outcomes of the NMAs conducted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5.1, page 9, states: The company has presented evidence from the QUASAR trial programme (consisting of a phase IIb randomised controlled trial [RCT] and phase III RCT) and the ASTRO phase III RCT.	Please amend as follows: The company has presented evidence from the QUASAR trial programme (consisting of a phase IIb randomised controlled trial [RCT] and **two** phase III RCT**s**) and the ASTRO phase III RCT.	The QUASAR phase III programme consists of two trials: phase III induction trial and phase III maintenance trial.	Text amended in the EAG report.
Section 1.5.1, page 9, states: The company reports that the guselkumab safety results were consistent with the safety profile of guselkumab	Please amend as follows: The company reports that the guselkumab safety results were consistent with the safety profile of guselkumab **in its licensed indications of plaque psoriasis and psoriatic arthritis**.	To clarify that the safety of guselkumab has been well established in the indications that guselkumab currently has marketing authorisation for.	Text amended in the EAG report for clarity, as suggested.
Section 2.5.3, page 11, states: A recent publication reporting NMAs for clinical response, clinical remission and endoscopic healing was identified by the EAG. This publication only reported	Please amend as follows: A recent publication reporting NMAs for clinical response, clinical remission and endoscopic healing was identified by the EAG. This publication only reported	As per the Ananthakrishnan et al, 2024 publication, the point estimate of the relative risk for guselkumab versus vedolizumab and guselkumab versus mirikizumab were in favour of guselkumab for both clinical remission and	Text amended in the EAG report for clarity, as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
results for guselkumab in the induction period; guselkumab was found to be superior to vedolizumab in relation to endoscopic healing, but other results for guselkumab versus vedolizumab or versus mirikizumab were not statistically significantly different.	results for guselkumab in the induction period; guselkumab was found to be superior to vedolizumab in relation to endoscopic healing, but the point estimates of the relative risk in relation to the other endpoints for guselkumab versus vedolizumab or versus mirikizumab **favoured guselkumab but** were not statistically significantly different.	endoscopic improvement however, there was a statistically higher likelihood with guselkumab for endoscopic improvement versus vedolizumab only.	
Section 2.4, page 17, states: Notably, it is proposed that induction treatment with guselkumab may be administered by IV infusion (similar to mirikizumab and risankizumab) or SC injection (unlike mirikizumab and risankizumab).	Please amend as follows: Notably, it is proposed that induction treatment with guselkumab may be administered by IV infusion (similar to mirikizumab**,** risankizumab **and vedolizumab**) or SC injection (unlike mirikizumab**,** risankizumab **and vedolizumab**).	Although the discussions focus on mirikizumab and risankizumab as they are in the same therapeutic class as guselkumab, it is important to note that the similarities and differences in mode of administration for the IL-23s stated also apply to vedolizumab which is a comparator to guselkumab in this cost comparison analysis.	As noted by the company, the focus of the text was on IL-23 inhibitors. However, as vedolizumab is a comparator to guselkumab in this cost comparison analysis, the text has been amended to also refer to vedolizumab.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.5.1, page 18, states: The QUASAR trials[8,31] enrolled patients with moderately to severely active UC who had demonstrated an inadequate response to or a failure to tolerate conventional therapy (6-mercaptopurine, azathioprine or corticosteroids) or ADT (TNFi, vedolizumab or tofacitinib).	Please amend as follows: The QUASAR trials[8,31] **are randomised withdrawal trials and** enrolled patients with moderately to severely active UC who had demonstrated an inadequate response to or a failure to tolerate conventional therapy (6-mercaptopurine, **5-ASA,** azathioprine or corticosteroids) or ADT (TNFi, vedolizumab or tofacitinib).	Given that QUASAR and ASTRO have different trial designs, it is important to highlight the respective design for each study. In NHS clinical practice, 5-ASA is routinely used as conventional therapy.	Text regarding trial design amended for clarity, as suggested. The EAG agrees 5-ASA is routinely used in NHS clinical practice and notes this was a permitted concomitant medication in the QUASAR trials. However, 5-ASA is not mentioned as a type of conventional therapy that patients may have had an inadequate response or a failure to tolerate in the eligibility criteria reported in the QUASAR trial data on file or QUASAR trial publications. No changes made to reporting of trial eligibility criteria.
Section 2.5.2, page 19, states: The ASTRO phase III trial[9] is an ongoing double-blind, multicentre RCT that enrolled patients with moderately to severely active UC who had	Please amend as follows: The ASTRO phase III trial[9] is an ongoing double-blind, multicentre **treat-through** RCT that enrolled patients with moderately to severely	Given that QUASAR and ASTRO have different trial designs, it is important to highlight the respective design for each study. In NHS clinical	Text regarding trial design amended for clarity, as suggested. The EAG agrees 5-ASA is routinely used in NHS clinical practice and notes this was a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
demonstrated an inadequate response to or an intolerance to conventional therapy (6-mercaptopurine, azathioprine or corticosteroids) or ADT (TNFi, vedolizumab, ozanimod or an approved JAKi).	active UC who had demonstrated an inadequate response to or an intolerance to conventional therapy (6-mercaptopurine, **5-ASA,** azathioprine or corticosteroids) or ADT (TNFi, vedolizumab, ozanimod or an approved JAKi).	practice, 5-ASA is routinely used as conventional therapy.	permitted concomitant medication in the ASTRO trial. However, 5-ASA is not mentioned as a type of conventional therapy that patients may have had an inadequate response or a failure to tolerate in the eligibility criteria reported in the ASTRO trial data on file. No changes made to reporting of trial eligibility criteria.
Section 3.2, page 25, states: As described in CS, Table 2, the recommended induction dose is:	Please amend as follows: As described in CS, Table 2, **as per the draft SmPC** the recommended induction dose is:	To highlight that the recommended dosing for guselkumab is based on the draft SmPC for UC.	Text amended in the EAG report for clarity, as suggested.
Section 3.2, page 26, states: While the recommended maintenance dose in clinical practice is 200mg for patients considered not to be receiving adequate therapeutic benefit, in the QUASAR phase III trial,[8]	Please amend as follows: While the recommended maintenance dose in clinical practice, **as per the draft SmPC** is 200mg for patients considered not to be receiving adequate therapeutic benefit,	To highlight that the recommended dosing for guselkumab is based on the draft SmPC for UC.	Text amended in the EAG report for clarity, as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the 200mg dose was available to:	in the QUASAR phase III trial,[8] the 200mg dose was available to:		
Section 3.3, page 27, states: The first subcutaneous dose should be administered in place of the next scheduled IV dose and Q2W thereafter.	Please amend as follows: **The recommended dose regimen of subcutaneous vedolizumab as a maintenance treatment, following at least 2 intravenous infusions, is 108 mg administered by subcutaneous injection once every 2 weeks.** The first subcutaneous dose should be administered in place of the next scheduled IV dose and Q2W thereafter.	Dosing recommendations stated in section 4.2 in the SmPC for vedolizumab.	Text amended in the EAG report, as suggested.
Section 3.4, page 29, states: The company assumes that there are no differences in clinical response rates or safety between guselkumab, vedolizumab and mirikizumab.	Please amend as follows: The company assumes that **as similar or greater efficacy and safety has been demonstrated in the NMA outcomes, there are unlikely to be any consequential**	Although the current wording states the assumptions that Johnson & Johnson have made, the rationale of these assumptions has not been provided, i.e., based on the outcomes of the NMAs conducted. The current	Text amended in the EAG report to highlight the rationale of these assumptions is based on the outcomes of the NMAs conducted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	differences in clinical response rates or safety between guselkumab, vedolizumab and mirikizumab.	wording implies these assumptions were made in the absence of evidence.	
Section 3.5, page 30, states: The EAG considers that a lack of definitive evidence to demonstrate that guselkumab provides similar or greater health benefits to other drugs in the ADT-failure setting means that it is not clear if a cost comparison analysis approach is appropriate.	The EAG considers that a lack of definitive evidence to demonstrate that guselkumab provides similar or greater health benefits to **vedolizumab and mirikizumab** in the ADT-failure setting means that it is not clear if a cost comparison analysis approach is appropriate.	The current statement is not specific to the advanced therapies considered in this appraisal i.e., vedolizumab and mirikizumab and therefore could be interpreted to include other treatments outside of those considered in this submission.	Text amended in the EAG report for clarity, as suggested.
Section 4.3, page 33, states: The safety NMAs were performed using the overall trial population of each of the included trials, rather than only patients with ADT-failure.	Please amend as follows: The safety NMAs were performed using the overall trial population of each of the included trials, rather than only patients with ADT-failure **as the relevant ADT-failure subgroup data for**	The current wording suggests that Johnson & Johnson did not intentionally conduct analysis for the ADT-failure population however, it is important to note that this is due to data for the subgroup not being available in the	Text amended in the EAG report for clarity, as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	vedolizumab and mirikizumab is not currently in the public domain.	public domain for the comparators.	
Section 4.4.8, page 52, states: Maintenance period NMA (with delayed responders) results favoured guselkumab 100mg SC Q8W over vedolizumab 108mg SC Q2W (clinical remission data only) and vedolizumab 300mg IV Q8W (clinical response and clinical remission).	Please amend as follows: Maintenance period NMA (with delayed responders) results favoured guselkumab 100mg SC Q8W over vedolizumab 108mg SC Q2W (**only clinical remission data is available for vedolizumab 108 SC Q2W in the public domain)** and vedolizumab 300mg IV Q8W (clinical response and clinical remission).	Amended wording provides additional clarity as to why only clinical remission outcomes from the NMA are available for vedolizumab 108 SC Q2W dose.	Text amended in the EAG report for clarity, as suggested.
Section 4.4.9, page 53-54, states: It is also unclear to the EAG why the numbers of re-randomised induction responders in the QUASAR	Please amend as per the justification provided in Appendix 1	Appendix 1 presents further detail of how the number of re-randomised induction responders (n=334) for the maintenance period has been derived.	Thank you for clarifying this. Paragraph deleted from EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
phase III trial (maintenance period)[8] are reported to be 137 in the ADT-failure population, and 197 in the ADT-non failure population (Appendix L to the NMA report[44]). These values sum to 334, which is considerably less than the total number of re-randomised induction responders in the QUASAR phase III trial (maintenance period)[8] (n=568). In the company's response to clarification question D5 the company confirms that patients that responded to guselkumab 400mg IV Q4W in the QUASAR phase IIb induction trial[31] were excluded from the maintenance period NMAs. However, only 87 patients from the QUASAR phase IIb induction trial guselkumab 400mg IV Q4W arm entered the maintenance period of the QUASAR phase			Sentence relating to this point also deleted from summary, Section 1.5.2, page 10.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
III trial[8], so exclusion of these patients does not account for the discrepancy. The EAG therefore considers that the reason for the discrepancy, and the associated impact on NMA results, is unknown			
Section 4.4.9, pages 54-55, states: To demonstrate that guselkumab offers similar or greater health benefits to a comparator treatment, the EAG considers that 95% CrIs for the ORs (for all outcomes) ought to exclude the possibility of a clinically important treatment effect in favour of a relevant comparator treatment. However, the EAG highlights that all reported 95% CrIs (for all relevant comparators, all outcomes, base-case and sensitivity NMAs) include ORs that indicate a clinically important	Please amend as follows (if Johnson & Johnson's understanding is correct): To demonstrate that guselkumab offers similar or greater health benefits to a comparator treatment, the EAG considers that 95% CrIs for the ORs (for all outcomes) ought to exclude the possibility of a clinically important treatment effect in favour of a relevant comparator treatment. However, the EAG highlights that all reported 95% CrIs (for all relevant comparators, all outcomes, base-case and sensitivity NMAs) include ORs that	Based on the EAG's conclusions in section 8.1, page 66 (presented below), Johnson & Johnson assume that the EAG is referring to a greater treatment effect in favour of the intervention (guselkumab). Please could the EAG clarify this. "Results from the company NMAs showed that the point estimate of the odds ratio favours guselkumab versus relevant comparators in most instances."	The EAG is highlighting the uncertainty with the wide credible intervals. Wide credible intervals suggest a clinically important treatment effect favouring the intervention **or** comparator. Text of first sentence amended in the EAG report for clarity to: ""To demonstrate that guselkumab offers similar or greater health benefits to a comparator treatment, the EAG considers that **the** 95% CrIs for the ORs (for all outcomes) ought to exclude the possibility of a clinically important treatment effect in favour of a relevant

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
treatment effect in favour of the comparator treatment. Indeed, all 95% credible intervals included either a doubling or a halving (or both) of the odds of the event. Furthermore, if the company had accounted for imputation uncertainty, the 95% CrIs would have been wider, including even greater clinically important treatment effects in favour of the relevant comparators.	indicate a clinically important treatment effect in favour of the **intervention** treatment. Indeed, all 95% credible intervals included either a doubling or a halving (or both) of the odds of the event. Furthermore, if the company had accounted for imputation uncertainty, the 95% CrIs would have been wider, including even greater clinically important treatment effects in favour of the **intervention**.		comparator treatment. However, the EAG highlights that all reported 95% CrIs (for all relevant comparators, all outcomes, base-case and sensitivity NMAs) **that indicate a clinically important treatment effect in favour of the intervention also** include ORs that indicate a clinically important treatment effect in favour of the comparator treatment." Text in second sentence remains unchanged in the EAG report. The 95% credible intervals for all results had lower/upper credible intervals at least 2 times smaller **or** at least 2 times greater than the point estimate (usually at least 2 times smaller **and** at least 2 times greater). Text in third sentence remains unchanged in the EAG report. If the company had accounted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			for imputation uncertainty, the 95% CrIs would have been wider, therefore including the possibility of even greater clinically important treatment effects in favour of either the intervention or comparator. Therefore, it cannot be ruled out, based on the NMA results alone, that there is not a clinically important treatment effect favouring the comparator for any of the outcomes.
Section 4.6, page 57, states: The EAG also summarised results from NMAs conducted by Ananthakrishnan 2024.[53] While guselkumab was found to be superior to vedolizumab in relation to endoscopic healing as induction treatment and there was no statistically significant difference between guselkumab and mirikizumab,	Please amend as follows: The EAG also summarised results from NMAs conducted by Ananthakrishnan 2024.[53] While guselkumab was found to be superior to vedolizumab in relation to endoscopic healing as induction treatment and there was no statistically significant difference between guselkumab and mirikizumab,	As per the Ananthakrishnan et al, 2024 publication, the point estimate of the relative risk for guselkumab versus vedolizumab and guselkumab versus mirikizumab were in favour of guselkumab for both clinical remission and endoscopic improvement however, there was a statistically higher likelihood with guselkumab for	Thank you for highlighting the error with the reporting of clinical response as an outcome. Text amended in the EAG report for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the results did not find guselkumab to be superior to vedolizumab or mirikizumab in relation to clinical response or clinical remission	the results did not find guselkumab to be **statistically** superior to vedolizumab or mirikizumab in relation to ~~clinical response or~~ clinical remission **and to mirikizumab in relation to endoscopic improvement.**	endoscopic improvement versus vedolizumab only.	
Section 5.1, page 58, states: The EAG considers that a lack of definitive evidence to demonstrate that guselkumab provides similar or greater health benefits to other drugs in the ADT-failure setting means that it is not clear if a cost comparison analysis approach is appropriate.	Please amend as follows: The EAG considers that a lack of definitive evidence to demonstrate that guselkumab provides similar or greater health benefits to **vedolizumab and mirikizumab** in the ADT-failure setting means that it is not clear if a cost comparison analysis approach is appropriate.	The current statement is not specific to the advanced therapies considered in this appraisal i.e., vedolizumab and mirikizumab and therefore could be interpreted to include other treatments outside of those considered in this submission.	Text amended in the EAG report for clarity, as suggested.
Section 5.1, page 58, column “parameter” and “company base case”	Please amend as follows: **Delayed responders**, guselkumab: yes	As per the draft SmPC, patients who do not show adequate therapeutic benefit to induction treatment according to clinical	Text amended in the EAG report for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Extended induction, guselkumab: yes		judgement, a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered. This is considered as delayed responders as opposed to extended induction.	
Section 5.2, page 59, states: The EAG has also reorganised the disaggregated results for guselkumab so that total induction costs include extended induction. The EAG has calculated extended induction costs for guselkumab in the same way that extended induction costs are calculated for vedolizumab and mirikizumab.	Please amend as follows: The EAG has also reorganised the disaggregated results for guselkumab so that total induction costs include **delayed responders in**. The EAG has calculated **delayed responders** induction costs for guselkumab in the same way that extended induction costs are calculated for vedolizumab and mirikizumab.	As per the draft SmPC, patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered. This is considered as delayed responders as opposed to extended induction.	Text amended in the EAG report, as suggested
Section 5.2.3, page 61, states:	Please amend as follows:	Johnson & Johnson do not agree with the EAG's	Text amended in the EAG report for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG has revised the company model so that dose escalation and reinduction are implemented from Week 46.	The EAG has revised the company model so that dose escalation ~~and reinduction are~~ **is** implemented **in line with the publication. Although median time to dose escalation for vedolizumab was reported as 46 weeks, the EAG incorporated dose escalation from 48 weeks onwards instead, due to the model dosing structure.**	assumption to incorporate re-induction for mirikizumab at week 48 in the absence of evidence for mirikizumab. This is because dose escalation/re-induction is treatment dependent. Dose escalation and reinduction is implemented at week 48 in the model and not week 46. Clarity has been added regarding the rationale.	
Section 6.1, page 62, states: Details of the EAG corrections and revisions to the company model are presented in Appendix 2 (Section **Error! Reference source not found.**).	Details of the EAG ~~corrections and~~ revisions to the company model are presented in Appendix 2 (Section **Error! Reference source not found.**).	As the EAG states at the beginning of section 5 that "The EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the model match the values presented in the CS and in the original sources", Johnson & Johnson do not believe that any corrections were made to the model.	Text amended in the EAG report for clarity, as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 8.1, page 67, states: Induction period NMAs conducted by Ananthakrishnan 2024[53] did not show guselkumab to be superior to vedolizumab or mirikizumab for efficacy outcomes apart from versus vedolizumab for endoscopic healing.	Please amend as follows: Induction period NMAs conducted by Ananthakrishnan 2024[53] did not show guselkumab to be **statistically** superior to vedolizumab or mirikizumab for efficacy outcomes apart from versus vedolizumab for endoscopic healing.	As per the Ananthakrishnan et al, 2024 publication, the point estimate of the relative risk for guselkumab versus vedolizumab and guselkumab versus mirikizumab were in favour of guselkumab for both clinical remission and endoscopic improvement however, there was a statistically higher likelihood with guselkumab for endoscopic improvement versus vedolizumab only.	Text amended in the EAG report for clarity, as suggested.
Section 10.3, page 74, states: The major secondary outcomes in the trials of guselkumab[8,9,31] at Week 12 included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal healing, Inflammatory Bowel Disease Questionnaire (IBDQ) remission, fatigue response, endoscopic normalisation and symptomatic normalisation	Please amend as follows: The major secondary outcomes in the trials of guselkumab[8,9,31] at Week 12 included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal healing, Inflammatory Bowel Disease Questionnaire (IBDQ) remission, fatigue response, endoscopic normalisation and	Clinical response is a major secondary endpoint in the trials and is missing. Symptomatic normalisation is not an endpoint included in the trials.	The list of secondary outcomes is intended to be of major secondary outcomes other than clinical response or clinical remission. This has now been made clearer by the title to Section 10.3 including the words “(other than clinical response or clinical remission)” In addition, the following text has now been added to the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	clinical response ~~symptomatic normalisation~~		beginning of Sections 10.1 and 10.2, respectively: "Clinical response was either a primary outcome or a major secondary outcome in all trials." "Clinical remission was either a primary outcome or a major secondary outcome in all trials."
Section 10.3, page 75, states: The only major secondary outcome in the GEMINI-1 trial[42] was endoscopic healing	Please amend as follows: The ~~only~~ major secondary outcome**s** in the GEMINI-1 trial[42] **were** endoscopic healing **and clinical remission.**	As per Feagan et al, 2013, clinical remission at week 6 was also a major secondary endpoint in the GEMINI-1 trial.	The list of secondary outcomes is intended to be of major secondary outcomes other than clinical response or clinical remission. Text amended in the EAG report for clarity.
Section 10.3, page 75, states: Major secondary outcomes in the LUCENT-1/2 trial[39] included endoscopic healing, symptomatic remission and an	Please amend as follows: Major secondary outcomes in the LUCENT-1/2 trial[39] included endoscopic healing, symptomatic remission, an improvement in bowel movement urgency, **clinical**	Major secondary endpoints for LUCENT also included clinical response and histo-endoscopic mucosal improvement.	The list of secondary outcomes is intended to be of major secondary outcomes other than clinical response or clinical remission. The list was not intended to be exhaustive. However, we have amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
improvement in bowel movement urgency	**response and histo-endoscopic mucosal improvement.**		text in the EAG report for clarity (histo-endoscopic mucosal improvement now listed).
Section 10.11, page 83 states: The major secondary outcomes in the trials of guselkumab[8,9,31] at Maintenance Week 44 included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal healing, IBDQ remission, fatigue response, endoscopic normalisation and maintenance of clinical remission	The major secondary outcomes in the trials of guselkumab[8,9,31] at Maintenance Week 44 included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal healing, IBDQ remission, fatigue response, endoscopic normalisation**,** ~~and~~ maintenance of clinical remission, **maintenance of clinical response and corticosteroid-free clinical remission**	Maintenance of clinical response and corticosteroid-free clinical remission are major secondary outcomes in the guselkumab trials	The list of secondary outcomes was not intended to be exhaustive. However, it would have been clearer had we also listed the outcomes highlighted by the company and so we have amended text in the EAG report for clarity.
Section 10.11, page 83 states: Major secondary outcomes in the LUCENT-1/2 trial[39] included endoscopic healing, symptomatic remission,	Major secondary outcomes in the LUCENT-1/2 trial[39] included endoscopic healing, symptomatic remission, histologic-endoscopic mucosal	Bowel urgency remission is a major secondary outcome in LUCENT.	The list of secondary outcomes was not intended to be exhaustive. However, it would have been clearer had we also listed the outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
histologic-endoscopic mucosal healing, IBDQ remission, endoscopic remission and maintenance of clinical remission	healing, IBDQ remission, endoscopic remission**,** ~~and~~ maintenance of clinical remission **and bowel urgency remission.**		highlighted by the company and so we have amended text in the EAG report for clarity.

Issue 2 Data and Reporting Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.4.8, page 52, Table 12, column "Guselkumab 200mg SC Q4W" states: [redacted]	Please amend as follows: [redacted]	This is incorrect as per the company submission, section B.3.8.5.	Thank you for highlighting this error. Table amended.
Section 4.4.8, page 52, Table 12, column "Mirikizumab 200mg SC Q4W"states: [redacted]	Please amend as follows: [redacted]	This is incorrect as per the company submission, section B.3.8.5.	Thank you for highlighting this error. Table amended.
Section 4.4.8, page 52, Table 13, column "Vedolizumab 300mg IV Q4W" states: [redacted]	Please amend as follows: [redacted]	This is incorrect as per the company submission, section B.3.8.5.	Thank you for highlighting this error. Table amended.
Section 4.5.2, page 56 states:	Please amend as follows: Compared with placebo, there was moderate-certainty evidence that	Incorrect as per the Ananthakrishnan et al, 2024 publication.	Thank you for highlighting this error. Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Compared with placebo, there was moderate-certainty evidence that guselkumab and mirikizumab (relative risk [RR] 2.86; 95% CI: 1.39 to 5.88 and RR 2.83; 95% CI: 1.30 to 416, respectively) were associated with a higher likelihood of achieving clinical remission whereas there was low-certainty evidence with vedolizumab (RR 1.64; 95% CI: 0.82 to 3.36)	guselkumab and mirikizumab (relative risk [RR] 2.86; 95% CI: 1.39 to 5.88 and RR **2.33**; 95% CI: 1.30 to **4.16**, respectively) were associated with a higher likelihood of achieving clinical remission whereas there was low-certainty evidence with vedolizumab (RR 1.64; 95% CI: 0.82 to 3.36)		
Section 5.2.1, page 59 states: ([redacted]]	Please amend as follows: ([redacted]	This is incorrect as per the company submission, section B.3.8.5.	Thank you for highlighting this error. Text amended.
Section 5.2.1, page 59 states: ([redacted]).	Please amend as follows: [redacted]).	It is unclear how the credible intervals have been calculated as these are not reported in the model or company submission given that this is calculated from other inputs	The EAG has amended the text for clarity but has not amended the credible intervals.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		(the proportion of responders is based calculated using the placebo absolute probability and OR of guselkumab vs placebo). In the model, in the absence of SE, a 20% arbitrary value is used to estimate uncertainty, the suggested amendment is based on this.	The credible intervals are derived from the company model using the upper and lower bounds of the OR for guselkumab versus placebo to calculate the guselkumab odds of response, which are then transformed into response rates. This is the same method as is used to calculate the guselkumab response rate in the company base case. The EAG has not used these credible interval values to calculate model results but has included them in the report to illustrate the uncertainty around the estimate of guselkumab response rates when using the NMA results.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 10.2, page 73, states: It was noticeable that placebo response varied across the trials in the FAS populations (2.9% to 13.3%)	Please amend as follows: It was noticeable that placebo response varied across the trials in the FAS populations (**5.4%** to 13.3%)	This is incorrect, as per Table 22 of the EAG report, the lowest response for placebo in the FAS population is 5.4%	Thank you for highlighting this error. Text amended.
Section 10.13, page 88, Table 30, column "Placebo SC Q4W (n=192) Maintenance Week 44" states: 0.7%	Please amend as follows: **0%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Placebo SC Q4W (n=192) Maintenance Week 44" states: 49.3%	Please amend as follows: **68.2%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Placebo SC Q4W (n=192)	Please amend as follows: **0.5%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Maintenance Week 44" states: 25.7%			
Section 10.13, page 88, Table 30, column "Placebo SC Q4W (n=192) Maintenance Week 44" states: 17.1%	Please amend as follows: **6.8%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Placebo SC Q4W (n=192) Maintenance Week 44" states: 7.1%	Please amend as follows: **0%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Guselkumab 100mg SC Q8W (n=186) Maintenance	Please amend as follows: **0%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Week 44" states: 0.2%			
Section 10.13, page 88, Table 30, column "Guselkumab 100mg SC Q8W (n=186) Maintenance Week 44" states: 49.4%	Please amend as follows: **64.5%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Guselkumab 100mg SC Q8W (n=186) Maintenance Week 44" states: 131.6%	Please amend as follows: **2.7%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Guselkumab 100mg SC	Please amend as follows: **3.8%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Q8W (n=186) Maintenance Week 44" states: 14.5%			
Section 10.13, page 88, Table 30, column "Guselkumab 100mg SC Q8W (n=186) Maintenance Week 44" states: 2.9%	Please amend as follows: **0.5%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Guselkumab 200mg SC Q4W (n=190) Maintenance Week 44" states: 0.7%	Please amend as follows: **0%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Guselkumab 200mg SC	Please amend as follows: **70.0%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Q4W (n=190) Maintenance Week 44" states: 49.3%			
Section 10.13, page 88, Table 30, column "Guselkumab 200mg SC Q4W (n=190) Maintenance Week 44" states: 25.7%	Please amend as follows: **6.3%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Guselkumab 200mg SC Q4W (n=190) Maintenance Week 44" states: 17.1%	Please amend as follows: **2.6%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.
Section 10.13, page 88, Table 30, column "Guselkumab 200mg SC	Please amend as follows: **1.1%**	Incorrect as per the company submission, page 101, Table 43.	Thank you for highlighting this error. Table amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Q4W (n=190) Maintenance Week 44” states: 7.1%			

Issue 3 Minor Typographical and Grammatical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1, page 25, states: This population is similar to that used to derive evidence for other IL-23 inhibitors in TA92519 and TA998.20	Please add the relevant citations for references 19 (TA925) and 20 (TA998)	Minor formatting error	Thank you for highlighting this error. Text amended.
Section 3.2, page 26, states: While the recommended maintenance dose in clinical practice is 200mg for patients considered not to be receiving adequate therapeutic benefit, in the QUASAR phase III trial,[8] the 200mg dose was available to:	Please amend as follows: While the recommended maintenance dose in clinical practice is 200mg for patients considered not to be **achieving** adequate therapeutic benefit, in the QUASAR phase III trial,[8] the 200mg dose was available to:	Minor grammatical error	Thank you for highlighting this error. Text amended.
Section 4.4.2, page 37, states: Clinical advice to the EAG is consistent with that received in the recent appraisal of	Please amend as follows: Clinical advice to the EAG is consistent with that received in the recent appraisal of risankizumab (TA998[20]) that results would not be expected to	Repetition of statement.	Thank you for highlighting this error. Text deleted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
risankizumab (TA998[20]) that results would not be expected to differ in patients who had prior exposure to only TNFi versus other advanced therapies such as JAK inhibitors or ozanimod. Clinical advice to the EAG is that, overall, the trial eligibility criteria were broadly similar for all trials. Clinical advice to the EAG is consistent with that received in the recent appraisal of risankizumab (TA998[20]) that results would not be expected to differ in patients who had prior exposure to only TNFi versus other advanced therapies such as JAK inhibitors or ozanimod.	differ in patients who had prior exposure to only TNFi versus other advanced therapies such as JAK inhibitors or ozanimod. Clinical advice to the EAG is that, overall, the trial eligibility criteria were broadly similar for all trials. ~~Clinical advice to the EAG is consistent with that received in the recent appraisal of risankizumab (TA998[20]) that results would not be expected to differ in patients who had prior exposure to only TNFi versus other advanced therapies such as JAK inhibitors or ozanimod.~~		
Section 4.4.9, page 53, states: With the exception of values obtained from IPD for trials conducted by the	Please remove references 50-52 as these relate to publications for infliximab, golimumab and ustekinumab respectively.	The statement related to the trials conducted by Johnson & Johnson that are utilised in the NMA; QUASAR phase IIb induction and QUASAR	Thank you for highlighting this error. Text deleted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
company,[8,31,50-52] the EAG was able to verify most data inputs used in the NMAs		phase III induction and maintenance studies. Therefore, references for comparator trials are not relevant.	

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 5.1, page 58, column “EAG comment” Guselkumab marketing authorisation is expected for IV induction only in the first instance (Section **Error! Reference source not found.**)	Please amend as follows: [redacted]	This statement should be highlighted as confidential as it indicates [redacted]	Thank you for highlighting this. Text highlighted as confidential.

Appendix 1

As discussed in question D5 of the clarification questions, patients who were on guselkumab 400mg IV at induction were omitted from the analysis however, it was not clarified that patients who were on placebo at induction were also omitted. This is because the values in question were those pertaining to the guselkumab arms and the goal was to normalise the trial design to that expected in a treat-through trial, where patients would be randomised to a guselkumab-based treatment sequence from induction through maintenance (i.e., no placebo component).

Table TEFKEY624A in the QUASAR maintenance CSR, presents a breakdown of sample sizes for the Randomised Full Analysis Set in QUASAR across the maintenance arms (which total N = 568, as the EAG noted), while also showing the sample sizes after restricting to those patients who received guselkumab 200mg IV induction treatment (which total N = 334, as used in our analysis).

The table below is taken from the NMA report (appendix L) and presents a breakdown of how the sample sizes align with the N = 334 found in QUASAR's CSR Table TEFKEY624A:

Table Error! No text of specified style in document.**-1. Re-calculation of ITT sample size for QUASAR**

Treatment Sequence	Population	Induction ITT N	Maintenance N (re-randomized induction responders)	% maintenance N of the total re-randomized	Re-calculated ITT N for treatment sequence
Guselkumab to placebo	ADT non-failure	268	70	NA	NA
Guselkumab to guselkumab 100mg Q8W	ADT non-failure		65	65 / 197 = 32.99%	32.99% X 268 = 88.4

Treatment Sequence	Population	Induction ITT N	Maintenance N (re-randomized induction responders)	% maintenance N of the total re-randomized	Re-calculated ITT N for treatment sequence
Guselkumab to guselkumab 200mg Q4W	ADT non-failure		62	62 / 197 = 31.47%	31.47% X 268 = 84.3
Total	ADT non-failure	268	197	NA	NA
Guselkumab to placebo	ADT-failure	254	42	NA	NA
Guselkumab to guselkumab 100mg Q8W	ADT-failure		46	46 / 137 = 33.58%	33.58% X 254 = 85.3
Guselkumab to guselkumab 200mg Q4W	ADT-failure		49	49 / 137 = 35.77%	35.77% X 254 = 90.9
Total	ADT-failure	254	137	NA	NA
Sources: QUASAR IPD					

For treatment sequence “Guselkumab [200 mg IV Q4W] to placebo”, adding sample sizes 70 (ADT-non-failure) and 42 (ADT-failure) equates to N = 112, matching that shown in CSR Table TEFKEY624A.

For treatment sequence “Guselkumab [200 mg IV Q4W] to guselkumab 100 mg [SC] Q8W”, adding sample sizes 65 (ADT-non-failure) and 46 (ADT-failure) equates to N = 111, matching that shown in CSR Table TEFKEY624A.

For treatment sequence “Guselkumab [200 mg IV Q4W] to guselkumab 200 mg [SC] Q4W”, adding sample sizes 62 (ADT-non-failure) and 49 (ADT-failure) equates to N = 111, matching that shown in CSR Table TEFKEY624A.