NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guselkumab for previously treated moderately to severely active Crohn's disease [ID6238]

Committee Papers

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Cost Comparasion

Guselkumab for previously treated moderately to severely active Crohn's disease [ID6238]

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

2. **Clarification questions and company responses**

3. NICE medicines optimisation team (MOT) report

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

5. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group, University of Liverpool

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Guselkumab for treating previously treated moderately to severely active Crohn's disease [ID6238]

Document B

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6238 Guselkumab CD NICE CC Doc B_CIC_11022025	Final	Yes	11 February 2025

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Abbreviations

Abbreviation	Definition
AE	Adverse event
BNF	British National Formulary
BSG	British Society of Gastroenterology
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CrI	Critical interval
EIM	Extra-intestinal manifestations
EMA	European Medicines Agency
eMIT	Electronic market information tool
FDA	US Food and Drug Administration
GI	Gastrointestinal
HBI	Harvey Bradshaw Index
HCRU	Healthcare resource utilisation
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
NHS	National Health Service
NMA	Network meta-analysis
ONS	Office for National Statistics
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBO	Placebo
PICOS	Population, intervention, comparators, outcomes, study design
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient reported outcome
PSSRU	Personal Social Services Research Unit
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of life
RCT	Randomised controlled trial
SC	Subcutaneous
SE	Standard error

SES-CD	Simple Endoscopic Score for Crohn’s Disease
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TNF	Tumour necrosis factor
TSD	Technical Support Document
UC	Ulcerative colitis

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 Crohn's disease (CD) was issued by the National Institute for Health and Care Excellence (NICE) in July 2024, and guselkumab was selected to be appraised via a cost-comparison.(2) Guselkumab is concurrently being appraised for previously treated moderately to severely active ulcerative colitis [ID6237](3)

B.1.1.1. Population

The population relevant to this submission is narrower than the marketing authorisation and includes adult patients with moderately to severely active CD who have had an inadequate response, lost response or were intolerant to a biologic treatment (hereafter referred to as 'BIO-failure'). In line with the NICE recommendation for the 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 risankizumab and vedolizumab, which are both recommended by NICE. (4, 6) The published NICE guidance for these comparators recommends risankizumab and vedolizumab for subpopulations within their marketing authorisations, 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 three registrational Phase III studies: GALAXI-2, GALAXI-3 and GRAVITI.(7-11) 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 the relevant outcomes as per final scope, and in the population that is most informative to the decision problem (described in Section B.1.1.1). Details of these analyses are presented in Section B.3.

B.1.1.5. Cost-comparison analysis

To demonstrate the cost-comparability of guselkumab against risankizumab, and vedolizumab in a similar 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 and TA998) and another that is currently in progress (ID6244).(4, 12-16) Details of these analyses are presented in Section B.4.

The decision problem addressed in this submission is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE – (2)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderately to severely active CD who have had an inadequate response to or demonstrated intolerance to either conventional therapy or biologic treatment	Adult patients with moderately to severely active CD who have had an inadequate response, lost response or were intolerant to a biologic treatment, including patients for whom TNFis are deemed unsuitable	Aligned to the population recommended in NICE guidance for the comparators in the submission (vedolizumab and risankizumab)(4, 5)
Intervention	Guselkumab	Guselkumab	Not applicable
Comparator(s)	At least one of the following treatments, according to NICE guidance: • Tumour necrosis factor-alpha inhibitors (infliximab and adalimumab) • Ustekinumab • Vedolizumab • Risankizumab • Upadacitinib	• Risankizumab • Vedolizumab	• Vedolizumab and risankizumab are established in clinical practice and are substantially used in NHS England for this indication, thereby fulfilling NICE requirements for relevant comparators as per the process and methods guide for cost-comparison (Section 2.6.1)(17) • Recent data on UK real-world clinical practice demonstrate a substantial proportion of patients using vedolizumab as second-line advanced therapy(18) • Both guselkumab and risankizumab are IL-23 inhibitors and share a similar mechanism of action
Outcomes	• Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Change in hospitalisation • Adverse effects of treatment	• Disease activity (remission and response) • Endoscopic efficacy (response and remission) • Surgery • Hospitalisation rates	• Relapse was not an efficacy outcome in GALAXI-2/3 and GRAVITI. However, clinical remission was the primary efficacy endpoint. Since relapse is defined as a loss of remission, clinical remission is indicative of relapse rates • Endoscopic healing (the absence of mucosal ulcerations) in GALAXI trials may be considered

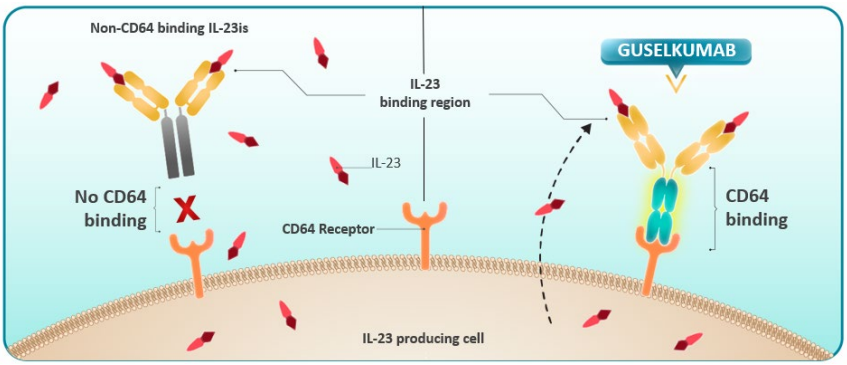
	Final scope issued by NICE – (2)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• HRQoL	• Adverse effects of treatment • HRQoL	equivalent to mucosal healing as defined in NICE final scope and previous NICE appraisals in CD (TA888)(4) • In GALAXI-2, GALAXI-3 and GRAVITI, endoscopic response measures the proportion of patients with ≥ 50% improvement in SES-CD score, while endoscopic remission measures SES-CD score ≤ 2. Both outcomes are related to mucosal healing, with low SES-CD scores indicative of mucosal healing
Economic analysis	• This technology has been selected to be appraised as a cost-comparison • The time horizon should be sufficient to reflect any differences in costs between the technologies being compared • Costs will be considered from an NHS and PSS perspective • The availability of any commercial arrangements for the intervention and comparator technologies will be taken into account	• A cost-comparison analysis has been conducted to estimate the incremental costs of guselkumab versus risankizumab 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 • A PAS for guselkumab has been included as part of the analysis	• This analysis compares the drug acquisition and administration costs for guselkumab versus those associated with risankizumab and vedolizumab • A 10-year time horizon was adopted to align with the NICE health technology evaluations manual (PMG36)

Key: CD, Crohn's disease; HRQoL, health-related quality of life; IL, interleukin; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PSS, Personal Social Services; QALY, quality-adjusted life year; SES-CD, Simple Endoscopic Score for Crohn's Disease.

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.1.

Table 2: Technology being evaluated

UK approved name and brand name	Guselkumab (Tremfya®)
Mechanism of action	Guselkumab is a human IgG1λ monoclonal antibody that binds selectively to the IL-23 protein with high specificity and affinity through the antigen binding site.(1) IL-23 is a cytokine that is involved in inflammatory and immune responses. IL-23 binds its cognate receptor IL-23R on cell-surfaces. In CD, IL-23 binds IL-23R on multiple types of immune cells; this can increase the release of pro-inflammatory cytokines, causing a positive feedback loop that promotes chronic inflammation and GI damage. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of pro-inflammatory cytokines. (1) Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in CD. (1) 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 production (Figure 1). (1) **Figure 1: Inhibition of IL-23 and CD64 by guselkumab** 
Marketing authorization/CE mark status	The application for MHRA filing was submitted in [redacted]. The anticipated date of marketing authorisation is [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is [redacted]. 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 CD. Induction therapy: 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. Maintenance therapy: The recommended maintenance dose is 100 mg administered by SC injection at Week 16 and every 8 weeks thereafter after completion of induction dosing. A dose of 200 mg administered by SC injection at Week 12 and every 4 weeks 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) = [redacted] • 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 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 CD at net price is [redacted] for the 100 mg Q8W SC regimen and [redacted] for the 200 mg Q4W SC regimen.
Key: CD, Crohn's disease; GI, gastrointestinal; Ig, immunoglobulin; IL, interleukin; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SmPC, Summary of Product Characteristics. **Source:** Guselkumab 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

CD is a form of IBD characterised by transmural inflammation that can affect the entire gastrointestinal (GI) tract. In CD, inflammatory lesions develop a 'patchy' presentation where healthy sections of the GI tract are found alongside sites of inflammation.(19) Along the GI tract, the most common site of inflammation is the terminal ileum of the small intestine and the colon.(20, 21)

B.1.3.1.2. Diagnosis and disease severity

Patients typically start to show symptoms of CD in early adulthood, with the highest incidence in people between 20 and 29 years of age.(21-23) Clinical disease activity is classified as mild, moderate and severe, and depends on heterogeneous clinical measures, impact on quality of life (QoL) and complications of disease and therapy.(24) When CD is not active, patients are in remission. Commonly used measures for determining disease activity include the Crohn's Disease Activity Index (CDAI), the Harvey Bradshaw Index (HBI), the Simple Endoscopic Score for Crohn's disease (SES-CD) and other patient-reported outcome (PRO) tools. CDAI values greater than 150 indicate active disease; values between 220 and 450 indicate moderate to severe disease, and values greater than 450 indicate the most severe forms of disease.(25) For the HBI, a score of 0–4 indicates remission, 5–7 indicates mild disease, and ≥ 8 indicates moderate or severe disease.(24, 26) SES-CD grades ulcer size, ulcerated surface, affected surface and presence of narrowing/strictures

in the bowel from an endoscopy; scores of 7–15 indicate moderate CD, while scores > 15 indicate severe disease.(27)

Aetiology and pathogenesis

The aetiology and pathogenesis of CD is complex and not fully understood.(28) However, there is consensus that CD results from a complex interplay of genetic, immunological, microbiological and environmental factors.(20, 28-30) In general, these factors contribute to dysbiosis (disruption of the gut microbiota leading to a rise in pathogenic bacteria), disruption of the intestinal mucosa, and dysregulation of innate and adaptive immune system responses. Ultimately, the interaction of these factors results in an uncontrolled immune response to pathogens or environmental triggers, leading to chronic inflammation of the GI walls and preventing a return to homeostasis.(21, 28, 31, 32)

B.1.3.1.3. Epidemiology

It is reported that at least 0.3% of people in the UK are living with CD; based on 2023 Office for National Statistics (ONS) population estimates, this leads to approximately 174,1856 people in England living with CD. (33, 34) Of those with CD, 40% are estimated to have moderately to severely active disease. (12) A real-world study of 1,368 patients with CD and their physicians, including within the UK, reported that approximately 50% of patients were receiving biological therapy, but approximately 66% of the total number of patients had failed at least one biological therapy.(35) Applying those percentages to the population of people in England with CD, 69,674 patients have moderate or severe disease; of those patients, 25,480 people have failed biological therapy.(12)

B.1.3.2. Disease burden

CD is an incurable, lifelong disease.(21, 22, 31) Patients must constantly manage symptoms, and many worry when the next relapse will come during periods of remission.(22) While early treatment can reduce burden and risk of complications, CD has a progressive and destructive course; 25% of patients experience complications within 5 years, and this rises to 33% in 10 years.(36, 37)

B.1.3.2.1. Symptom burden

Onset of relapses are unpredictable, with periods of active disease characterised by diarrhoea, abdominal pain, rectal bleeding and fatigue.(22) Prolonged symptom-free periods are rare, occurring in approximately 10% of patients.(38-40) Relapses result in progressive damage to the GI tract, with chronic inflammation driving progression and complications that impair intestinal function.(25, 41-44) Chronic inflammation in the intestine commonly leads to the formation of fibrotic tissue due to the accumulation of scar tissue, formation of fistulas (abnormal connection between epithelial surfaces), strictures (narrowing of the GI tract due to abnormal remodelling), fissures and abscesses that lead to further complications that require costly surgical interventions.(45-48) These chronic inflammation-driven abnormalities can cause symptoms beyond the GI tract termed extra-intestinal manifestations (EIMs). Examples of EIMs include inflammation to the eyes, skin and joints. Furthermore, chronic inflammation restricts GI function and impairs digestion and the absorption of nutrients, which can then cause symptoms such as aphthous stomatitis, kidney/gall stones and anaemia.(22, 38, 49)

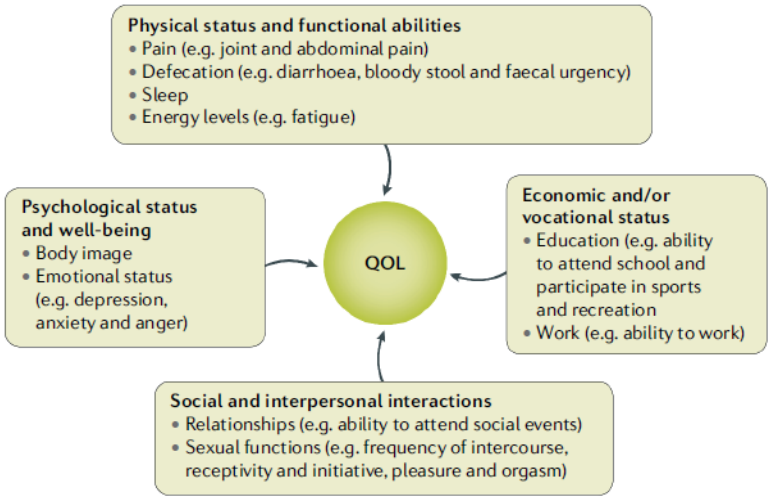
Patients with moderately to severely active CD have a considerable symptom burden compared with patients with mild disease.(50) Symptoms such as tenesmus, back pain, thirst/dehydration, weakness, joint pain, joint stiffness and general body pain were reported more in patients with moderately to severely active CD than in patients whose disease was in remission or who had mildly active CD.(51) With enhanced phenotypes such as stricture or penetrating CD, patients are more likely to report general and night-time bowel urgency, liquid stools and faecal incontinence during sleep.(41) Moderate to severe CD and more complicated phenotypes are also associated with increased risk of EIMs and are associated with an unfavourable prognosis, including medication escalation, surgery, poor QoL, increased risk for cancer, and increased morbidity and mortality.(52, 53)

B.1.3.2.2. Quality of life burden

Health-related quality of life (HRQoL) is also profoundly affected by the symptoms of CD.(54) The HRQoL impact of CD is multifaceted, driven by chronic and unpredictable symptom flare-ups that often begin in early adulthood. These can

impact physical health and mental health, activities of daily living, work productivity and social relationships, as summarised in Figure 2.(38)

Figure 2: Factors that affect QoL domains in CD



Key: CD, Crohn's disease; QoL, quality of life.
Source: Roda et al. (2020).(38)

Studies have shown that disease status and symptom severity exacerbate HRQoL. HRQoL is reduced during periods of active disease versus remission, and this decline is augmented with a greater number of relapses per year.(38, 50, 54-56) During periods of remission, HRQoL is still decreased compared with healthy controls.(57) Furthermore, patients with moderate or severe active CD have significantly lower HRQoL compared with those with mild symptoms.(50) This decrease in HRQoL is driven by multiple factors including fatigue, anxiety and exposure to multiple biological agents as part of treatment.(50)

Symptoms are a major driver of poor HRQoL. Multiple studies report that the most common and bothersome symptoms are GI/abdominal pain, loose or liquid bowel movements, high frequency of bowel movements and fatigue/tiredness. Of these symptoms, abdominal pain and bowel movement urgency cause the most distress.(51, 58-60) Symptoms then go on to impact multiple elements of daily life, as shown by a study in which semi-structured interviews were carried out with 36 patients. Participants reported effects on: activities of daily living (100% of patients surveyed); work/school (92%); and emotional (94%), social (89%) and physical (78%) functioning, with fatigue compounding all of these issues.(51, 61)

A 2024 Crohn's & Colitis UK report surveyed 970 patients in the UK with IBD (53% with CD and 41.9% with ulcerative colitis [UC]), to find the top 10 impact of living with IBD.(62) 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, as well as embarrassment around the potential social stigma of bowel symptoms and dealing with incontinence/bowel urgency. All of these increase anxiety and the likelihood of patients being unable to freely travel and attend social and work events.(62)

Across the entire disease course, anxiety and depression are drivers of poor HRQoL due to the psychological impacts of the disease and symptoms.(63) Treatment can also drive poor HRQoL.(38) Patients treated with systemic steroids or azathioprine and those who need surgery have reduced HRQoL. Those who undergo surgery have lower physical role, general health and physical health summary scores in the SF-36® health survey compared with patients who did not have surgery.(56)

Carers and family members also experience an HRQoL impact due to caring for a patient with CD. Family carers report significantly worse SF-36 Mental Component Summary scores and Self-Rating Anxiety and Depression Scale scores relative to healthy controls.(63, 64) Further work shows that family members see declines in emotional well-being, relationship with the patient, social life, work and finances, and leisure time, and partners experience strain due to a reduction in sexual functioning and romantic activities.(65) Of the 1,930 patients with CD surveyed across 12 European countries, 32% required informal care during remission, and 48.6% required care during active disease. This amounted to an average of 5.1 hours (22.4) total and 1.7 hours (11.12) of absence from work per week.(66)

B.1.3.2.3. Societal and economic burden

CD is associated with a considerable societal and economic burden. The severity of symptoms during active periods of disease and the chronic, relapsing and incurable nature of the disease leads to considerable healthcare resource utilisation (HCRU)

and costs.(67-72) Furthermore, as CD often affects patients of working age, there are high indirect costs associated with absenteeism, decreased workplace productivity, unemployment, and caregiving burden/costs.(73) Patients with moderate to severe CD incur higher direct and indirect costs compared with patients with mild symptoms or those in remission.(50)

Patients with CD have a high risk of hospitalisation and surgery, and current treatment options have increased outpatient visits compared with the general population. Patients with CD have a 29.3% chance of hospitalisation in the first year of diagnosis and a 44.3% risk after 5 years.(74) Once again, severity of active disease is associated with increased HCRU and cost.(50)

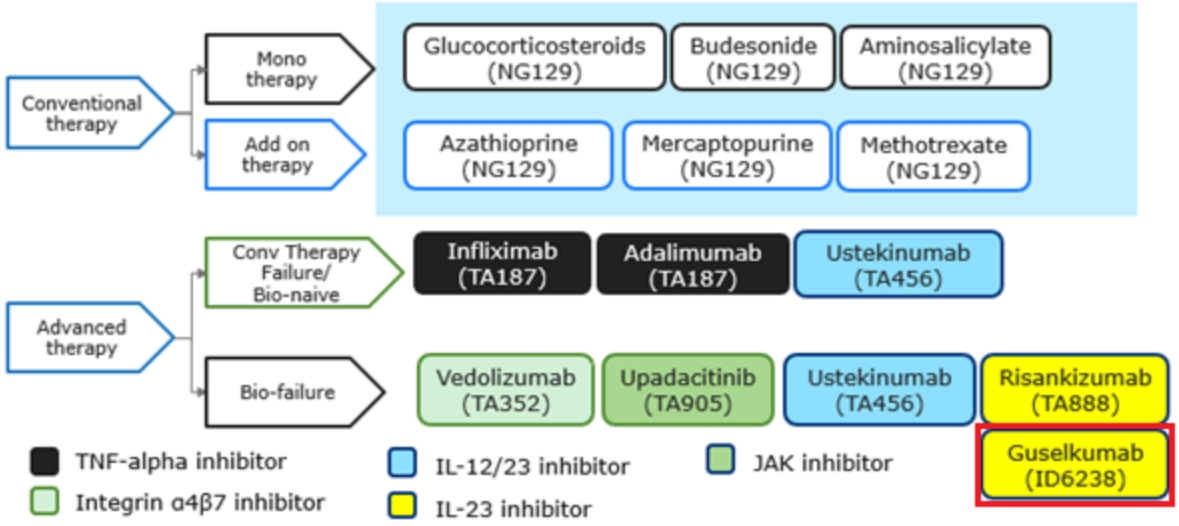
B.1.3.3. Current pathway of care and the anticipated positioning of guselkumab

A variety of conventional and advanced therapies with different mechanisms of action are licensed for the treatment of CD, and guidelines are available from NICE and the British Society of Gastroenterology (BSG) to guide treatment decision-making (Appendix G).(75, 76) The primary goal of treatment is to reduce inflammation, control symptoms and induce remission (Figure 3). Based on NICE Guideline 129 and the BSG guidelines, newly diagnosed patients are recommended a course of corticosteroids (prednisolone, methylprednisolone or IV hydrocortisone), budesonide or aminosalicylates. If necessary, azathioprine or mercaptopurine may be offered as an add-on treatment. In patients who do not respond to conventional therapies, an advanced therapy may be offered in line with the more recent NICE Guideline 129 and TA187, such as a TNF inhibitor (infliximab and adalimumab), or based on the more recent recommendation TA456, an interleukin (IL)-12/23 inhibitor (ustekinumab).(6, 77) Recent NICE appraisals recommend that patients for whom a first-line biologic therapy has failed, or who are contraindicated/unsuitable to receive a TNF inhibitor, may also be offered vedolizumab (TA352), upadacitinib (TA905) or risankizumab (TA888).(4, 5, 12) NICE recommendations for advanced therapy are supported by the BSG for ustekinumab, vedolizumab and upadacitinib.(76)

The proposed positioning of guselkumab is for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, lost

response to, or were intolerant to a biologic treatment and anticipated to sit in the treatment pathway in the BIO-failure population. This proposed positioning is highlighted in red in Figure 3 below. (75)

Figure 3: Current management of CD and anticipated positioning of guselkumab



Key: CD, Crohn's disease; IL, interleukin; JAK, Janus kinase; NICE, National Institute for Health and Care Excellence; TNF, tumour necrosis factor.
Source: Based on NICE NG129, 2019 and TA187, TA456, TA352, TA905, and TA888.(4-6, 12, 75, 77)

B.1.3.4. Unmet need

Real-world evidence published in 2020 suggests that up to 50% of patients progress onto advanced therapies such as biological therapies (e.g. anti-TNFs, Janus kinase [JAK] inhibitors, IL-23 inhibitors). Such change in treatment occurs because conventional therapies fail to control their disease, patients are contraindicated to conventional therapies, or the adverse events (AEs) of conventional therapies become intolerable.(35)

However, current advanced therapies to treat moderately to severely advanced active CD may still do not control the disease adequately. TNF inhibitors are usually used first-line if patients progress or are not suitable for conventional therapy. While these are effective, approximately 25% of patients receiving TNF inhibitors are primary non-responders, approximately 50% have a secondary loss of response, and 8% experience an AE that lead to treatment discontinuation.(78, 79) In fact,

approximately 80% of patients do not achieve the guideline recommended target of endoscopic remission set out by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD) when taking TNF inhibitors.(80, 81) Lifestyle factors such as smoking and obesity, and disease characteristics such as increased inflammatory biomarkers of disease activity and immunogenicity are associated with low drug concentrations and non-remission.(78)

If patients lose response to advanced treatment and have active disease, symptoms such as diarrhoea, fatigue and abdominal pain have a high QoL impact, as detailed in Section B.1.3.2.(82) Up to 20% of patients with active CD cannot work.(83)

In addition, many patients are not suitable for TNF inhibitors due to heart disease, old age, presence of malignancies, or risk of infection or recurrent infection. (84)

There remains a substantial unmet need for therapies with new mechanisms of actions that are more effective and more tolerable than current therapies to sustain remission and improve patient outcomes. This could limit the risk of further progression, complications, QoL impairment and costs associated with this debilitating disease.

B.1.3.5. Relevance of current appraisal to NHS England

In the UK, reducing the number of outpatient visits required is one way to reach the key goal of reducing National Health Service (NHS) waiting lists.(85) Treatments that reduce outpatient visits, hospitalisations and surgeries thus represent a much-needed addition to the treatment options for moderately or severely active CD.(85)

Patients who progress onto biological therapies mostly require a hospital-administered induction phase, which has a considerable burden on patients. Regular outpatient visits to hospital are required that have considerable HCRU increasing the burden on stretched NHS waiting lists – and resulting in a loss of work productivity for patients. Carers also experience a burden due to these outpatient visits as they may need to take patients to appointments and consequentially may also experience loss of work productivity. Many patients still do not achieve long-term remission with advanced therapies, as evidenced by low adherence/persistence, dose escalations,

treatment augmentation with steroids, and frequent treatment-switching.(86) All of these are prominent indicators that current therapies are not sufficient to reduce NHS burden of care. Real-world evidence also demonstrates that approximately 66% of patients experience frequent or very frequent treatment failure when receiving a biological therapy.(35)

An effective biological treatment, such as guselkumab, that can be initiated at home via an SC injection could further reduce HCRU and reduce NHS waiting lists. Additionally, an effective treatment with a flexible dosing option may provide clinicians the option to help patients better manage disease control and stay on treatment for longer. The SC administration of guselkumab means patients do not need to wait for appointments for IV induction and instead can begin to receive treatment quickly. This reduces the impact of advanced therapy on both patients and carers, while reducing waiting times.

B.1.4. Equality considerations

Living with IBD is not classed as a disability under the Equality Act. However, it may be classed as a disability depending on the effect it has on a patient's daily life.(87) 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 CD and UC experience at least one flare-up per year.(88)

More than one quarter of people with CD and UC had to wait over 1 year for diagnosis, with almost half visiting accident and emergency departments during this time.(89) 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.

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, the comparators considered in this appraisal are vedolizumab and risankizumab. Both treatments have received a positive recommendation from NICE, which includes the proposed population in this submission. This section provides an overview of the clinical outcomes and measures considered in TA352 and TA888.(4, 5)

In the appraisal of risankizumab (TA888), a cost-effectiveness analysis was initially developed but was deemed more appropriate as a cost-comparison analysis after committee review. In both TA352 and TA888, the submitted models were similar in structure, typically consisting of two phases: a short-term induction phase, after which patients in response or remission continued to a longer-term maintenance phase. This two-phase approach is in line with clinical practice and reflects the clinical trials informing these models.(4, 5)

Across both appraisals (TA352 and TA888), clinical remission and response were defined by the CDAI score system (see Section B.1) and were used to assess patients' disease activity during the induction and maintenance phases. Although the CDAI is not commonly used to assess disease severity in UK clinical practice, it is the measure most frequently used in clinical trials for this indication. Furthermore, the NICE Committees accepted the use of CDAI in both TA352 and TA888; this was due to its historical use in evaluating responses to other biological treatments and its recognition as a clinically valid and comprehensive tool for CD assessment. (4, 5)

The appraisals varied in terms of how they applied assumptions relating to discontinuation. The vedolizumab analysis (TA352) incorporated discontinuation based on the loss of response during the maintenance period, while the risankizumab analysis (TA888) assumed no discontinuation in the base case but explored several scenarios with different treatment discontinuation assumptions. (4, 5) The impact of these scenarios was minimal, and generally the Committees stated

preference for considering discontinuation due to lack of efficacy during the maintenance period. In addition, the vedolizumab model included the management of patients who lost response in the form of dose escalation.

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
Vedolizumab (TA352)(5)					
Clinical response and remission	CDAI	Clinical response: CDAI-70 Remission: CDAI < 150	Substantial	Clinical response: The ERG preferred response assessment at Week 10 instead of Week 6 as was submitted in the base case. Remission: The ERG observed that the proportion of patients in remission on conventional non-biologic therapies was higher in GEMINI II compared with the economic model, which underestimated their efficacy. This discrepancy arose because the model used data from the maintenance phase in patients initially responding to vedolizumab rather than from those on	As CDAI scores are not routinely used in English clinical practice, the definition of response may have limited relevance. Adopting the ERG's preferred assumption to assess remission may lead to underestimation of the efficacy of conventional non-biologic therapies.

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
				placebo. The ERG recommended using the observed data from the placebo arm of the GEMINI II trial instead.	
Treatment discontinuation	Discontinuation due to insufficient response or adverse events	Since not all trials reported discontinuation data, the model reflects data from trials that did report discontinuation due to adverse events	Minimal	The model did not include discontinuation due to lack of efficacy in the maintenance phase, which the ERG recommended incorporating. Additionally, the assumption of no increase in relapse after withdrawal of biological treatment in patients in remission or with mild disease was inconsistent with clinical expert opinion received by the ERG.	N/A
Dose escalation	The proportion of patients who receive dose escalation due to loss of response	For patients who do not respond, a dose of vedolizumab at Week 10 may be beneficial. Some patients experiencing reduced response may	Unclear	The Committee did not discuss this.	N/A

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
		benefit from an increased dosing frequency to vedolizumab 300 mg every 4 weeks.			
Surgery	The approach to modelling surgery states	Since surgery was included as a health state and post-surgical health states were not modelled, the incidence of surgical complications was incorporated within the surgery health state.	Minimal	The ERG acknowledged that modelling surgery as a single health state might oversimplify the situation, as subsequent surgeries likely depend on the type of initial procedure. However, they attributed this approach to data limitations and anticipated minimal impact on the outcomes. The ERG opted to use rates from the GEMINI trial instead of the HES-based estimates provided in the company's submission. Following analysis of HES data, the ERG recommended reducing the costs	N/A

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
				associated with surgery.	
Mortality	Annual mortality rate	The annual mortality rate was calculated using ONS mortality rates and then adjusted for each model health state based on published literature to determine a relative risk.	Minimal	The ERG recommended applying the same excess mortality risk to all CD health states.	The model predicted improved survival outcomes for patients receiving biologics compared with patients receiving conventional therapy. However, the study used by the company in its model did not demonstrate statistically significant differences in excess mortality rates based on disease severity at baseline or in mortality between patients who received infliximab and those who did not.
Adverse events	Adverse events considered in the model	Adverse event rates derived from clinical trials; specific adverse events chosen based on expert opinion	Minimal	N/A	It remained ambiguous whether the model included all adverse events or only Grade 3 or 4 events. The ERG criticised the calculations as overly simplistic and likely inaccurate due to their failure to consider trial duration. Furthermore, it was unclear why the model

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
					did not incorporate the incidence of serious adverse events.
Risankizumab (TA888)(4)					
Clinical response and remission	CDAI	Clinical response: ≥ 100-point drop in CDAI score from baseline to end of induction Remission: CDAI < 150	N/A	N/A	N/A
Treatment discontinuation	Discontinuation due to insufficient response or adverse events	Base case: assume no discontinuation Scenario analysis: treatment-specific annual discontinuation probability applied, sourced from the literature	When treatment discontinuation is considered, vedolizumab becomes less expensive than risankizumab irrespective of dose escalation assumptions, with the contrast between the two figures demonstrating the sensitivity of the model to treatment discontinuation assumptions.	The EAG has implemented an exploratory scenario whereby annual evidence-based discontinuation rates across treatments are implemented each year.	N/A
Dose escalation	The proportion of patients who receive dose	Adalimumab, infliximab, ustekinumab and vedolizumab are offered in	The company's CCA results are influenced by the	N/A	The EAG questioned that in the CCA, dose escalation was assumed to

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER?	Committee's preferred assumption	Uncertainties
	escalation due to loss of response	both standard and high doses for maintenance therapy. The distribution of patients between standard and high doses of these comparator interventions is informed by input from UK clinical experts. Risankizumab is administered as a fixed dose and therefore has no high-dose maintenance therapy option.	assumed proportion of patients receiving standard- versus high-dose maintenance therapy.		occur at time zero for all patients affected, which deviated from the company's CEA approach and favoured risankizumab where dose escalation was not incorporated. Hence, exploratory EAG scenarios were conducted to illustrate the impact of varying the proportion of standard- versus high-dose maintenance assumptions on the company's CCA results.
Surgery	Surgery was not modelled, as the equal efficacy assumption implies that these down-stream costs would be similar for all treatments.		N/A	N/A	N/A
Mortality	Annual mortality rate. The annual mortality rate was calculated using ONS mortality rates. CD was assumed not to cause excess mortality.		N/A	N/A	N/A
Adverse events	Adverse events were not included, as the equal efficacy assumption means that adverse event costs are also the same.		N/A	N/A	N/A

Key: CCA, cost-comparison analysis; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CEA, cost-effectiveness analysis; EAG, External Assessment Group; ERG, Evidence Review Group; HES, Hospital Episode Statistics; ICER, incremental cost-effectiveness ratio; N/A, not available; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics.

B.2.2. Resource use assumptions

The initial cost-effectiveness model for risankizumab (TA888) presented similar costs to those presented in vedolizumab (TA352) which included costs associated with drug acquisition, drug administration, health care resource use, surgery and adverse events. The subsequent cost comparison model in TA888 included only drug acquisition and administration costs. (4, 5)

In line with the risankizumab cost comparison appraisal (TA888), only drug acquisition and administration costs are considered in this analysis. It is 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. Although these costs are not considered in this appraisal, they have been described below for completeness, and a summary is presented in Table 4.

B.2.2.1. Drug acquisition costs

For both appraisals (TA352 and TA888), 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.(90-92) These costs were modelled separately for the induction phase and maintenance phase, and are consistent with those used in TA352 and TA888. (4, 5)

B.2.2.1.1. Dose escalation

As discussed in Section B.2.1, TA888 included dose escalation for vedolizumab and ustekinumab in line with their SmPCs. The proportion of patients assumed to be on escalated dosing on vedolizumab was 30%.(4)

B.2.2.2. 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 TA352 and TA888). Where IV administration is required, the

associated costs were informed by the cost of an outpatient visit; the costs used in TA352 were sourced from NHS Payment by Results tariffs.(93)

B.2.2.3. Health state and adverse event costs

As described in Section B.2.1, TA352 modelled health state costs such as active CD, response without remission, remission, surgery and post-surgery. AE costs were modelled in TA352, and costs for serious infections were based on a weighted average of different infections sourced from NHS reference costs.(5)

Table 4: Comparator resource use assumptions in past TAs

Cost category	TA352(5)	TA888(4)
Drug acquisition costs	Derived from BNF, eMIT and MIMS No dose escalation Assuming a 14-week stopping rule in the induction phase	Derived from BNF, eMIT and MIMS Included dose escalation for 30% of patients for vedolizumab IV and 92.5% for ustekinumab SC No stopping rule
Drug administration costs	IV costs were based on NHS tariff FZ37F SC costs: nurse administration of £39.00 was sourced from the PSSRU 2015 report (face-to-face contact in district nursing services)	IV costs: assumed to incur per administration cost based on the NHS Payment by Results tariff 2020/21 (item code FD02H). SC costs: initial training cost on first administration (based on one 1-hour of nurse time) and no subsequent costs.
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; eMIT, Electronic Market Information Tool; IV, intravenous; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SC, subcutaneous.

B.3. Clinical effectiveness

Evidence base for guselkumab in Crohn's disease

- The efficacy and safety data for guselkumab versus placebo are derived from the GALAXI-2, GALAXI-3 (referred to as GALAXI-2/-3) and GRAVITI Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre trials:
  - GALAXI-2/-3 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)
  - GRAVITI 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 bio-failure subgroups in GALAXI-2/-3 and GRAVITI, 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

Summary of clinical efficacy data

- A significantly greater proportion of patients in GALAXI-2/-3 achieved clinical remission, endoscopic response, PRO-2 remission, fatigue response and endoscopic remission at Week 12 in the guselkumab 200 mg IV group compared with the placebo group in both the Full Analysis Set and bio-failure population
- Both guselkumab maintenance dose regimens (200 mg SC and 100 mg SC) in GALAXI-2/-3 demonstrated robust efficacy and improved outcomes compared with placebo across primary and secondary endpoints
- A greater proportion of patients in GRAVITI achieved the primary and secondary endpoints in the guselkumab treated groups compared with placebo, in both the Full Analysis Set and the bio-failure populations

Summary of clinical safety data

- In GALAXI-2/-3 trial, the overall frequency of serious adverse events (SAEs), AEs leading to discontinuation, and serious infections through Week 48 were low for both placebo and guselkumab

- The guselkumab safety results from GALAXI-2/-3 and GRAVITI were consistent with the well-characterised and favourable safety profile of guselkumab in its approved indications of plaque psoriasis and psoriatic arthritis

Summary of indirect treatment comparisons

- 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 risankizumab and vedolizumab
- Guselkumab was numerically better than risankizumab and vedolizumab for the outcomes of clinical response, clinical remission and endoscopic response 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 CD 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

See Appendix D for full details of the systematic literature review (SLR) process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

An SLR was conducted on the 27th July 2023 to identify and select evidence on the efficacy of treatments for patients with moderately to severely active CD.(94) This SLR covered a broad range of interventions used globally, 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 GALAXI trials (GALAXI-1, GALAXI-2 and GALAXI-3) and GRAVITI are the only trials to provide direct evidence for guselkumab in the treatment of moderately to severely active CD. These studies form the basis of the clinical effectiveness evidence provided in this submission. The methodology and results are of these trials are presented in Sections B.3.3 to B.3.5. The results of the comparator trials (ADVANCE, MOTIVATE, FORTIFY, GEMINI-2 and GEMINI-3) informed the indirect treatment comparisons, and are presented in B.3.8.

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 CD.

The three pivotal trials for guselkumab in patients with moderately to severely active CD are the Phase III GALAXI-2, GALAXI-3 and GRAVITI trials.(7, 8) These trials are designed to support the marketing authorisation of guselkumab and are the largest and most robust Phase 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 trials are provided in Sections B.3.3 to B.3.5 of this submission. Supportive data from GALAXI-1 (Phase II dose-ranging trial) are presented in Appendix I.

GALAXI-2 and GALAXI-3 (hereafter referred to as 'GALAXI-2/-3') are two identical confirmatory Phase III randomised, double-blind, placebo- and active-controlled, parallel-group, multicentre trials designed to determine the efficacy and safety of IV induction followed by SC maintenance with guselkumab compared with placebo or ustekinumab in adult patients with moderately to severely active CD.

Table 5: Clinical effectiveness evidence

Study	**GALAXI-2/-3(7, 9, 10)**	**GRAVITI(8, 11)**
Study design	Phase III, randomised, double-blind, placebo- and active-controlled, parallel-group, treat-through, confirmatory, multicentre studies	Phase III, randomised, double-blind, placebo-controlled, treat-through, parallel-group, multicentre study
Population	≥ 18 years of age with moderately to severely active CD (of ≥ 3	≥ 18 years of age with moderately to severely active CD

Study	GALAXI-2/-3(7, 9, 10)	GRAVITI(8, 11)
	months' duration), CON-failure or BIO-failure	(of ≥ 3 months' duration), CON-failure or BIO-failure
Dose Regimens	2:2:2:1 ratio to receive one of the following: • GUS 200 mg IV at Weeks 0, 4, 8 → GUS 200 mg SC Q4W • GUS 200 mg IV at Weeks 0, 4, 8 → GUS 100 mg SC Q8W • UST ~6 mg/kg IV at Week 0 → UST 90 mg SC Q8W • PBO at Weeks 0, 4, 8 → PBO Q4W or UST 90 mg SC Q8W (crossover at Week 12)	1:1:1 ratio to receive one of the following: • GUS 400 mg SC at Weeks 0, 4, 8 → GUS 200 mg SC Q4W • GUS 400 mg IV SC at weeks 0, 4, 8 → GUS 100 mg SC Q8W • PBO SC at Weeks 0, 4, 8 → PBO SC or GUS rescue at Week 16
Indicate if study supports application for marketing authorisation	Yes	Yes
Reported outcomes specified in the decision problem	• Clinical remission • Endoscopic remission • Endoscopic response • CD-related surgeries • CD-related hospitalisations • Adverse events • HRQoL	• Clinical remission • Clinical response • Endoscopic remission • Endoscopic response • Adverse events • HRQoL
All other reported outcomes	• Fatigue response • Corticosteroid-free clinical remission	N/A

Key: CD, Crohn's disease; CSR, clinical study report; GUS, guselkumab; HRQoL, health-related quality of life; IV, intravenous; N/A, not applicable; PBO, placebo; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneous; UST, ustekinumab.
Notes: CON-failure: participants who had previously demonstrated an inadequate response to, or had failed to tolerate, at least one conventional therapy (i.e. immunomodulators or oral corticosteroids) for CD and had not demonstrated failure to a biologic; **BIO-failure**: participants who had previously demonstrated an inadequate response to, or had failed to tolerate, at least one or more biologic therapies at a dose approved for the treatment of CD.
Sources: GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week CSR, 2024; GRAVITI CSR 48-Week CSR, 2024. (7-11)

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

B.3.3.1. GALAXI-2 and GALAXI-3

B.3.3.1.1. Study design

The development programme for guselkumab in CD included three trials conducted under a single protocol (CNTO1959CRD3001; GALAXI).(7) The three trials were randomised, double-blind, placebo- and active-controlled, parallel-group, multicentre trials that evaluated the safety and efficacy of guselkumab in adults with moderately to severely active CD (of ≥ 3 months' duration), who demonstrated an inadequate response to or failure to tolerate previous conventional therapy (CON-failure) or biologic therapy (BIO-failure).(7)

Phase II dose-ranging trial

The Phase II dose-ranging trial GALAXI-1 was conducted to inform the induction and maintenance dose for the Phase III studies.(7) Patients were randomised in a 1:1:1:1:1 ratio to receive(7):

- Guselkumab 1,200 mg IV induction Q4W x3 → 200 mg SC Q4W maintenance
- Guselkumab 600 mg IV induction Q4W x3 → 200 mg SC Q4W maintenance
- Guselkumab 200 mg IV induction Q4W x3 → 100 mg SC Q8W maintenance
- Ustekinumab 6 mg/kg IV induction → 90 mg SC Q8W maintenance
- Placebo IV Q4W x3 → placebo SC Q4W (for responders at Week 12) or ustekinumab crossover at Week 12 (for non-responders at Week 12)

An interim analysis of the first 250 randomised participants who completed the Week 12 visit or had terminated study participation before Week 12 was performed to inform the Phase III dose. (95) The results showed no apparent incremental benefit with the higher guselkumab induction dose across key efficacy measures, and thus guselkumab 200 mg IV induction Q4W x3 → 200 mg SC Q4W maintenance and guselkumab 200 mg IV induction Q4W x3 → 100 mg SC Q8W maintenance were used as doses in the Phase III induction and maintenance studies. Maintenance

doses were chosen as follows: 1) a high maintenance dose (200 mg) was selected to maximise the potential to achieve and maintain efficacy by sustaining exposures only slightly lower than the exposures achieved during induction; 2) a lower dose (100 mg SC Q8W), which is the approved dose for psoriasis and psoriatic arthritis, was selected to evaluate whether efficacy is maintained with lower exposures than used during induction. These dosing regimens were intended to allow further characterisation of the dose–response / exposure–response relationship of guselkumab maintenance treatment in Phase III. (95) Further details of GALAXI-1 are presented in Appendix I.

Pivotal Phase III induction and maintenance studies

GALAXI-2 and GALAXI-3 (hereafter referred to as 'GALAXI-2/-3') are two identical confirmatory Phase III randomised, double-blind, placebo- and active-controlled, parallel-group, multicentre trials designed to determine the efficacy and safety of IV induction followed by SC maintenance with guselkumab compared with placebo or ustekinumab in adult patients with moderately to severely active CD.(7, 9, 10) Both studies were conducted with a treat-through study design, i.e. each participant was randomised to a treatment regimen at Week 0 and remained on that regimen through Week 48 of each study regardless of their clinical response status, with the exception of participants randomised to placebo at Week 0. Participants randomised to placebo at Week 0 who did not achieve clinical response at Week 12 crossed over to treatment with the active comparator ustekinumab, which is globally approved for the treatment of CD and has a well-characterised safety profile.

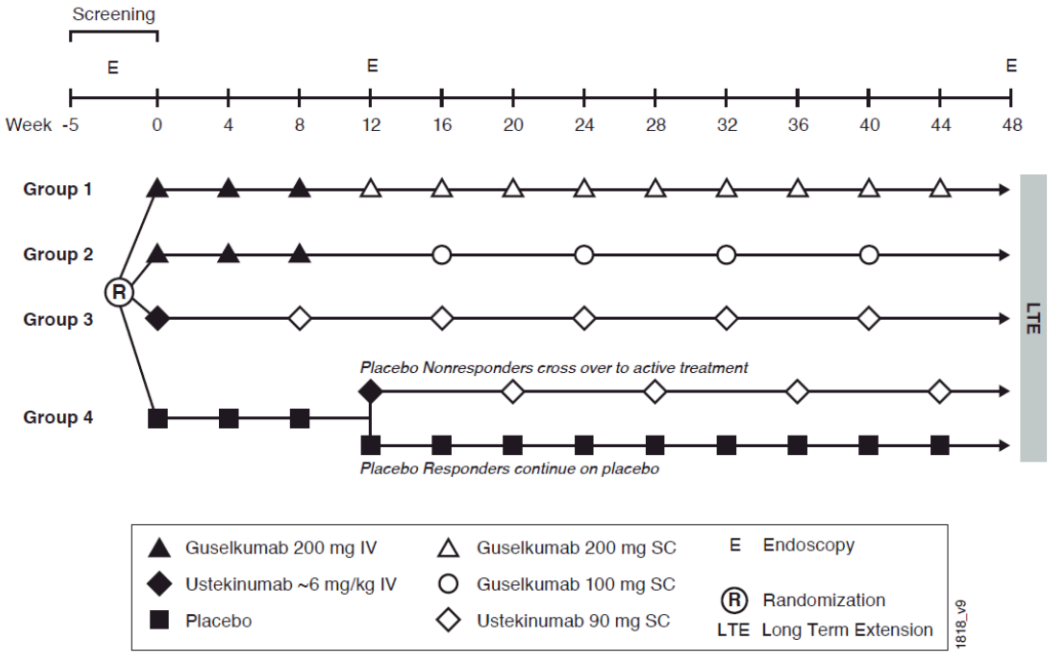
Eligible patients were randomised at a 2:2:2:1 ratio to receive one of the following treatment regimens, with primary and major secondary endpoints assessed at Week 12 by CDAI score (reduction from baseline of ≥ 100 or total score < 150; Table 6 and Figure 4). (7, 9, 10)

Table 6: Treatment regimens in GALAXI-2/-3

Regimen name	Regimen
Guselkumab Regimen 1	Guselkumab 200 mg IV induction at Weeks 0, 4 and 8 → guselkumab 200 mg SC maintenance Q4W from Weeks 12 to 44
Guselkumab Regimen 2	Guselkumab 200 mg IV induction at Weeks 0, 4 and → guselkumab 100 mg SC maintenance Q8W from Weeks 16 to 40
Active Control	A single ustekinumab (~6 mg/kg) IV induction dose at Week 0 → ustekinumab 90 mg SC maintenance Q8W from Weeks 8 to 40
Placebo → Placebo or Ustekinumab crossover	Placebo as IV induction at Weeks 0, 4 and Week 8 → maintenance based on clinical response status at Week 12: • Placebo responders continued placebo SC Q4W from Weeks 12 to 44 • Placebo non-responders: received a single ustekinumab IV induction dose (~6 mg/kg) at Week 20 → ustekinumab maintenance 90 mg SC Q8W from Weeks 28 to 44

Key: CSR, clinical study report; IV, intravenous; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneous.
Source: GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week, CSR, 2024. (7, 9, 10)

Figure 4: Study scheme for GALAXI-2 and GALAXI-3



Key: CSR, clinical study report; E, endoscopy; IV, intravenous; LTE, long-term extension; SC, subcutaneous.
Source: GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week CSR, 2024. (7, 9, 10)

B.3.3.1.1.1 Eligibility criteria

Key inclusion criteria were age ≥ 18 years and a confirmed diagnosis of moderately to severely active CD of at least 3 months' duration. (7, 9, 10) At baseline, patients must have had active CD with a baseline CDAI score ≥ 220 and ≤ 450 and either mean daily stool frequency > 3 or mean daily abdominal pain score > 1. Patients must also have had endoscopic evidence of ileocolonic CD, with an SES-CD score ≥ 6 (or ≥ 4 for isolated ileal disease) and ulceration in at least one of the five ileocolonic segments. Participants who had demonstrated inadequate response to or failed conventional or biological therapy were included. A subset of the CON-failure population was also naïve to biological therapy (including TNF antagonists) or could have been exposed to biologic therapy but not demonstrated inadequate response or intolerance. The main exclusion criteria were that patients must not have had complications of CD or prior exposure to IL-12/23 or IL-23 inhibitory agents, apart from patients who had limited exposure and who had not experienced failure or intolerance to ustekinumab. (7, 9, 10)

B.3.3.1.1.2 Study endpoints

As a result of different regulatory authority interactions, the GALAXI protocol contains two separate modules related to endpoints and hypotheses for the GALAXI-2/-3 Phase III studies: the first refers to global endpoints and hypotheses (based on Food and Drug Administration [FDA] advice) and the second to region-specific endpoints and hypotheses (based on European Medicines Agency [EMA] advice). The region-specific module applies to the Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation, and only endpoints that apply to the region-specific module will be discussed in this submission, unless otherwise specified (Table 7). (7, 9, 10)

Table 7: Definitions of key region-specific endpoints in GALAXI-2/-3 trials

Endpoint	Definition
Clinical remission	CDAI < 150
Clinical response	≥ 100-point reduction from baseline in CDAI score or CDAI score < 150
Clinical remission and endoscopic response	CDAI < 150 and ≥ 50% improvement from baseline in the SES-CD or SES-CD score ≤ 2

Endpoint	Definition
Corticosteroid-free clinical remission	CDAI score < 150 and not receiving corticosteroids
Durable clinical remission	CDAI score < 150 for ≥ 80% of all visits between Week 12 and Week 48 (i.e. at least 8 of 10 visits), which must include Week 48
Endoscopic remission	SES-CD score ≤ 2
Endoscopic response	≥ 50% improvement from baseline in the SES-CD or SES-CD score ≤ 2
Fatigue response	Improvement of ≥ 7 points in the PROMIS-Fatigue SF 7a
PRO-2 remission	AP mean daily score ≤ 1 AND SF mean daily score ≤ 3, and no worsening of AP or SF from baseline

Key: AP, abdominal pain; CDAI, Crohn's Disease Activity Index; CSR, clinical study report; PRO, patient-reported outcome; PROMIS-Fatigue SF, Patient-Reported Outcomes Measurement Information System-Fatigue Short Form; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.
Source: GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week CSR, 2024. (7, 9, 10)

The co-primary endpoints were clinical remission at Week 12 and endoscopic response at Week 12, with reported comparisons made between the combined guselkumab induction dose group and the placebo group. The major secondary endpoints included three sets of comparisons (Table 8). Further details of the trial methodology and outcomes are provided in Appendix I.

Table 8: Key secondary endpoint comparison sets

Comparison sets	Endpoints
Short-term endpoints at Week 12 evaluating guselkumab compared with placebo	• PRO-2 remission • Fatigue response • Endoscopic remission
Long-term endpoints at Week 48 evaluating guselkumab compared with placebo	• Corticosteroid-free clinical remission • Endoscopic response
Long-term endpoints at Week 48 evaluating guselkumab compared with ustekinumab	• Clinical remission and endoscopic response • Endoscopic remission • Clinical remission • Endoscopic response • PRO-2 remission • Corticosteroid-free clinical remission • Durable clinical remission

Key: CSR, clinical study report; PRO, patient reported outcome.
Source: GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week CSR, 2024. (7, 9, 10)

B.3.3.1.2. Summary of statistical analysis

B.3.3.1.2.1 Analysis sets in the GALAXI-2/-3 trials

The data sets analysed and number of patients in each analysis population for the GALAXI-2/-3 studies relevant to this submission are presented in Table 9.

Table 9: Analysis sets in GALAXI-2/-3

Analysis set	Description
Primary Analysis Set GALAXI-2/-3 (n = 508, 513)	All randomised patients who received at least one (partial or complete) dose of study intervention with a screening SES-CD score ≥ 6 or ≥ 4 for patients with isolated ileal disease.
BIO-failure Subgroup GALAXI-2/-3 (n = 268, 266)	A subpopulation of the Primary Analysis Set, which includes participants who had previously demonstrated an inadequate response to, or had failed to tolerate, at least one or more biologic therapies at a dose approved for the treatment of CD.
Primary Safety Analysis Set GALAXI-2/-3 (n = 508, 513)	All randomised patients who received at least one (partial or complete) dose of study intervention with a screening SES-CD score ≥ 6 or ≥ 4 for patients with isolated ileal disease.
Key: CD, Crohn's disease; CSR, clinical study report; SES-CD, Simple Endoscopic Score for Crohn's Disease. **Source**: GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week CSR, 2024. (7, 9, 10)	

B.3.3.1.2.2 Statistical analysis

All co-primary endpoints, major secondary endpoints and subgroup analyses were based on the Primary Analysis Set. (7, 9, 10) All safety analyses were based on the Primary Safety Analysis Set. The regional testing procedure began with sequential tests of superiority of the combined guselkumab dose group compared with placebo relative to the co-primary endpoints at the 2-sided 0.05 significance level. (7, 9, 10) After testing of the co-primary endpoints, and if all p-values were significant (i.e. $p < 0.05$), the testing procedure continued with superiority tests for the major secondary endpoints, which were grouped into four tiers. (7, 9, 10) Within each tier, the Hochberg procedure was used to test all endpoints in that tier with a 2-sided alpha of 0.05. If all tests within a tier were significant, then testing continued to the next tier. If any test within a tier was not significant, the other tests in the same tier were declared significant if they met the Hochberg thresholds, but the formal testing

stopped and all values in subsequent tiers were considered nominal for that testing procedure. (7, 9, 10) A graphical presentation of the region-specific hierarchical testing procedure can be found in Appendix I.

No interim analyses were performed in GALAXI-2/-3. (7, 9, 10) Primary analysis was performed from Week 0 to Week 48 of treatment, and the data cut-off date was October 2023. A summary of the statistical analyses performed during GALAXI-2/-3 is provided in Table 10.

Table 10: Summary of statistical analyses for GALAXI-2/-3

Hypothesis objective	The primary hypothesis was that guselkumab treatment is superior to placebo as assessed by the proportion of participants achieving clinical remission at Week 12 and the proportion of participants with endoscopic response at Week 12.
Statistical analysis	The change from baseline in CDAI was analysed using a MMRM approach. A multiple testing procedure was used to control the Type 1 error at α = 0.05 (2-sided) over the comparisons of guselkumab with placebo.
Analysis sets	**Efficacy Analysis Sets** • Primary Analysis Set (GALAXI-2: n = 508; GALAXI-3: n = 513): all randomised patients who received at least one (partial or complete) dose of study intervention with a screening SES-CD score ≥ 6 or ≥ 4 for patients with isolated ileal disease • All-treated Analysis Set (GALAXI-2: n = 523; GALAXI-3: n = 525): all randomised participants who received at least one (partial or complete) dose of study intervention • Modified Primary Analysis Set (GALAXI-2: n = 508; GALAXI-3: n = 513): same as the Primary Analysis Set but excludes participants who have data that could not be verified as specified by the Global Monitoring Plan due to the inability to access sites because of a major disruption (specifically, the regional crisis in Ukraine and Russia, or COVID-19-related site restrictions such as site closures, and other potential events that restrict site access) **Safety Analysis Sets** • Primary Safety Analysis Set (GALAXI-2: n = 508; GALAXI-3: n = 513): all randomised patients who received at least one (partial or complete) dose of study intervention with a screening SES-CD score ≥ 6 or ≥ 4 for patients with isolated ileal disease • All-treated Safety Analysis Set (GALAXI-2: n = 523; GALAXI-3: n = 525): all randomised participants who received at least one (partial or complete) dose of study intervention
Sample size, power calculation	• For the co-primary endpoint of clinical remission at Week 12: In each of the Phase III studies, assuming a clinical remission rate of approximately 12–15% for placebo and a minimum of 20% difference between guselkumab and placebo, 440 participants in the combined

	guselkumab induction dose group and 110 participants in the placebo group, respectively, provides greater than 99% power for clinical remission at Week 12 at an overall Type 1 error rate controlled at a 0.05 (2-sided) alpha level • In each of the Phase III studies, assuming an endoscopic response rate of approximately 10–13% for placebo and a minimum of a 15% difference between guselkumab and placebo, 440 participants in the combined guselkumab induction dose group and 110 participants in the placebo group, respectively, provides approximately 94% power for endoscopic response at Week 12 at an overall Type 1 error rate controlled at a 0.05 (2-sided) alpha level • For non-inferiority, a margin of 7% was set based on previous studies
Data management, patient withdrawals	Patients who withdrew due to any reason but COVID-19 before an analysis time point were considered to have not met the endpoint. Patients with missing data for specific endpoints were considered non-responders.
Key: CDAI, Crohn's Disease Activity Index; CSR, clinical study report; MMRM, mixed model for repeated measures; SES-CD, Simple Endoscopic Score for Crohn's Disease. **Source**: GALAXI-2 48-week CSR, 2024; GALAXI-2 48-week CSR, 2024. (9, 10)	

B.3.3.1.3. Patient disposition and baseline characteristics

In GALAXI-2, 524 patients were randomised and 523 patients were treated in 186 centres across 36 countries/territories.(9) Of these, 148 patients were randomised to the guselkumab 200 mg SC Q4W treatment group, 149 patients to the guselkumab 100 mg SC Q8W treatment group, 150 patients to the ustekinumab treatment group, and 77 patients to the placebo treatment group. At Week 12, 49 of the patients randomised to placebo crossed over to ustekinumab. All but one of the randomised patients were treated, as they met an exclusion criterion after randomisation and before receiving the first dose. During the induction period, 1.2% of patients discontinued study intervention and 10.4% of patients discontinued study intervention before completing maintenance dosing. Before Week 12, 1.4% of patients terminated study participation and 5.1% terminated before Week 48.(9)

In GALAXI-3, 525 patients were randomised and treated in 198 centres across 39 countries/territories.(10) Of these, 151 patients were randomised to the guselkumab 200 mg SC Q4W treatment group, 148 patients to the guselkumab 100 mg SC Q8W treatment group, 150 to the ustekinumab treatment group, and 76 to the placebo treatment group. At Week 12, 49 of the patients in the Primary Analysis Set randomised to placebo crossed over to ustekinumab. During the induction period,

2.7% of patients discontinued study intervention, and a total of 17.2% of patients discontinued study intervention before completing maintenance dosing. Before Week 12, 2.7% of patients terminated the study and a total of 9.6% of patients terminated before Week 48. (10) Patient flow diagrams for GALAXI-2/-3 are presented in Appendix D.2.

Details of baseline and disease characteristics for GALAXI-2/-3 are presented in Table 11. In the Primary Analysis Set of GALAXI-2/-3, baseline characteristics were generally balanced across all treatment groups. (9, 10)

Table 11: Baseline characteristics of patients in GALAXI-2/-3

Characteristic	GALAXI-2			GALAXI-3		
	PBO (N = 76)	GUS, combined (N = 289)	UST (N = 143)	PBO (N = 72)	GUS, combined (N = 293)	UST (N = 148)
Age, mean (SD)	34.2 (11.86)	36.7 (12.99)	36.9 (12.70)	35.4 (12.52)	36.3 (12.56)	37.9 (13.69)
Male, no (%)	41 (53.9)	156 (54.0)	84 (58.7)	47 (65.3)	176 (60.1)	84 (56.8)
Race*, no (%)						
Asian	17 (22.4)	62 (21.5)	32 (22.4)	18 (25.0)	66 (22.5)	22 (14.9)
Black/African American	0	4 (1.4%)	3 (2.1)	3 (4.2)	1 (0.3)	4 (2.7)
Native Hawaiian/Other Pacific Islander	2 (2.6)	0	0	2 (2.8)	1 (0.3)	1 (0.7)
White	55 (72.4)	218 (75.4)	104 (72.7)	47 (65.3)	220 (75.1)	115 (77.7)
Not reported	2 (2.6)	5 (1.7)	4 (2.8)	2 (2.8)	5 (1.7)	6 (4.1)
CD duration, mean years (SD)	6.36 (7.48)	7.60 (6.96)	6.58 (6.51)	7.97 (7.55)	6.59 (6.98)	8.02 (8.27)
CDAI Score, mean (SD)	292.0 (51.70)	295.7 (52.06)	295.3 (52.35)	294.9 (54.09)	296.4 (54.87)	291.0 (51.73)
SES-CD, mean (SD)	13.9 (7.80)	12.7 (7.07)	13.3 (7.50)	12.7 (7.27)	13.0 (7.59)	12.4 (6.55)
Involved GI areas (assessed by central reader), no (%)						
Ileum only	17 (22.4)	68 (23.5)	25 (17.5)	14 (19.4)	71 (24.2)	30 (20.3)
Colon only	29 (38.2)	118 (40.8)	58 (40.6)	33 (45.8)	107 (36.5)	58 (39.2)
Ileum and colon	30 (39.5)	103 (35.6)	60 (42.0)	25 (34.7)	115 (39.2)	60 (40.5)
Medication use at baseline and treatment failures, no (%)						
Immunomodulatory drugs	21 (27.6)	89 (30.8)	42 (29.4)	19 (26.4)	95 (32.4)	41 (27.7)
Oral corticosteroid use	25 (32.9)	109 (37.7)	56 (39.2)	26 (36.1)	106 (36.2)	53 (35.8)
BIO-failure	39 (51.3)	150 (51.9)	79 (55.2)	39 (54.2)	150 (51.2)	77 (52.0)
CON-Failure	37 (48.7)	139 (48.1)	64(44.8)	33 (48.9)	143 (48.8)	71 (48.0)
BIO-Naïve	34 (44.7)	121 (41.9)	58 (40.6)	27 (37.5)	123 (42.0)	63 (42.6)

Key: BIO-failure, biologic therapy failure; CDAI, Crohn's Disease Activity Index; CSR, clinical study report; CON-failure, conventional therapy failure; GI, gastrointestinal; GUS, guselkumab; PBO, placebo; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; UST, ustekinumab.
Notes: *Races without any included patients are omitted. †Includes the UK.**Source:** GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week CSR, 2024. (9, 10)

B.3.3.2. GRAVITI

B.3.3.2.1. Study design

GRAVITI is an ongoing Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre trial to evaluate the efficacy and safety of guselkumab SC induction dosing.(8) The GRAVITI trial evaluated the efficacy and safety of guselkumab SC treatment through 12 weeks of induction therapy and 12 weeks of SC maintenance therapy for a total of 24 weeks in the main trial. Similar to GALAXI, the GRAVITI trial was conducted using a treat-through trial design.

Dose selection

A single SC induction dose regimen (400 mg SC at Weeks 0, 4 and 8) was evaluated and was anticipated to provide comparable overall guselkumab exposure (area under the curve) to the 200 mg IV dose regimen at Weeks 0, 4 and 8 (GALAXI Phase III induction dose regimen) based on an estimated bioavailability of approximately 50% for guselkumab SC.(1) The same two maintenance doses studied in GALAXI were also included in GRAVITI. This was to enable cross-study comparison of SC induction followed by SC maintenance regimen (in GRAVITI) versus IV induction followed by SC maintenance regimen (in the GALAXI studies).

Eligible patients were randomised at a 1:1:1 ratio to one of the below treatment arms (Figure 5).(8) Response was measured at Week 12 by CDAI score (reduction from baseline of ≥ 100 or total score < 150).

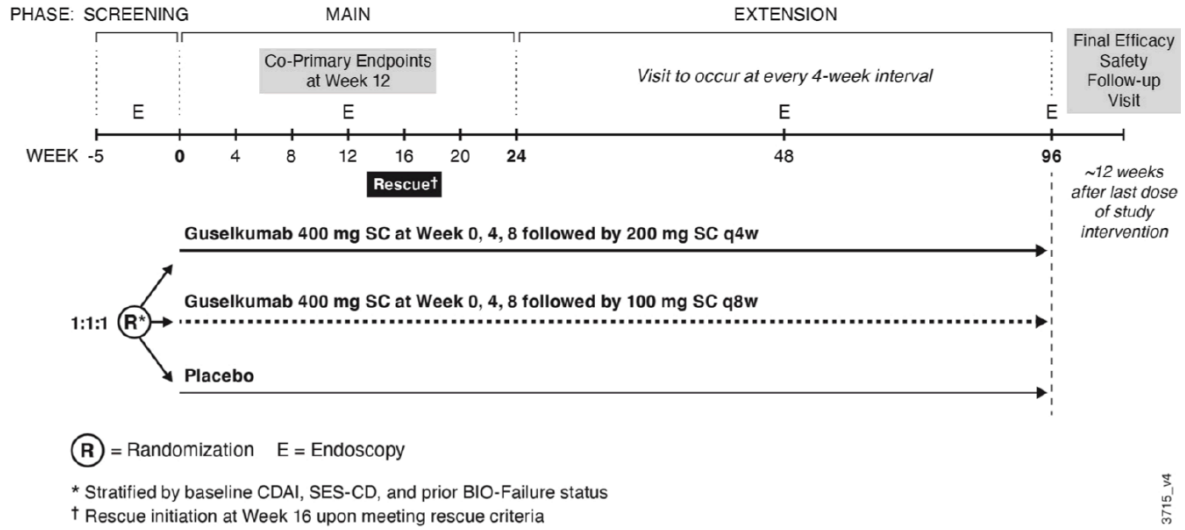
- Guselkumab 400 mg SC induction at Weeks 0, 4 and 8 → guselkumab 200 mg SC maintenance Q4W from Weeks 12 to 24
- Guselkumab 400 mg SC induction at Weeks 0, 4 and 8 → guselkumab 100 mg SC maintenance Q8W from Weeks 16 to 24
- Placebo SC Q4W from Weeks 0 to 24

All participants in the placebo group who met at least one of the rescue criteria at Week 12 and Week 16, as applicable, received rescue treatment, i.e. guselkumab 400 mg SC at Weeks 16, 20 and 24, followed by guselkumab 100 mg SC Q8W. Rescue criteria were based on meeting either CDAI score > 220 and a < 70-point

improvement from baseline in the CDAI score at both Week 12 and Week 16, or an increase in SES-CD score by at least 50% from baseline at Week 12.

At Week 24, patients entered the extension phase and received the same treatment they were on at Week 24 up to 96 weeks. (8)

Figure 5: Study scheme for GRAVITI



Key: CDAI, Crohn's Disease Activity Index; CSR, clinical study report; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Source: GRAVITI 48-week CSR, 2024.(8)

B.3.3.2.1.1 Eligibility criteria

Key inclusion criteria were adults (≥ 18 years) with CD or fistulising CD of at least 3 months with colitis, ileitis or ileocolitis, confirmed by radiography, histology and/or endoscopy. (8) Active CD was defined as a baseline CDAI score of both ≥ 220 and ≤ 450, and either mean daily stool frequency ≥ 4 or mean daily abdominal pain score ≥ 2. Patients must also have had endoscopic evidence of ileocolonic CD with an SES-CD score ≥ 6 (or ≥ 4 for isolated ileal disease) and ulceration in 1/5 ileocolonic segments. Participants who had failed either conventional or biological therapy were included, and some were naïve to biological therapy. Patients were excluded if they had complications from CD or received biological agents up to 12 weeks before baseline or received any IL-12/IL-23 therapy and had an inadequate response. (8)

B.3.3.2.1.2 Study endpoints

The co-primary endpoints for GRAVITI were clinical remission at Week 12 and endoscopic response at Week 12.(8) Key secondary endpoints included clinical remission at Week 24, PRO-2 remission at Week 12 and clinical response at Week 12. Definitions of these endpoints are aligned with the corresponding endpoints described for GALAXI-2/-3 (Table 7).(8) Further details of the trial methodology and outcomes are provided in Appendix I.

B.3.3.2.2. Summary of statistical analysis

B.3.3.2.2.1 Analysis sets in the GRAVITI trial

The data sets analysed and number of patients in each analysis population for the GRAVITI studies relevant to this submission are presented in Table 12.

Table 12: Analysis sets in GRAVITI

Analysis set	Description
Full Analysis Set GRAVITI, n = 347	All randomised participants who received at least one (partial or complete) dose of study intervention and satisfied the SES-CD eligibility criteria (i.e. screening SES-CD score ≥ 6 [or ≥ 4 for participants with isolated ileal disease]).
BIO-failure subgroup GRAVITI, n = 161	A subset of the Full Analysis Set, which includes participants who had previously demonstrated an inadequate response to, or had failed to tolerate, at least one or more biologic therapies at a dose approved for the treatment of CD.
Safety Analysis Set GRAVITI, n = 347	All randomised participants who received at least one (partial or complete) dose of study intervention.
Key: CD, Crohn's disease; CSR, clinical study report; SES-CD, Simple Endoscopic Score for Crohn's Disease. **Source:** Johnson & Johnson, Data on File 2025. (8)	

B.3.3.2.2.2 Statistical analysis

A fixed-sequence testing procedure was used to control the overall Type 1 error rate at the 0.05 level across the co-primary and secondary endpoints. (8) The endpoints were tested sequentially based on the testing procedure illustrated in Appendix I.

Primary analysis was performed from Week 0 to Week 24 of treatment, and the data cut-off date was 01 March 2024. A summary of the statistical analysis performed during GRAVITI is shown in Table 13.

The analyses of the co-primary endpoints and secondary endpoints were based on the Full Analysis Set. All safety analyses were based on the Safety Analysis Set.(8) No interim analyses were performed.

Table 13: Summary of statistical analyses for GRAVITI

Hypothesis objective	The co-primary hypotheses of this trial were that guselkumab is superior to placebo in inducing clinical remission at Week 12 and guselkumab is superior to placebo in inducing endoscopic response at Week 12 among participants with moderately to severely active CD.
Statistical analysis	• Using the co-primary estimands, an analysis of the co-primary endpoints was performed for each region, country and investigator site. This analysis was descriptive, and statistical testing was not applied • For the co-primary and secondary endpoints, the Cochran–Mantel–Haenszel chi-square test (2-sided) stratified by baseline CDAI score (≤ 300 or > 300), baseline SES-CD score (≤ 12 or > 12), and BIO-failure status (Yes or No) at baseline was used to compare guselkumab dose regimens versus placebo • A sensitivity analysis was performed using a tipping point analysis with Bernoulli draws to impute missing clinical remission status at Week 12 and missing endoscopic response status at Week 12 after the intercurrent event rules were applied, when the number of missing participants (after accounting for the intercurrent event strategies) was > 5% in any treatment group • To control the Type 1 error, a fixed sequence testing approach was used for the co-primary endpoints
Analysis sets	• Randomised Analysis Set: all randomised patients • Full Analysis Set: all randomised patients who received at least one dose of study intervention • Safety Analysis Set: all randomised patients who received at least one dose of study intervention
Sample size, power calculation	Sample sizes were determined by the power to detect a significant difference in clinical remission at Week 12 and in endoscopic response at Week 12 (co-primary endpoints) between the combined guselkumab group and the placebo group, using a 2-sided chi-square test with a 0.05 significance level. The assumed rates were 50% versus 15% (guselkumab versus placebo) for clinical remission and 30% versus 13% for endoscopic response. The trial was sized such that the guselkumab therapy would achieve > 90% power for the co-primary endpoints compared with placebo. This sample size also provides > 90% power for all secondary endpoints. In this trial, 212 participants in the combined guselkumab group and 106 participants in the placebo group provides at

	least 90% power for achieving the co-primary endpoints.
Data management, patient withdrawals	Patients with missing response status for binary endpoints were considered to not have achieved their respective endpoint.
Key: CDAI, Crohn's Disease Activity Index; CD, Crohn's disease; CSR, clinical study report; SES-CD, Simple Endoscopic Score for Crohn's Disease. **Source:** GRAVITI 48-week CSR, 2024. (8)	

B.3.3.2.3. Patient disposition and baseline characteristics

In GRAVITI, 350 patients were randomised and 347 patients were treated in 143 centres across 23 countries/territories.(8) Of these, 115 patients were randomised to the guselkumab 400 mg SC Q4W treatment → guselkumab 100 mg SC Q8W group, 115 patients to the guselkumab 400 mg SC Q4W treatment → guselkumab 200 mg SC Q4W group, and 117 patients to the placebo treatment group. All but three randomised patients were treated. The three patients were all enrolled at a site in Poland and were excluded from all analysis sets because neither the identification of the participants nor the source data could be verified, and study intervention administration could not be confirmed. During the induction period, 4% of patients discontinued study intervention and 15.3% of patients discontinued study intervention before completing maintenance dosing. Before Week 12, 2.9% of patients terminated study participation and 6.9% terminated before Week 48. (8, 11) A patient flow diagram for GRAVITI is presented in Appendix D.2.

The baseline characteristics for the GRAVITI trial are presented in Table 14. Baseline demographic characteristics were generally balanced across the treatment groups and are representative of a population with moderately to severely active CD. (8, 11)

Table 14: Baseline characteristics of patients in GRAVITI

Characteristic, n (%)	PBO (N = 117)	GUS, 100 mg SC (N = 115)	GUS, 200 mg SC (N = 115)	GUS, combined (N = 230)	Overall (N = 347)
Age, mean (SD)	36.0 (12.71)	37.4 (13.32)	39.1 (12.56)	38.2 (12.95)	37.5 (12.89)
Male, no (%)	67 (57.3)	66 (57.4)	70 (60.9)	136 (59.1)	203 (58.5)
Race*, no (%)					
Asian	28 (23.9)	26 (22.6)	22 (19.1)	48 (20.9)	76 (21.9)
Black/African American	5 (4.3)	0	4 (3.5)	4 (1.7)	9 (2.6)
White	71 (60.7)	79 (68.7)	79 (68.7)	158 (68.7)	229 (66.0)
Not reported	13 (11.1)	10 (8.7)	10 (8.7)	20 (8.7)	33 (9.5)
CD duration, mean years (SD)	6.96 (7.752)	9.17 (9.079)	7.89 (7.126)	8.53 (8.168)	8.00 (8.053)
CDAI Score, mean (SD)	293.0 (49.09)	300.4 (54.32)	297.3 (54.69)	298.8 (54.41)	296.9 (52.68)
SES-CD, mean (SD)	12.0 (6.89)	12.2 (6.85)	11.8 (7.12)	12.0 (6.97)	12.0 (6.94)
Involved GI areas (assessed by central reader), no (%)					
Ileum only	22 (18.8)	25 (21.7)	27 (23.5)	52 (22.6)	74 (21.3)
Colon only	40 (34.2)	41 (35.7)	40 (34.8)	81 (35.2)	121 (34.9)
Ileum and colon	55 (47.0)	49 (42.6)	48 (41.7)	97 (42.2)	152 (43.8)
Medication use at baseline and treatment failures, no (%)					
Immunomodulatory drugs	80 (68.4)	83 (72.2)	81 (70.4)	164 (71.3)	244 (70.3)
Oral corticosteroid use	94 (80.3)	101 (87.8)	96 (83.5)	197 (85.7)	291 (83.9)
BIO-failure	53	55	53	108	161
CON-failure	64	60	62	122	186
BIO-naïve	56	53	52	105	161

Key: CDAI, Crohn's Disease Activity Index; CD, Crohn's disease; CSR, clinical study report; GI, gastrointestinal; GUS, guselkumab; PBO, placebo; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Source: GRAVITI 48-week CSR, 2024. (11)

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

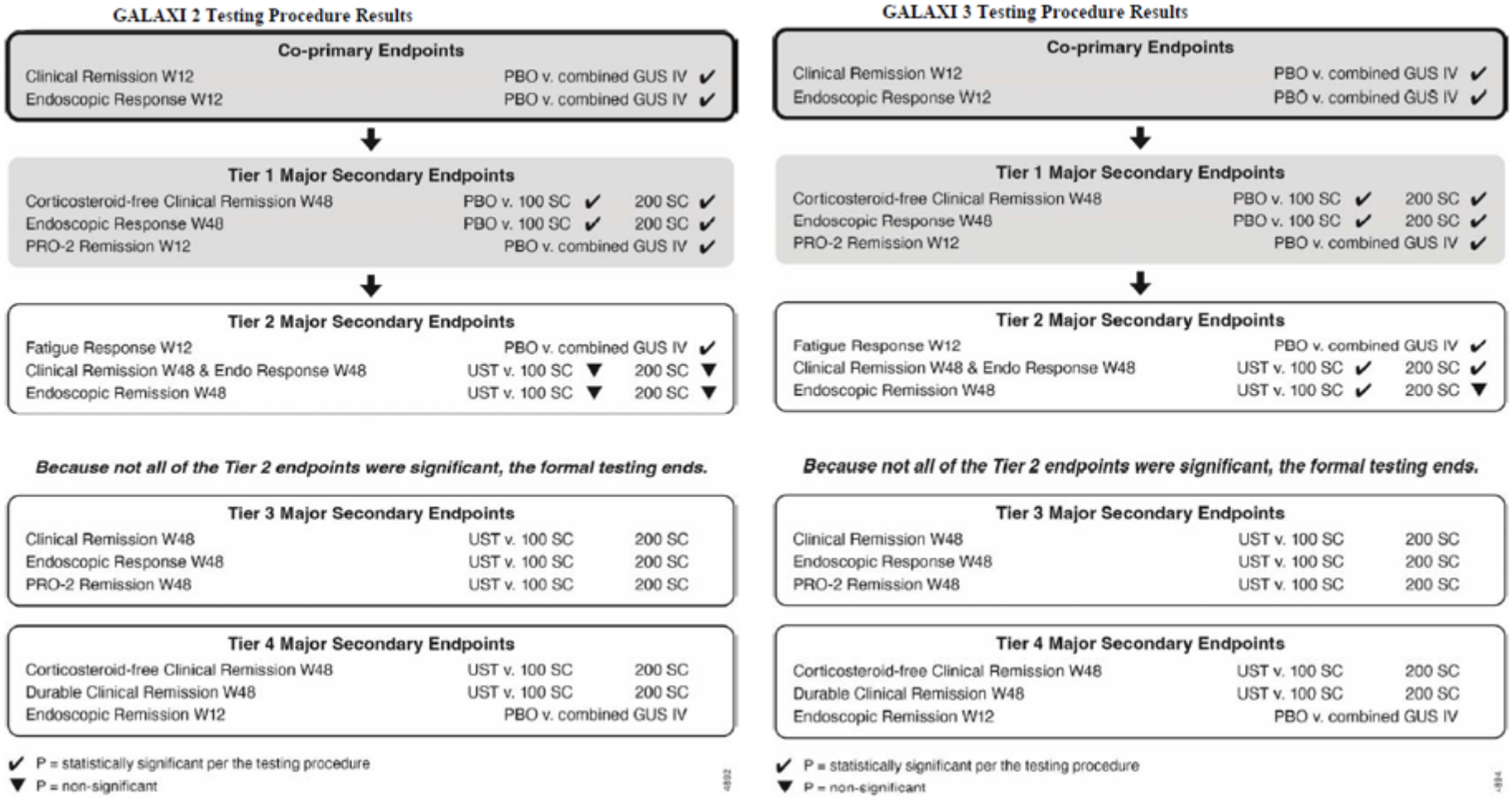
GALAXI-2/-3 and GRAVITI were conducted in accordance with the ethical principles of Good Clinical Practice and were both considered to be good-quality studies. A complete quality assessment in accordance with the NICE quality assessment checklist is presented in Appendix D.3.

B.3.5. Clinical effectiveness results of the relevant studies

B.3.5.1. GALAXI-2/-3

Based on the region-specific testing procedure presented in Section B.3.3.1.2.2, the GALAXI trials met the co-primary endpoints and the Tier 1 major secondary endpoints. Additionally, numerically greater proportions of participants treated in the combined guselkumab 200 mg IV treatment group achieved endoscopic remission at Week 12 compared with the placebo treatment group (Figure 6). Furthermore, guselkumab showed numerically similar or greater efficacy compared with ustekinumab across the Week 48 major secondary endpoints (Appendix I).

Figure 6: Summary of results of the region-specific testing procedure



Key: CSR, clinical study report; GUS, guselkumab; IV, intravenous; PBO, placebo; PRO, patient-reported outcome; SC, subcutaneous; UST, ustekinumab.
Source: GALAXI-2 48-week CSR, 2024; GALAXI-3 48-week CSR, 2024. (9, 10)

In this section, we describe the results for the region-specific short-term and long-term efficacy comparisons between guselkumab and placebo of GALAXI-2/-3 as pooled data. Short-term efficacy comparisons are presented as a 'combined' guselkumab treatment group versus placebo, as patients in the two guselkumab treatment arms received the same induction dosing up to Week 12. Long-term efficacy comparisons are presented for the individual maintenance treatment arms (either 100 mg or 200 mg guselkumab treatment group) versus placebo. For each endpoint, results are presented for the Primary Analysis Set, as the trial was powered to detect differences between the treatment groups for this population. Results are also described for the pre-specified BIO-failure subgroup, as this is the population of interest relevant to the decision problem in this submission. The endpoints presented for the BIO-failure subgroup were not part of the hierarchical testing procedure, and they were not controlled for multiplicity; as such, all statistical significance is considered nominal.

Results are presented for the pooled GALAXI-2 and GALAXI-3 studies. This pooled approach is appropriate from a statistical perspective; as the studies are identical and were conducted simultaneously at the same sites, and as each participant is randomised into one of the two trials, the designation of 'trial' here is essentially another stratification factor. Therefore, pooling would keep the randomisation intact and would be statistically justified.(96) Individual trial outcomes for the BIO-failure group comparing guselkumab with placebo and long-term efficacy comparisons between guselkumab and ustekinumab in the Primary Analysis Set are presented in Appendix I.

B.3.5.1.1. Co-primary endpoints

B.3.5.1.1.1 Clinical remission at Week 12

A statistically significantly greater proportion of patients in the combined guselkumab group achieved clinical remission at Week 12 compared with the placebo treatment group in the pooled GALAXI-2/-3 Primary Analysis Set (47.1% vs 18.9%) (Table 15).(97) Results were consistent within the BIO-failure population, with a statistically significantly greater proportion of patients achieving clinical remission at Week 12 in

the combined guselkumab group compared with the placebo treatment group in the pooled GALAXI-2/-3 BIO-failure subpopulation (46.0% vs 19.2%) (Table 15).(97)

Table 15: Clinical remission at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference*, % (95% CI)	P-value
Primary Analysis Set	28/148 (18.9)	274/582 (47.1)	28.2 (20.8, 35.6)	<0.001†
BIO-failure	15/78 (19.2)	138/300 (46.0)	26.9 (16.7, 37.1)	<0.001†

Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; GUS, guselkumab; IV, intravenous.
Notes: Clinical remission at Week 12 defined as CDAI score < 150. * Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Panaccione et al, 2024, Afzali et al, 2025.(97, 98)

B.3.5.1.1.2 Endoscopic response at Week 12

A statistically significantly greater proportion of patients in the combined guselkumab group achieved endoscopic response at Week 12 compared with the placebo treatment group in the pooled GALAXI-2/-3 Primary Analysis Set (36.9% vs 12.2%) (Table 16).(97) Results were consistent within the BIO-failure population, with a statistically significantly greater proportion of patients achieving endoscopic response at Week 12 in the combined guselkumab group compared with the placebo treatment group in the pooled GALAXI-2/-3 BIO-failure subpopulation (29.0% vs 6.4%) (Table 16).(98)

Table 16: Endoscopic response at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference*, % (95% CI)	P-value
Primary Analysis Set	18/148 (12.2)	215/582 (36.9)	25.0 (18.5, 31.5)	< 0.001†
BIO-failure	5/78 (6.4)	87/300 (29.0)	22.6 (15.2, 30.1)	< 0.001†

Key: CI, confidence interval; GUS, guselkumab; IV, intravenous; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Notes: Endoscopic response at Week 12 defined as ≥ 50% improvement from baseline in SES-CD score or SES-CD Score ≤ 2. * Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Panaccione et al, 2024, Afzali et al, 2025.(97, 98)

B.3.5.1.2. Short-term efficacy comparisons versus placebo

B.3.5.1.2.1 PRO-2 remission at Week 12

A statistically significantly greater proportion of patients in the combined guselkumab group achieved PRO-2 remission at Week 12 compared with the placebo treatment group in the pooled GALAXI-2/-3 Primary Analysis Set ([redacted]) (Table 17).(99) Results were consistent within the BIO-failure population, with a statistically significantly greater proportion of patients achieving PRO-2 remission at Week 12 in the combined guselkumab group compared with the placebo treatment group in the pooled GALAXI-2/-3 BIO-failure subpopulation ([redacted]) (Table 17). (99)

Table 17: PRO-2 remission at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference*, % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Key: AP, abdominal pain; CI, confidence interval; GUS, guselkumab; IV, intravenous; PRO, patient-reported outcome; SF, stool frequency.
Notes: PRO-2 remission at Week 12 was defined as AP mean daily score ≤ 1 AND SF mean daily score ≤ 3, and no worsening of AP or SF from baseline. * Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Johnson & Johnson. Data on file (2025). (99)

B.3.5.1.2.2 Fatigue response at Week 12

A statistically significantly greater proportion of patients in the combined guselkumab group achieved fatigue response at Week 12 compared with the placebo treatment group in the pooled GALAXI-2/-3 Primary Analysis Set ([redacted]) (Table 18).(99) Results were consistent within the BIO-failure population, with a statistically significantly greater proportion of patients achieving fatigue response at Week 12 in the combined guselkumab group compared with the placebo treatment group in the pooled GALAXI-2/-3 BIO-failure subpopulation ([redacted]) (Table 18). (99)

Table 18: Fatigue response at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference*, % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; GUS, guselkumab; IV, intravenous; PROMIS-Fatigue SF, Patient-Reported Outcomes Measurement Information System-Fatigue Short Form.
Notes: Fatigue Response at Week 12 was defined as an improvement of ≥ 7 points in the PROMIS-Fatigue SF 7a. * Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Johnson & Johnson. Data on file (2025).(99)

B.3.5.1.2.3 Endoscopic remission at Week 12

A statistically significantly greater proportion of patients in the combined guselkumab group achieved endoscopic remission at Week 12 compared with the placebo treatment group in the pooled GALAXI-2/-3 Primary Analysis Set ([redacted]) (Table 19).(99) Results were consistent within the BIO-failure population, with a statistically significantly greater proportion of patients achieving endoscopic remission at Week 12 in the combined guselkumab group compared with the placebo treatment group in the pooled GALAXI-2/-3 BIO-failure subpopulation ([redacted]) (Table 19).(99)

Table 19: Endoscopic remission at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference, % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; GUS, guselkumab; IV, intravenous; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Notes: Endoscopic remission at Week 12 defined as SES-CD Score ≤ 2. * Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Johnson & Johnson. Data on file (2025).(99)

B.3.5.1.3. Long-term efficacy comparisons versus placebo

B.3.5.1.3.1 Corticosteroid-free clinical remission at Week 48

A statistically significantly greater proportion of patients in the 100 mg and 200 mg SC guselkumab groups achieved corticosteroid-free clinical remission at Week 48 compared with the placebo treatment group in the pooled GALAXI-2/-3 Primary Analysis Set [redacted] (Table 20).(99) Results were consistent within the BIO-failure population with a statistically significantly greater proportion of patients achieving corticosteroid-free clinical remission at Week 48 in the 100 mg and 200 mg SC guselkumab groups compared with placebo in the pooled GALAXI-2/-3 BIO-failure subpopulation ([redacted]) (Table 20). (99)

Table 20: Corticosteroid-free clinical remission at Week 48 in pooled GALAXI-2/-3

Population	Placebo	GUS 200 mg IV + 100 mg SC Q8W	GUS 200 mg IV + 200 mg SC Q4W
Primary Analysis Set			
Number of patients, n/N (%)	[redacted]	[redacted]	[redacted]
Adjusted treatment difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
BIO-failure			
Number of patients,	[redacted]	[redacted]	[redacted]

Population	Placebo	GUS 200 mg IV + 100 mg SC Q8W	GUS 200 mg IV + 200 mg SC Q4W
n/N			
Relative treatment difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value†	[redacted]	[redacted]	[redacted]

Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; GUS, guselkumab; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.
Notes: Corticosteroid-free clinical remission is defined as CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48. † Nominal p-value.
Source: Johnson & Johnson. Data on file (2025).(99)

B.3.5.1.3.2 Endoscopic response at Week 48

A statistically significantly greater proportion of patients in the 100 mg and 200 mg SC guselkumab groups achieved endoscopic response at Week 48 compared with the placebo treatment group in the pooled GALAXI-2/-3 Primary Analysis Set [redacted] (Table 21).(99) Results were consistent within the BIO-failure population with a statistically significantly greater proportion of patients achieving endoscopic response at Week 48 in the 100 mg and 200 mg SC guselkumab groups compared with placebo in the pooled GALAXI-2/-3 BIO-failure subpopulation ([redacted]) (Table 21).(99)

Table 21: Endoscopic response at Week 48 in pooled GALAXI-2/-3

Population	Placebo	GUS 200 mg IV + 100 mg SC Q8W	GUS 200 mg IV + 200 mg SC Q4W
Primary Analysis Set			
Number of patients, n/N (%)	[redacted]	[redacted]	[redacted]
Adjusted treatment difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
BIO-failure			
Number of patients, n/N (%)	[redacted]	[redacted]	[redacted]
Adjusted treatment difference, % (95% CI)	[redacted]	[redacted]	[redacted]
P-value†	[redacted]	[redacted]	[redacted]

Population	Placebo	GUS 200 mg IV + 100 mg SC Q8W	GUS 200 mg IV + 200 mg SC Q4W
Key: CI, confidence interval; GUS, guselkumab; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease. **Notes:** Endoscopic response is defined as ≥ 50% improvement from baseline in SES-CD score or SES-CD Score ≤ 2. † Nominal p-value. **Source:** Johnson & Johnson. Data on file (2025).(99)			

B.3.5.1.4. Additional outcomes

CD-related hospitalisations and/or surgeries are presented in Appendix I.

B.3.5.1.5. Health-related quality of life

HRQoL results from GALAXI-2/-3 are presented in Appendix I using the Inflammatory Bowel Disease Questionnaire (IBDQ) and EQ-5D™ questionnaire scales at Week 12. Patients treated with guselkumab showed a significant improvement in IBDQ score compared with patients treated with placebo. For the EQ-5D questionnaire, scores were variable by domain, but guselkumab generally showed a numerical improvement compared with placebo.(9, 10)

B.3.5.2. GRAVITI

In this section, we describe the results for the co-primary endpoints and the key secondary endpoints between guselkumab and placebo. Similar to the GALAXI trials, GRAVITI had two different guselkumab treatment arms with the same induction dose, and results for the Week 12 induction endpoints are presented as a combined guselkumab SC treatment group (400 mg SC induction dose).(8, 11) Week 24 efficacy comparisons are presented for the individual maintenance treatment arms (either 100 mg or 200 mg guselkumab treatment group) versus placebo.

For each endpoint, results are presented for the Full Analysis Set, as the trial was powered to detect differences between the treatment groups for this population. Results are also described for the pre-specified BIO-failure subgroup, as this is the population of interest relevant to the decision problem in this submission.

B.3.5.2.1. Co-primary endpoints

B.3.5.2.1.1 Clinical remission at Week 12

A greater proportion of patients in the guselkumab combined SC induction group achieved clinical remission at Week 12 compared with the placebo group (56.1% vs 21.4%) with statistically significant differences reported between treatment groups (Table 22).(11) Results were found to be consistent within the BIO-failure population, with greater proportions of patients achieving clinical remission at Week 12 in the combined guselkumab group compared with patients in the placebo group (60.2% vs 17.0%) and statistically significant differences between the treatment groups.(100)

Table 22: Clinical remission at Week 12 in GRAVITI

Number of patients, n/N (%)	Placebo	Combined GUS 400 mg SC	Difference*, (95% CI)	P-value
Full Analysis Set	25/117 (21.4)	129/230 (56.1)	34.9 (25.1, 44.6)	< 0.001
BIO-failure	9/53 (17.0)	65/108 (60.2)	43.4 (30.1, 56.6)	< 0.001†

Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CSR, clinical study report; GUS, guselkumab; SC, subcutaneous.
Notes: Clinical remission at Week 12 was defined as a CDAI score < 150. * Full Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Hart et al, 2025. (100)

B.3.5.2.1.2 Endoscopic response at Week 12

A greater proportion of patients in the guselkumab combined SC induction group achieved an endoscopic response at Week 12 compared with the placebo group (41.3% vs 21.4%) with statistically significant differences reported between treatment groups (Table 23).(11) Results were found to be consistent within the BIO-failure population, with greater proportions of patients achieving clinical remission at Week 12 in the combined guselkumab group compared with patients in the placebo group (33.3% vs 17.0%) and statistically significant differences between the treatment groups. (100)

Table 23: Endoscopic response at Week 12 in GRAVITI

Number of patients, n/N (%)	Placebo	Combined GUS 400 mg SC	Difference, (95% CI)	P-value
Full Analysis Set	25/117 (21.4)	95/230 (41.3%)	19.9 (10.2, 29.6)	< 0.001
BIO-failure	9/53 (17.0)	36/108 (33.3%)	16.7 (3.2, 30.2)	< 0.001†

Key: CI, confidence interval; CSR, clinical study report; GUS, guselkumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Notes: Endoscopic response at Week 12 was defined as ≥ 50% improvement from baseline in the SES-CD score. * Full Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Hart et al, 2025. (100)

B.3.5.2.2. Key secondary efficacy endpoints

B.3.5.2.2.1 Clinical response at Week 12

A greater proportion of patients in the guselkumab combined SC induction group achieved a clinical response at Week 12 compared with the placebo group (73.5% vs 33.3%) with statistically significant differences reported between treatment groups (Table 24).(11) Results were found to be consistent within the BIO-failure population, with greater proportions of patients achieving clinical response at Week 12 in the combined guselkumab group compared with patients in the placebo group (77.8% vs 28.3%) and statistically significant differences between the treatment groups. (100)

Table 24: Clinical response at Week 12 in GRAVITI

Number of patients, n/N (%)	Placebo	Combined GUS 400 mg SC	Difference*, (95% CI)	P-value
Full Analysis Set	39/117 (33.3)	169/230 (73.5)	40.3 (29.9, 50.7)	< 0.001
BIO-failure	15/53 (28.3)	84/108 (77.8)	49.7 (35.1, 64.3)	< 0.001†

Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CSR, clinical study report; GUS, guselkumab; SC, subcutaneous.
Notes: Clinical response at Week 12 was defined as ≥ 100-point reduction from baseline in CDAI or a CDAI score < 150. * Full Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Hart et al, 2025. (100)

B.3.5.2.2.2 PRO-2 remission at Week 12

A greater proportion of patients in the guselkumab combined SC induction group achieved a PRO-2 remission at Week 12 compared with the placebo group (49.1% vs 17.1%) with statistically significant differences reported between treatment groups

(Table 25).(11) Results were found to be consistent within the BIO-failure population, with greater proportions of patients achieving PRO-2 remission at Week 12 in the combined guselkumab group compared with patients in the placebo group (51.9% vs 17.0%) and statistically significant differences between the treatment groups. (100)

Table 25: PRO-2 remission at Week 12 in GRAVITI

Population, n/N (%)	Placebo	Combined GUS 400 mg SC	Difference, (95% CI)	P value
Full Analysis Set	20/117 (17.1)	113/230 (49.1)	32.1 (22.9, 41.2)	< 0.001
BIO-failure	9/53 (17.0)	56/108 (51.9)	35.0 (21.8, 48.2)	< 0.001†

Key: AP, abdominal pain; CI, confidence interval; CSR, clinical study report; GUS, guselkumab; PRO, patient-reported outcome; SC, subcutaneous; SF, stool frequency.
Notes: PRO-2 remission at Week 12 was defined as AP mean daily score ≤1 AND SF mean daily score ≤ 3, and no worsening of AP or SF from baseline. * Full Analysis Set is adjusted treatment difference and BIO-failure is relative difference. † Nominal p-value.
Source: Hart et al, 2025. (100)

B.3.5.2.2.3 Clinical remission at Week 24

A greater proportion of patients in the guselkumab 100 mg SC Q8W maintenance group and the 200 mg SC Q4W maintenance group achieved clinical remission at Week 24 compared with the placebo group (100 mg 60.9%; 200 mg 58.3% vs 21.4%) with statistically significant differences reported between treatment groups (Table 26).(11) Results were found to be consistent within the BIO-failure population, with greater proportions of patients achieving clinical remission at Week 24 in the guselkumab 100 mg SC Q8W maintenance group and the 200 mg SC Q4W maintenance group compared with patients in the placebo group (100 mg 63.6%; 200 mg 52.8% vs 18.9%) and statistically significant differences between the treatment groups. (100)

Table 26: Clinical remission at Week 24 in GRAVITI

	Placebo	GUS 100 mg SC maintenance Q8W	GUS 200 mg SC maintenance Q4W
Full Analysis Set			
Number of patients, n/N (%)	25/117 (21.4)	70/115 (60.9)	67/115 (58.3)
Adjusted treatment difference, (95% CI)	-	39.3 (28.0, 50.7)	37.0 (25.6, 48.4)
P-value	-	< 0.001	< 0.001

	Placebo	GUS 100 mg SC maintenance Q8W	GUS 200 mg SC maintenance Q4W
BIO-failure			
Number of patients, n/N (%)	10/53 (18.9)	35/55 (63.6)	28/53 (52.8)
Relative treatment difference, (95% CI)	-	44.8 (29.2, 60.5)	34.0 (17.4, 50.6)
P-value†	-	< 0.001	<0.001

Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CSR, clinical study report; GUS, guselkumab; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.
Notes: Clinical remission is defined as CDAI score < 150. † Nominal p-value.
Source: Hart et al, 2025. (100)

B.3.5.3. Comparability of outcomes between GALAXI-2/-3 and GRAVITI

In the overall analyses of results from GALAXI-2/-3, and GRAVITI, similar trends were observed over time across multiple endpoints. For all the co-primary and secondary endpoints of GRAVITI, there were similar absolute rates of the guselkumab SC and IV induction doses and treatment effect of guselkumab compared with placebo, in the overall population and across subpopulations based on biologic failure status. The early onset of clinical response/remission and improvement of inflammatory burden was also similar, with efficacy observed as early as Week 4 (the first visit post-induction for assessments) for both SC and IV induction. The results for induction, as well as the clinical response/remission curves into maintenance dosing up to Week 24, had similar outcomes following both the SC and IV dose regimens.

B.3.6. Subgroup analysis

The pre-specified subgroup analyses relevant to the decision problem (i.e. BIO-failure subgroup) are presented in Section B.3.5. In line with the NICE final scope, 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 risankizumab and

vedolizumab was explored by indirect treatment comparisons, which is presented in Section B.3.8.

B.3.8. Indirect and mixed treatment comparisons

To date, guselkumab has not been directly compared with the other comparators relevant to this submission (risankizumab and vedolizumab). In the absence of such comparisons, an NMA was performed to determine the relative treatment effect among patients with moderately to severely active CD.

Indirect treatment comparisons were performed in the induction and maintenance treatment phases separately for the population of interest (bio-failure). The outcomes of the efficacy NMAs are presented in B.3.8.4 and are considered further in the economic analysis discussed in B.4..Identification and selection of relevant studies

Evidence for the efficacy of guselkumab, risankizumab and vedolizumab were identified as part of a broader SLR conducted in July 2023, details of which are described in Appendix D. Overall, eight trials identified by the global SLR included the selected comparators relevant to the decision problem addressed in this submission, with efficacy data available to inform the NMA (Table 27). 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 the NICE decision problem are presented in Appendix D.

Table 27: Summary of trials included in the NMA

Trial name	Relevant active treatment	Treat-through or re-randomised	Time points for assessments from first treatment, weeks	
			Induction	Maintenance
GALAXI-1	Guselkumab	Treat-through	4, 8, 12	48
GALAXI-2	Guselkumab	Treat-through	4, 12	48
GALAXI-3	Guselkumab	Treat-through	4, 12	48
ADVANCE	Risankizumab	Re-randomised	4, 8, 12	Not applicable
MOTIVATE	Risankizumab	Re-randomised	4, 8, 12	Not applicable
FORTIFY	Risankizumab	Re-randomised	Not applicable	20, 28, 36, 44, 52, 60, 64
GEMINI-2	Vedolizumab	Re-randomised	6	14, 22, 30, 38, 46, 52
GEMINI-3	Vedolizumab	Not applicable	6, 10	Not applicable

B.3.8.1. Feasibility assessment

A feasibility assessment was performed comparing the trial design of GALAXI-2/-3 to the comparator trials used in the NMA.(94) The assessment of NMA feasibility also aimed to ensure the underlying assumptions of the analysis were systematically explored, and that the risks and benefits of indirectly comparing treatment effects were clear and transparent. Trial design characteristics, patient eligibility criteria, baseline patient characteristics, outcome characteristics (i.e. definitions and methods of reporting outcomes), and placebo response were all sources of clinical heterogeneity explored in the feasibility assessment. Summaries of each analysis are presented below, with further details provided in Appendix D.

B.3.8.1.1. Population

The patient population eligibility criteria for the SLR stated that patients must have moderately to severely active CD. The inclusion criteria relevant to the decision problem of this submission was further refined to the BIO-failure subpopulation. Overall, there was little heterogeneity in baseline characteristics across included trials.(94)

B.3.8.1.2. Study design

All included studies were conducted in multicentre settings and were double-blind, comparative, randomised trials. (94) With respect to inclusion criteria, disease duration, disease location and baseline CDAI were relatively similar across trials in comparison to GALAXI-3. With respect to exclusion criteria, the GALAXI trials, ADVANCE, MOTIVATE and FORTIFY all excluded patients with any previous use of p19 and/or p40 inhibitors. Other trials had more specific criteria for previous all-time medication use.

B.3.8.1.3. Approved doses and regimens for treatments and comparators

All MHRA- and EMA-approved doses and regimens of targeted therapies for the treatment of moderately to severely active CD were included in the NMA. Different dosing arms of the same drug were treated as individual comparators within the NMA.

Table 27 shows the timepoints of analysis for outcomes of the induction and maintenance regimens of the trials featured in the NMA. Induction outcomes were measured at up to Week 12 in all trials apart from GEMINI-2 and GEMINI-3, where induction outcomes were measured at up to Week 6 and Week 10, respectively. (94) For maintenance, all trials measured outcomes up to Week 48, apart from FORTIFY and GEMINI-2, which measured at up Week 64 and Week 52, respectively. Differences in the timepoints may present limitations for ITC analyses.

B.3.8.1.4. Outcomes of interest

The feasibility assessment focussed on comparisons of clinical response, clinical remission and endoscopic response at both induction and maintenance. These endpoints are consistent with those presented in previous appraisals. The feasibility assessment used the clinical response definition from GALAXI-3 that was commonly used amongst comparator trials (i.e. the CDAI score). (94) The scoring criteria for clinical response were similar across the majority of comparator trials. All trials required an absolute CDAI score of < 150 to determine clinical remission.

GALAXI-1, ADVANCE, MOTIVATE and FORTIFY had a similar endoscopic response criteria as GALAXI-3. (94) Endoscopic response criteria required a ≥ 50% improvement from baseline in SES-CD score or SES-CD score ≤ 2. The GEMINI trials did not include endoscopic response.

B.3.8.1.5. Feasibility assessment conclusions

Based on the initial assessment of trial characteristics, eligibility criteria, and baseline characteristics, an NMA was deemed feasible. (94) NMAs were recommended for clinical response, clinical remission and endoscopic response.

B.3.8.2. NMA methodology

Bayesian NMAs were conducted using JAGS (Just another Gibbs sampler).(94) All NMA models were based on code outlined in NICE Technical Support Document (TSD) 2 or modifications thereof.(101) 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 a separately

estimated baseline model including reference-treatment-controlled studies to provide summaries on the relative risk scale. 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 models assume a shared estimate of the between-trial heterogeneity.(94) Informative prior distributions were assigned according to Turner et al. in all analyses for both unadjusted and meta-regression risk-adjusted models unless there was sufficient evidence for vague priors to converge to a reasonable posterior.(102) Fixed-effect NMAs were also conducted for comparison, but random-effects models were preferred a priori given differences in trial designs.(94)

For the induction phase of treatment, all analyses were conducted without any adjustments, as well as with adjustment for baseline risk in order to account for cross-trial heterogeneity in observed and unobserved effect modifiers.(94) In general, NMA results were described in comparison with guselkumab in both dosages. For all statistically significant differences, the results were described as “significantly more (or less) efficacious”, while non-significant differences were described as “numerically more (or less) efficacious”.(94) Sensitivity analyses applying imputation methods that do not account for delayed responders were conducted for maintenance outcomes.(94)

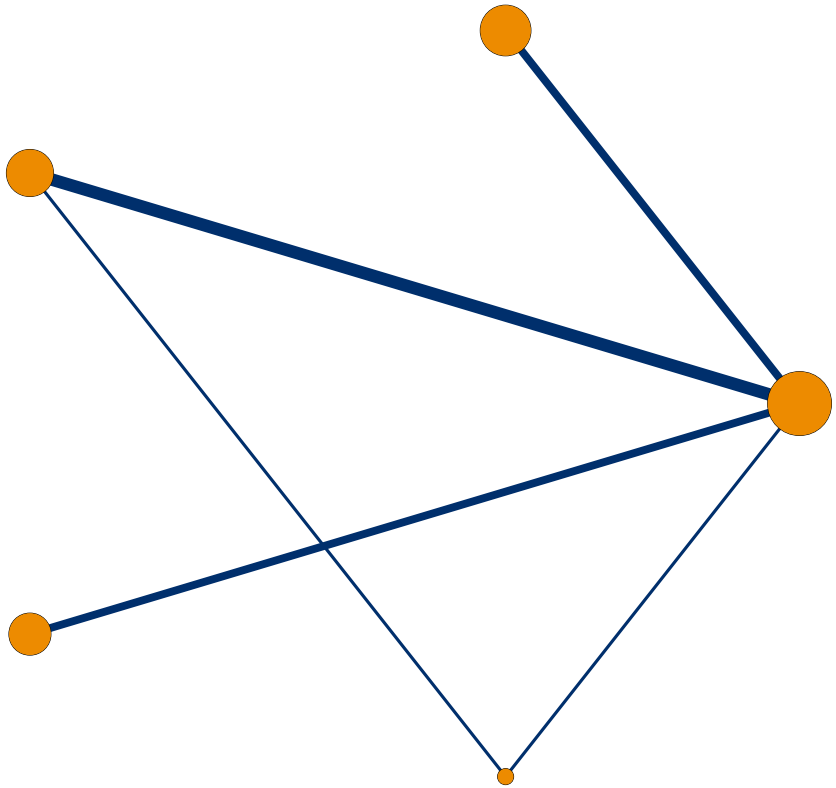
B.3.8.3. NMA networks

B.3.8.3.1. Induction

A network diagram for studies reporting clinical response and clinical remission, during the induction phase, in the BIO-failure population, is presented in Figure 7.(94) The network consisted of five treatment nodes (guselkumab 200 mg IV induction, guselkumab 600 mg IV induction, vedolizumab 300 mg IV induction and risankizumab 600 mg IV induction) informed by seven RCTs, all of which were placebo controlled.

A separate network diagram for studies reporting endoscopic response during the induction phase, in the BIO-failure population, is presented in Figure 8.(94) The network consisted of four treatment nodes (guselkumab 200 mg IV induction, guselkumab 600 mg IV induction and risankizumab 600 mg IV induction) informed by six RCTs, all of which were placebo controlled. Guselkumab 600 mg IV induction dosing was included in the NMA as it was an arm in GALAXI-1.

Figure 7: NMA network for clinical remission and response endpoints at induction



Key: GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RIS, risankizumab; VEDO, vedolizumab.
Notes: All doses are IV induction.
Source: Johnson & Johnson (Data on file, 2025) (94)

Figure 8: NMA network for endoscopic response at induction

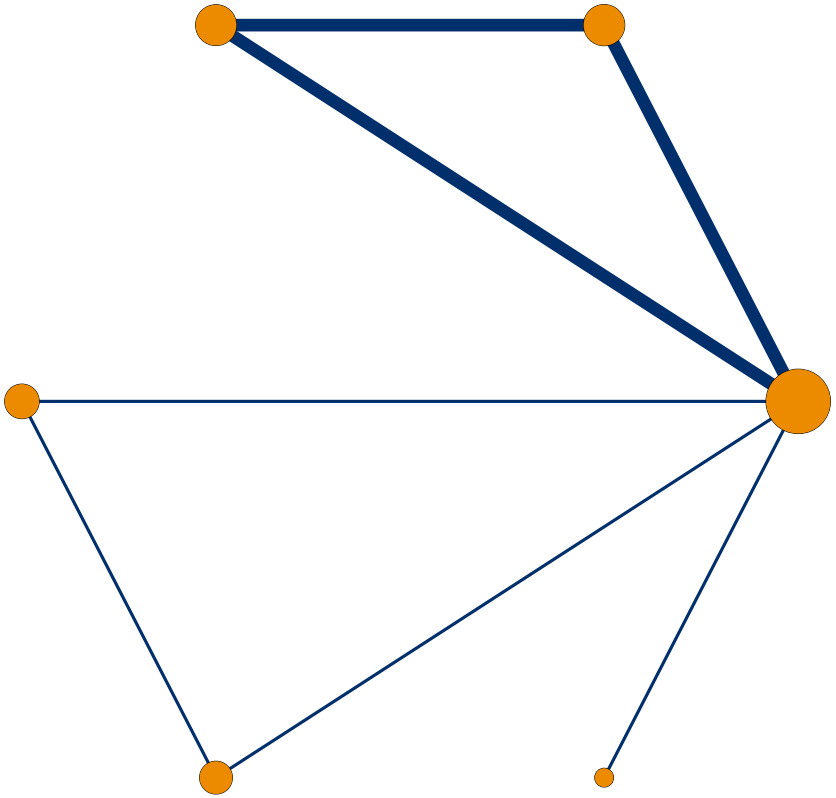
Key: GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RIS, risankizumab.
Notes: All doses are IV induction.
Source: Johnson & Johnson (Data on file, 2025) (94)

B.3.8.3.2. Maintenance

A network diagram for studies reporting clinical response and clinical remission, during the maintenance phase with delayed responders, in the BIO-failure population, is presented in Figure 9. (94) The network consisted of six treatment nodes (guselkumab 200 mg Q4W SC maintenance, guselkumab 100 mg Q8W SC maintenance, vedolizumab 300 mg Q8W IV maintenance, risankizumab 180 mg Q8W SC maintenance and risankizumab 360 mg Q8W SC maintenance) informed by five RCTs, all of which were placebo-controlled. Three out of seven connections were informed by multiple trials, all of which utilized the GALAXI trials.

A network diagram for studies reporting endoscopic response during the maintenance phase with delayed responders, in the BIO-failure population, is presented in Figure 10. (94) The network consisted of five treatment nodes informed by four RCTs, all of which were placebo-controlled. Three out of six connections were informed by multiple trials, all of which involved the GALAXI trials

Figure 9: NMA network for clinical remission and response endpoints at maintenance



Key: GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QNW, every N weeks; RIS, risankizumab; VEDO, vedolizumab.
Notes: All doses SC maintenance except VEDO 300 mg IV maintenance.
Source: Johnson & Johnson (Data on file, 2025) (94)

Figure 10: NMA network for endoscopic response at maintenance

Key: GUS, guselkumab; NMA, network meta-analysis; PBO, placebo; QNW, every N weeks; RIS, risankizumab; SC, subcutaneous.
Notes: All doses are SC maintenance.
Source: Johnson & Johnson (Data on file, 2025) (94)

B.3.8.4. Results

Unadjusted random-effects NMA results are presented below for the BIO-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 GALAXI-2/-3 and GRAVITI trials (Sections B.3.5.1 and B.3.5.2). Pairwise comparisons are provided in Appendix J.

B.3.8.4.1. Induction: Clinical response

The induction NMA results for clinical response are presented in Figure 11. Compared with vedolizumab 300 mg IV induction and risankizumab 600 mg IV induction, guselkumab 200 mg IV induction was significantly more effective (CrIs > 1) than vedolizumab 300 mg IV induction and placebo in the BIO-failure population. (94) Guselkumab 200 mg IV induction was not significantly more or less effective (CrIs include 1) compared with guselkumab 600 mg IV induction or risankizumab 600 mg IV induction.

Figure 11: Forest plot for random-effects NMA of clinical response in the induction phase, BIO-failure population

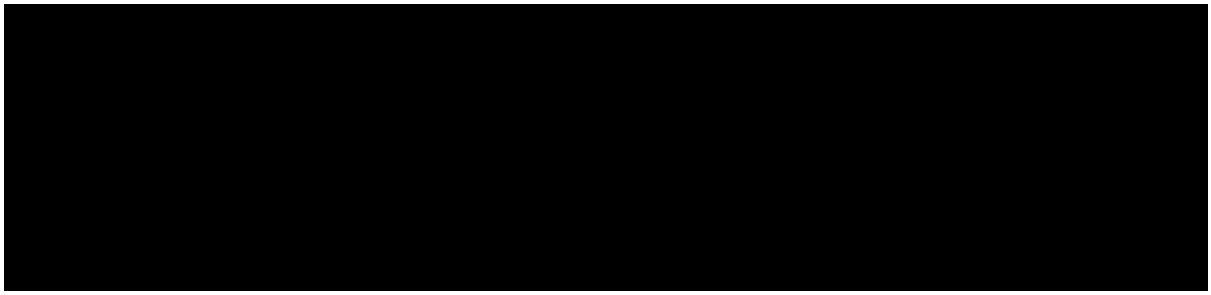
Key: CrI, credible interval; GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RIS, risankizumab; VEDO, vedolizumab.
Notes: All doses are IV induction.
Source: Johnson & Johnson (Data on File, 2025). (94)

B.3.8.4.2. Induction: Clinical remission

The induction NMA results for clinical remission in the BIO-failure population are presented in Figure 12. Compared with vedolizumab 300 mg IV induction and risankizumab 600 mg IV induction, guselkumab 200 mg IV induction was significantly more effective than vedolizumab 300 mg IV induction and placebo in the BIO-failure

population. (94) Guselkumab 200 mg IV induction was not significantly more or less effective compared with guselkumab 600 mg IV induction or risankizumab 600 mg IV induction.

Figure 12: Forest plot for random-effects NMA of clinical remission in the induction phase, BIO-failure population



Key: CrI, credible interval; GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RIS, risankizumab; VEDO, vedolizumab.
Notes: All doses are IV induction.
Source: Johnson & Johnson (Data on File, 2025). (94)

B.3.8.4.3. Induction: Endoscopic response

The induction NMA results for endoscopic response in the BIO-failure population are presented in Figure 13. Compared with risankizumab 600 mg IV induction, guselkumab 200 mg IV induction was significantly more effective than the placebo in the BIO-failure population.(94) Guselkumab 200 mg IV induction was not significantly more or less effective compared with guselkumab 600 mg IV induction or risankizumab 600 mg IV induction. No comparison was feasible versus vedolizumab within the bio-failure population.

Figure 13: Forest plot for random-effects NMA of endoscopic response in the induction phase, BIO-failure population

Key: CrI, credible interval; GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; RIS, risankizumab.
Notes: All doses are IV induction.
Source: Johnson & Johnson Medicine (Data on File, 2025). (94)

B.3.8.4.4. Maintenance: Clinical response with delayed responders

The maintenance NMA results for clinical response in the BIO-failure population, with delayed responders are presented in Figure 14. Data for the corresponding analyses without delayed responders are presented in Appendix J. Both maintenance doses of guselkumab (100 mg Q8W SC and 200 mg Q4W SC) were significantly more effective than vedolizumab 300 mg IV maintenance and placebo in the BIO-failure population. (94) Guselkumab 100 mg Q8W SC and 200 mg Q4W SC maintenance were not significantly more or less effective compared with the licensed maintenance dose of risankizumab (360 mg Q8W SC). There was also no significant difference in efficacy between the two maintenance doses for guselkumab. (94)

Figure 14: Forest plots for random-effects NMA of clinical response in the maintenance phase for guselkumab 100 mg and 200 mg, BIO-failure population

Key: CrI, credible interval; GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; RIS, risankizumab; SC, subcutaneous; VDZ, vedolizumab.
Notes: All doses are SC maintenance but VDZ 300 mg Q8W IV maintenance.
Source: Johnson & Johnson (Data on File, 2025). (94)

B.3.8.4.5. Maintenance: Clinical remission with delayed responders

The maintenance NMA results for clinical remission in the BIO-failure population, with delayed responders are presented in Figure 15. Data for the corresponding analyses without delayed responders are presented in Appendix J. Both maintenance doses of guselkumab (100 mg Q8W SC and 200 mg Q4W SC) were significantly more effective than vedolizumab 300 mg Q8W IV maintenance and placebo in the BIO-failure population. (94) Guselkumab 100 mg Q8W and 200 mg Q4W SC maintenance were not significantly more or less effective compared with the licensed maintenance dose of risankizumab (360 mg Q8W SC). There was also no significant difference in efficacy between the two maintenance doses of guselkumab. (94)

Figure 15: Forest plots for random-effects NMA of clinical remission in the maintenance phase for guselkumab 100 mg and 200 mg, BIO-failure population

Key: CrI, credible interval; GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; RIS, risankizumab; SC, subcutaneous; VDZ, vedolizumab.
Notes: All doses are SC maintenance but VDZ 300 mg Q8W IV maintenance.
Source: Johnson & Johnson (Data on File, 2025). (94)

B.3.8.4.6. Maintenance: Endoscopic response with delayed responders

The maintenance NMA results for endoscopic response in the BIO-failure population, with delayed responders are presented in Figure 16. Data for the corresponding analyses without delayed responders are presented in Appendix J Both maintenance doses of guselkumab (100 mg Q8W SC and 200 mg Q4W SC) were significantly more effective than placebo in the BIO-failure population. (94) Guselkumab 100 mg Q8W and 200 mg Q4W SC maintenance were not significantly more or less effective compared with the licensed maintenance dose of risankizumab (360 mg Q8W SC). There was also no significant difference in efficacy between the two doses of guselkumab SC maintenance. (94) No comparison was feasible versus vedolizumab within the bio-failure population.

Figure 16: Forest plots for random-effects NMA of endoscopic response in the maintenance phase for guselkumab 100 mg and 200 mg, BIO-failure population

Key: CrI, credible interval; GUS, guselkumab; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; RIS, risankizumab; SC, subcutaneous.
Notes: All doses SC maintenance.
Source: Johnson & Johnson (Data on File, 2025). (94)

B.3.8.5. Uncertainties in the indirect and mixed treatment comparisons

NMA is a well-established, valuable tool for health technology assessment (HTA) that allows for the estimation of indirect comparisons of multiple interventions, especially when there is no direct evidence from head-to-head trials. Although multiple therapies for CD are available, there have been few head-to-head RCTs of comparator therapies. In order to simultaneously compare guselkumab with risankizumab and vedolizumab, an SLR was conducted to identify relevant RCTs, and NMAs were performed for clinical response, clinical remission, and endoscopic response outcomes, which are identified as primary outcomes of interest from the UK HTA perspective, focused on both the induction phase and up to one year of treatment. Notably, comparative efficacy of vedolizumab versus guselkumab could not be assessed based on endoscopic response due to lack of data.

A major strength of the literature review is that it adheres to best practices for the conduct and reporting of systematic reviews, including detailed assessments of study quality, as per Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.(103) Similarly, NMA analyses were performed according to best practices for conducting and reporting NMAs, as described by NICE.(104) Most importantly, our analyses are strengthened by the implementation of imputation methods, which allowed for delayed responders to be accounted for where re-randomised studies were included.

Considering a previously published NMA of maintenance CD treatment by Varu et al., there is little overlap with our analyses in regards to the included comparators, due to differences in inclusion criteria for trials informing the analyses.(105) This difference precluded an evaluation of alignment. A much more recent report by Schreiber et al. included similar comparators (except guselkumab); however, it did not report detailed effect estimates for comparison.(106)

Across all of the conducted NMAs, a key limitation is that several connections within every evidence network were informed by single studies (although the inclusion of multiple GALAXI studies reduced this issue). Most trials were also placebo-controlled, rather than head-to-head, which further simplified network structures. These network characteristics increase the potential for biased treatment effect estimates, which limits the robustness of analyses. In addition, residual heterogeneity between studies may have reduced validity of one or more analyses, despite our best efforts to minimise bias by excluding insufficiently similar trials and/or trial data.

Considering NMAs of the induction phase, some specific limitations should be noted. Heterogeneity was identified in regard to induction timelines across the included trials; furthermore, direct results of head-to-head evidence have demonstrated that treatment differences may not manifest during the induction phase. (107) As such, the overall relevance of these analyses may be limited. It should be considered that most trials were open labelled during the induction phase, introducing additional risk of bias.

One limitation specific to treat-through trials should also be noted. Treat-through trials had variable drop-out rates, which may impact results. However, since drop-out rates and response rates were largely similar across these trials and all trials used non-responder imputation, the impact was judged to be minimal. Furthermore, the normalisation procedure could not perfectly replicate a true treat-through for all trials, since TYPE 2 treatment trials (which condition on response by strict timepoint) and TYPE 4 re-randomised trials with delayed response do not capture patients who had a response beyond this delay. 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, in particular placebo. This assumption is unlikely to be exactly true, since variations in placebo response across trials would be expected to induce differences in populations of patients evaluated for subsequent response, but replication of results from included treat-through studies suggests that residual bias is minimal.

B.3.8.6. Conclusions from the indirect and mixed treatment comparisons

The current analysis represents a robust systematic review and NMA focused on particular treatments in CD that are relevant from the UK perspective. The results of NMAs suggest that guselkumab has comparable efficacy to risankizumab and may have greater efficacy than vedolizumab for CD treatment based on outcomes examined, in patients who previously failed a biologic therapy. These analyses were made additionally robust due to the normalisation of trial designs, which reduced heterogeneity and allowed for the incorporation of delayed responders. Overall, guselkumab offers comparable outcomes for patients with CD in the UK treatment landscape and demonstrates how guselkumab is suitable for a cost-comparison appraisal.

B.3.9. Adverse reactions

Safety data in this section are presented for treated participants with SES-CD ≥ 6 (or ≥ 4 for participants with isolated ileal disease) during the placebo-controlled induction period (Weeks 0–12) for the GALAXI and GRAVITI studies and through the reporting period (Weeks 0–48 for GALAXI and Weeks 0–24 for GRAVITI).

B.3.9.1. Exposure in CD programme (GALAXI and GRAVITI)

The Phase II/III GALAXI and GRAVITI trials assess the safety of guselkumab in 1,054 patients with moderately to severely active CD at the doses described in Sections B.3.3.1.1 and B.3.3.2.1. Across all studies, 661 patients were exposed for 1 year or more. Across the Safety Analysis Sets of GALAXI and GRAVITI, 1,009 patients were exposed to either 200 mg IV (n = 649) or 400 mg SC (n = 230) guselkumab induction from Weeks 0 to 12.

B.3.9.2. Overall safety of guselkumab in CD and across diseases

Both IV and SC administration of guselkumab had safety results consistent with the well-characterised safety profile of guselkumab.(108) During the induction period of GALAXI and GRAVITI, guselkumab IV and SC induction had a similar safety profile to the placebo (Table 28). The favourable safety profile was maintained into the maintenance phase. Guselkumab SC maintenance had a similar safety profile and events per 100 patient-years for treatment-emergent AEs, serious AEs, AEs leading to discontinuations, infections, and serious infections up to Week 48 following IV induction in GALAXI or up to Week 24 following SC induction in GRAVITI regardless of dose (Table 29). (108) Further information on the pooled safety by outcome is provided in Appendix I.

Table 28: Overall summary of treatment-emergent AEs to Week 12 from GALAXI and GRAVITI

	GALAXI-1/-2/-3		**GRAVITI**	
	Placebo	**Guselkumab 200 mg IV Q4W**	**Placebo**	**Guselkumab 400 mg SC Q4W**
Safety Analysis Set, n	211	649	117	230
Average duration of follow-up, weeks	[redacted]	[redacted]	[redacted]	[redacted]
Average exposure, n of administrations	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n (%)	0	0	0	1 (0.4)
Patients with one or more, n (%)				
AEs	109 (51.7)	304 (46.8)	58 (49.6)	107 (46.5)
AEs by maximum intensity*				
Mild	[redacted]	[redacted]	[redacted]	[redacted]

	GALAXI-1/-2/-3		GRAVITI	
	Placebo	Guselkumab 200 mg IV Q4W	Placebo	Guselkumab 400 mg SC Q4W
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	13 (6.2)	19 (2.9)	9 (7.7)	5 (2.2)
AEs leading to discontinuation	9 (4.3)	11 (1.7)	3 (2.6)	1 (0.4)
Infections^	[redacted]	[redacted]	[redacted]	[redacted]
Serious infections^	0	1 (0.2)	0	1 (0.4)

Key: AE, adverse event; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; SAE, serious adverse event; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Notes *The maximum severity event experienced by the patient is used. ^Infections were defined as any adverse events which were coded to the MedDRA system organ class 'Infections and infestations'. Includes only patients with a screening SES-CD score ≥ 6 (or ≥ 4 for patients with isolated ileal disease).
Source: Danese S et al, 2025, Johnson & Johnson. Summary of Clinical Safety (Data on file2024).(108, 109)

Table 29: Overall summary of treatment-emergent AEs through to Week 48 in GALAXI and Week 24 GRAVITI

	GALAXI-1/-2/-3 to Week 48			GRAVITI to Week 24		
	Placebo	Guselkumab 200 mg IV Q4W →		Placebo	Guselkumab 400 mg SC Q4W →	
		100 mg SC Q8W	200 mg SC Q4W		100 mg SC Q8W	200 mg SC Q4W
Safety Analysis Set, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average duration of follow-up, weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average exposure, n of administrations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patient-years of follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events per 100 patient-years [number of events] (95% CI)						
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	GALAXI-1/-2/-3 to Week 48			GRAVITI to Week 24		
	Placebo	Guselkumab 200 mg IV Q4W →		Placebo	Guselkumab 400 mg SC Q4W →	
		100 mg SC Q8W	200 mg SC Q4W		100 mg SC Q8W	200 mg SC Q4W
SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections^	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious infections^	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease.
Notes *The maximum severity event experienced by the patient is used. ^Infections were defined as any adverse events which were coded to the MedDRA system organ class 'Infections and infestations'. Includes only patients with a screening SES-CD score ≥ 6 (or ≥ 4 for patients with isolated ileal disease).
Source: Johnson & Johnson, Summary of Clinical Safety (Data on file, 2024).(109)

B.3.9.2.1. Safety findings across diseases

The guselkumab 200 mg IV and 400 mg SC induction dose followed by guselkumab SC maintenance doses of 200 mg Q4W or 100 mg Q8W had safety results consistent with the well-characterised safety profile of guselkumab in its approved indications of plaque psoriasis and psoriatic arthritis.(109)

An analysis of AEs during the placebo-controlled induction period of the CD and UC studies supports a consistent safety profile between the two populations representing moderately to severely active IBD.(109) Pooled analyses of Phase II and III studies in CD, UC and psoriatic disease support a consistent safety profile for

guselkumab across disease indications. For treatment-emergent AEs, serious AEs, AEs leading to discontinuations of study intervention, severe AEs, infections, and serious infections, the number of participants with events per 100 patient-years was generally similar or not higher in the guselkumab-treated participants, compared with the placebo-treated participants across studies in CD, UC and psoriatic disease.(109) Additional details on the safety profile of guselkumab from the GALAXI and GRAVITI trials can be found in Appendix E.

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 CD who have had an inadequate response, lost response or were intolerant to a biological treatment. In this population, many treatment options have a lengthy hospital-administered induction phase that has considerable patient, carer and healthcare provider burden. In comparison, guselkumab has the option for at-home SC induction or hospital-administered IV induction to address an unmet need by reducing patient, carer and healthcare provider burden and NHS waiting lists for outpatient treatment. Furthermore, guselkumab offers two maintenance doses (100 mg and 200 mg), which provides flexibility for patients with inadequate response to guselkumab after completion of induction dosing. A greater range of dosing options ensures patients receive the dose they need, prevents wastage and reduces the risk of over-treatment.

GALAXI-2 and -3 are identical confirmatory Phase III randomised, double-blind, placebo- and active-controlled, parallel-group, multicentre trials designed to evaluate the efficacy and safety of IV induction followed by 100 mg or 200 mg SC maintenance with guselkumab compared to placebo (or ustekinumab) in adult patients with moderately to severely active CD.(9, 10) The trials were carried out in up to 39 countries globally, including the UK, and median age was 34 years in GALAXI-2 and -3, which is reflective of the UK population. Key inclusion criteria and previous treatments were reflective of NICE guidelines and therefore of the UK population. (9, 10) In a clinical advisory board consisting of UK clinicians (n = 10), participants agreed that the design of GALAXI-2/-3 reflected real-world clinical

practice and patient populations, improving on the designs of past trials to better reflect patients and practice. (9, 10)

GRAVITI is an ongoing Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre trial designed to evaluate the efficacy and safety of 400 mg SC induction followed by 100 mg or 200 mg SC maintenance with guselkumab compared with placebo dosing in adult patients with moderately to severely active CD.(11) The median age was 36 years, which is reflective of the UK population. Key inclusion criteria and previous treatments were reflective of NICE guidelines and, therefore, the UK population. (11)

Guselkumab has been shown to have comparable efficacy whether given as either an IV or SC induction followed by either 100 mg or 200 mg SC maintenance periods up to 48 weeks, based on the findings of both the GALAXI-2/-3 trials and the GRAVITI trial.(9-11) Compared with placebo, guselkumab showed significant improvement in the Primary Analysis Set and BIO-failure populations for all key primary and secondary endpoints, apart from endoscopic remission at Week 12 in the Primary Analysis Set of GALAXI-3 and fatigue response at Week 12 in the BIO-failure population of GALAXI-3. (9, 10) In both GALAXI-2 and -3, HRQoL was significantly improved in the guselkumab groups compared with placebo, and the numbers of hospitalisations and surgeries were low. The safety data for the guselkumab 200 mg IV induction dose and for both guselkumab SC long-term dosing regimens through Week 48 in participants with moderately to severely active CD were consistent with the well-characterised safety profile of guselkumab in its approved indications. In GRAVITI, guselkumab also showed significant improvements in efficacy compared with placebo in primary and secondary outcomes in the Full Analysis Set and BIO-failure populations. (11) Safety findings in GRAVITI show new AEs, matching the well-characterised safety profile of guselkumab. The findings of both GALAXI-2/-3 and GRAVITI show the comparable efficacy benefits of guselkumab given as IV or SC maintenance, and as either a 100 mg Q8W or 200 mg Q4W SC maintenance dose. These findings support the use of guselkumab in a wide variety of patients with CD with different induction needs and throughout the maintenance phase.

An NMA was performed to compare guselkumab's efficacy in the BIO-failure population relative to comparators where head-to-head trials were not available. (94) To compare guselkumab with the comparators risankizumab and vedolizumab, eight RCTs were compared, with a feasibility assessment confirming the comparisons made were suitable. Guselkumab 200 mg had comparable efficacy versus risankizumab and vedolizumab as well as placebo – in clinical remission, clinical response and endoscopic response, at induction and at both 100 mg Q8W and 200 mg Q4W doses at maintenance. (94)

Evidence from GALAXI-2/-3 and GRAVITI show that guselkumab provides a consistent clinical benefit to patients with CD whether administered by IV or SC methods, with a manageable and tolerable safety profile. (9-11) The clinical findings are supported by a robust NMA of eight clinical trials into key comparators. (94) Overall, guselkumab offers comparable outcomes for patients with CD in relation to comparator treatments.

B.3.11. Ongoing studies

Long-term extension studies of GALAXI-2/-3 are ongoing. Database locks are planned at Weeks 96, 144 and 192, and when the final participant has completed the final efficacy and safety visit in the long-term extension (to provide longer-term safety and efficacy data). Additional database locks may be added if necessary and will be specified in the Phase III statistical analysis plan.

GRAVITI is ongoing, and additional analyses will be performed at applicable timepoints through Week 48 and Week 96 at the corresponding database locks.

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.3.8) provides evidence of comparable efficacy in terms of clinical response, clinical remission and endoscopic response between guselkumab and the comparators vedolizumab and risankizumab. 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 risankizumab.
- Over the 10-year time horizon, the results show that guselkumab is cost saving versus vedolizumab and risankizumab, 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 risankizumab, 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 CD who have had an inadequate response, lost response or were intolerant to a biologic therapy

B.4.1. Changes in service provision and management

Nearly all injectable treatments currently available for previously treated CD in the NHS are approved as induction therapy via IV administration. The only biologic currently approved as an SC induction regimen is adalimumab, which is likely to be used earlier in the treatment pathway and therefore less likely to be offered to the BIO-failure population 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 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 use may 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 risankizumab 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 patients in the BIO-failure population from the GALAXI-2/-3 and GRAVITI trials (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 (B.3.3). To simplify the model, regardless of whether IV or SC induction is selected, baseline characteristics of the BIO-failure population from GALAXI-3 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 the GALAXI-2/-3 and GRAVITI trials. 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 risankizumab 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.(17) The model structure is aligned to the cost-comparison model accompanying a parallel submission for guselkumab for previously treated ulcerative colitis (ID6237), and informed by previous cost-effectiveness and cost-comparison analyses in IBD as identified by the economic SLR – further details are presented in Appendix F.(13) 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, 5) 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.(17)

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

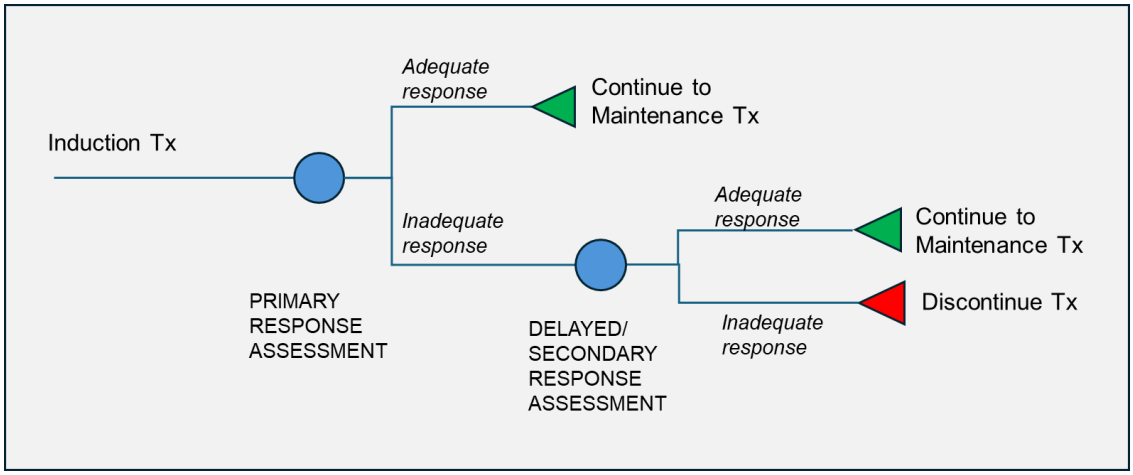
be equal across all treatments. Therefore, these costs are not considered in the model and associated analyses. This is consistent with risankizumab in TA888 and upadacitinib in TA9058 via cost-comparison approach submitted to NICE.(4, 12)

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, 110, 111) A schematic overview of the induction phase is given in Figure 17

Figure 17: 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, 110, 111) This timepoint varies depending on the treatment (Week 8 for patients receiving vedolizumab and Week 12 for those receiving guselkumab or risankizumab). 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, 110, 111)

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, 110, 111) 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 30 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 TA888 and adheres to the assumption of equivalence

Table 30: 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
Risankizumab	600 mg IV	0, 4, 8	12	360 mg SC	12, 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.(112)

Clinical response in the model was defined as a reduction in the CDAI by ≥ 100 points or achievement of a CDAI score of < 150, indicating decreased disease activity (as per the GALAXI-2/-3 and GRAVITI trials). (9-11) This definition was consistent with the NMA performed (Section B.3.8) 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 B.3.8.3.1.

The probability of response after extended induction was assumed to be 41.45% and was informed by overall response data from ustekinumab NICE appraisal (TA456).(6) 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 a recent appraisal in IBD.(13)

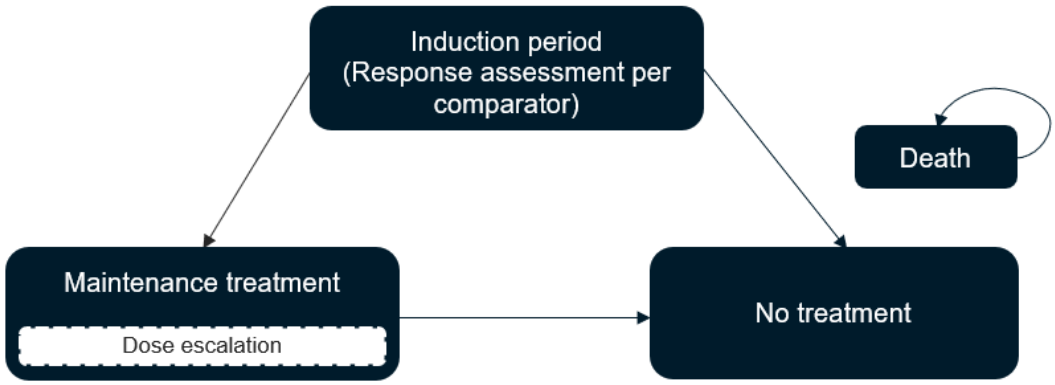
Table 31: Clinical response at the end of induction phase

Treatment	Response (including remission)	
	OR (95% CI) relative to placebo	**Absolute probability**
Guselkumab		
Biologic 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 18: Markov model structure



Maintenance treatment

The maintenance phase of the model consists of three states: maintenance treatment, no treatment, and death (Figure 18). 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 GALAXI-3 trial (Table 32). Given that the NMA presented in Section B.3.8 demonstrated equivalent efficacy between treatments, the same discontinuation rate was applied to all treatments.

Table 32: Combined probability of discontinuation before completing maintenance dosing (W48)

Treatment	Probability of all-cause discontinuation	
	OR (95% CI) relative	Absolute probability
Guselkumab		
Biologic failure		[redacted]

Key: CD, Crohn's disease; CI, confidence interval; OR, odds ratio.
Note: As per GALAXI protocol, all-cause discontinuation is defined as discontinuation of study intervention due to lack of efficacy, or an adverse event of worsening of CD, or Week 20/24 non-responder as specified at treatment discontinuation.

The observed probability of discontinuation at Week 48 is converted to a 2-weekly probability via geometric conversion through the steps below:

$$\gamma = -\ln(1 - P_{48\ weeks})$$

$$P_{2\ weeks} = 1 - e^{-\gamma/24}$$

$$48\ weeks\ probability = P_{48\ weeks}$$

$$Instantaneous\ rate = \gamma$$

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

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

Dose escalation

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. Therefore, dose escalation for vedolizumab is included in the model to reflect UK clinical practice. 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.

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 TA888 and a recent appraisal in IBD.(4, 13, 113) Dose adjustments required by dose escalation are outlined in Section B.4.2.2.

Patients are assumed to receive the escalated dosing schedule 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 TA888 and previous appraisals in IBD.(4, 13, 15)

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 the recent NICE TAs in IBD, CD is not associated with an increase in mortality.(12, 13, 114, 115) 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.(116)

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 33. Drug dosing schedules were derived from the SmPCs for each product, with drug acquisition costs sourced from MIMS.(1, 91, 110, 111). Details of intervention and comparator costs per formulation used in the model can be found in Appendix H.

Table 33: Acquisition costs of the intervention and comparator technologies

	Guselkumab	Risankizumab(110)	Vedolizumab(111)
Pharmaceutical formulation	200 mg solution for injection in pre-filled syringe (2 mL) 200 mg concentrate for solution for infusion vial (20 mL) 100 mg solution for injection in pre-filled pen (1 mL) 200 mg PushPen solution for injection in pre-filled pen (2 mL)	600 mg concentrate for solution for infusion vial (10 mL) 360 mg solution for injection in cartridge (2.4 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 price: £[redacted] per 100 mg 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 per 200 mg IV dose	List price: £3.326.09 per 600 mg injection List price £3.326.09 per 360 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**: 400 mg SC or 200 mg IV per administration • **Maintenance**: 100 mg SC per administration or 200 mg SC per administration	• **Induction**: 600 mg IV per administration • **Maintenance**: 360 mg SC per administration	• **Induction**: 300 mg IV per administration • **Maintenance**: 300 mg IV or 108 mg SC
Dosing frequency	**Induction**: Weeks 0, 4, 8	• **Induction**: Weeks 0, 4 and 8	• **Induction**: Weeks 0, 2, and 6

	Guselkumab	Risankizumab(110)	Vedolizumab(111)
	• **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.	• **Maintenance**: Week 12 and then every 4 weeks	• **Maintenance**: Week 10 and then every 8 weeks (IV) or every 2 weeks (SC)
Dose adjustments(extended induction, dose escalation)	None	• Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by Week 24	**Induction:** • Patients with Crohn's disease, who have not shown a response may benefit from a dose of IV 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 • 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			

	Guselkumab	Risankizumab(110)	Vedolizumab(111)
(Anticipated) number of repeat courses of treatment			
Key: IV, intravenous; PAS, patient access scheme; SC, subcutaneous.			

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 is being 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 posology described in the SmPC (Appendix C), and feedback from UK experts.(112)

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 33). The proportion of patients assumed to have escalated dosing for vedolizumab is 30%, Two administration forms are available for vedolizumab in the maintenance phase (SC and IV), as detailed in Table 33.

Table 34: Drug acquisition costs for the induction phase

Treatment	No. of doses used during induction	Package size	Package price	Total induction costs
Guselkumab	3	IV 200mg	[redacted]	[redacted]
	6	SC 200 mg	[redacted]	[redacted]
Vedolizumab	3	IV 300 mg	£2,050.00	£6,889.27
Risankizumab	3	IV 600 mg	£3,326.09	£9,977.51
Key: IV, intravenous; SC, subcutaneous.				

Table 35: Drug acquisition costs for the maintenance phase

Treatment	Maintenance phase dosage	Package size	Package price	Year 1 maintenance cost	Year 2+ maintenance 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	£8,538.79	£45,543.07
	108 mg Q2W	SC 108 mg	£512.50		
Risankizumab	360 mg Q8W	SC 360 mg	£3,326.09	£13,763.46	£64,624.26
Key: IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; 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 0, administration for guselkumab in the induction phase is flexible where patients can receive either IV infusion or SC injection. As presented in Table 33, administration for the comparators in the induction phase is by IV infusion only. In the maintenance phase, treatments aside from vedolizumab are administered via SC injection only, while patients receiving vedolizumab can have treatment administered as SC injection or IV infusion; 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. (117, 118)

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. For vedolizumab a 50%/50% assumption was validated from the expert feedback and is in line with the approach taken in TA888.(4, 112)

Table 36 outlines the proportion of patients receiving SC or IV formulations for guselkumab in the induction phase and vedolizumab in the maintenance phase.

Table 36: Proportion of patients on IV and SC in the cost-comparison model

Intervention	Proportion IV	Proportion SC	Source
Guselkumab induction (IV/SC split)	20%	80%	Assumption validated with expert feedback(112)
Vedolizumab maintenance (IV/SC split)	50%	50%	Assumption validated with expert feedback and TA888(4, 112)
Key: IV, intravenous; SC, subcutaneous.			

In accordance with previous appraisals in IBD, including TA888, 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). (119) Consistent with recent appraisals, it was assumed that SC injections have an initial cost attached, which 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.(120) As patients self-inject subsequent doses, no additional costs were assigned in the model. Table 37 shows the administration costs for IV and SC therapies included in the cost-comparison model.

Table 37: 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)
SC (first dose)	£42.00	PSSRU 2023 - Cost per working hour of band 5 hospital-based nurse (120)
SC (subsequent doses)	£0.00	Assumption (patients self-administer after 1st dose, in line with TA888 and TA925)(4, 13)
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 equivalent between guselkumab and its comparators by the NMA results presented in Section B.3.8, 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 comparison appraisals in IBD, including TA888. (4, 13)

B.4.2.4. Adverse reaction unit costs and resource use

The GALAXI trials had safety results consistent with the well-characterised safety profile of guselkumab in its approved indications of plaque psoriasis and psoriatic arthritis.(1, 121, 122) No new safety concerns for guselkumab were identified in GALAXI-2 and GALAXI-3.(121, 122) 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 identified comparators.(1, 110, 111)

In line with previous cost-comparison appraisals in IBD, including TA888, TA905 and TA925 AEs were not included in the model analysis.(4, 12, 13) In TA925 (mirikizumab in UC), it was discussed, 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. (13) Therefore, to maintain consistency across the different appraisals, and to simplify the cost-comparison model, 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

Four UK clinicians were consulted individually to validate posology and health economic assumptions described in the dossier.(112)

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 that 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. In addition, one-way

sensitivity analysis (OWSA) and scenario analyses were reviewed. The model underwent technical and stress tests to ensure it was accurate with the outputs considering the input data, and that the model was stable to uncertainty.(123)

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 38 and the key assumptions are presented in Table 39.

Table 38: 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	No	Section B.4.2.1.2
Model dose escalation	Yes	Section B.4.2.1.3
Patient characteristics		
Age in years, mean (SD)	37.0 (13.72)	Appendix I
Proportion male, mean	56.0	Appendix I
Efficacy inputs		
Efficacy (%) response after induction period	[redacted]	Section B.3.8
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
VDZ SC/IV maintenance (%)	50% / 50%	Section B.4.2.3.1
VDZ dose escalation	30%	Section B.4.2.1.3
Key: GUS, guselkumab; IV, intravenous; NHS, National Health Service; SC; subcutaneous; SD, standard deviation; VDZ, vedolizumab		

Table 39: Key assumptions of the cost-comparison analysis

Assumption	Rationale for assumption
Non-responders discontinue	As described in the relevant SmPCs and consistent with

Assumption	Rationale for assumption
treatment after the secondary response assessment	previous appraisals.
Non-responding patients at the end of induction phase or 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 the same across all treatments, as 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 B.3.8), guselkumab is similar in efficacy to vedolizumab and risankizumab.
The different formulations of guselkumab have similar efficacy	As shown by the trial results (Section B.3.5), 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 SectionB.4.2.1.2, guselkumab 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.
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 CD TAs..(4, 12)
No costs for disease management, AEs, monitoring, or concomitant medication are included	No new safety concerns for guselkumab were identified in GALAXI-2/-3 and GRAVITI. Additionally, the safety of guselkumab appears to be broadly similar to the identified 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 CD is a debilitating disease, it is not known to impact patient survival, in line with the pooled GALAXI and GRAVITI trials. Survival is therefore modelled using UK general population mortality, consistent with past appraisals in IBD.

B.4.3. Base case results

The results presented in Table 40 are inclusive of the existing PAS discount for guselkumab. As the 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 risankizumab, resulting in an average cost saving of [redacted] and [redacted] per patient, respectively over a 10-year time horizon. The majority of this cost saving was achieved in the maintenance phase, where guselkumab saved [redacted] and [redacted] compared with vedolizumab and risankizumab, respectively.

Table 40: 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]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
Key: PAS, patient access scheme.				

B.4.4. Sensitivity and scenario analyses

B.4.4.1. One-way sensitivity analysis

An 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 (SE), if available, or an assumed SE of 20%.

The top 10 most impactful parameters during the OWSA are shown per comparator in

Table 41 and Table 42, with the respective tornado plots in Figure 19 and Figure 20. In all analyses, the most impactful parameter was the discontinuation during maintenance. This is expected, as the lower the discontinuation rate, the higher the incremental costs between guselkumab and its comparators. Similarly, the guselkumab odds ratio of response after induction and placebo probability of response 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 41: Results of one-way sensitivity analyses versus vedolizumab

Top 10 most influential variables		Incremental costs	
Rank	**Name**	**Lower**	**Upper**
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

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

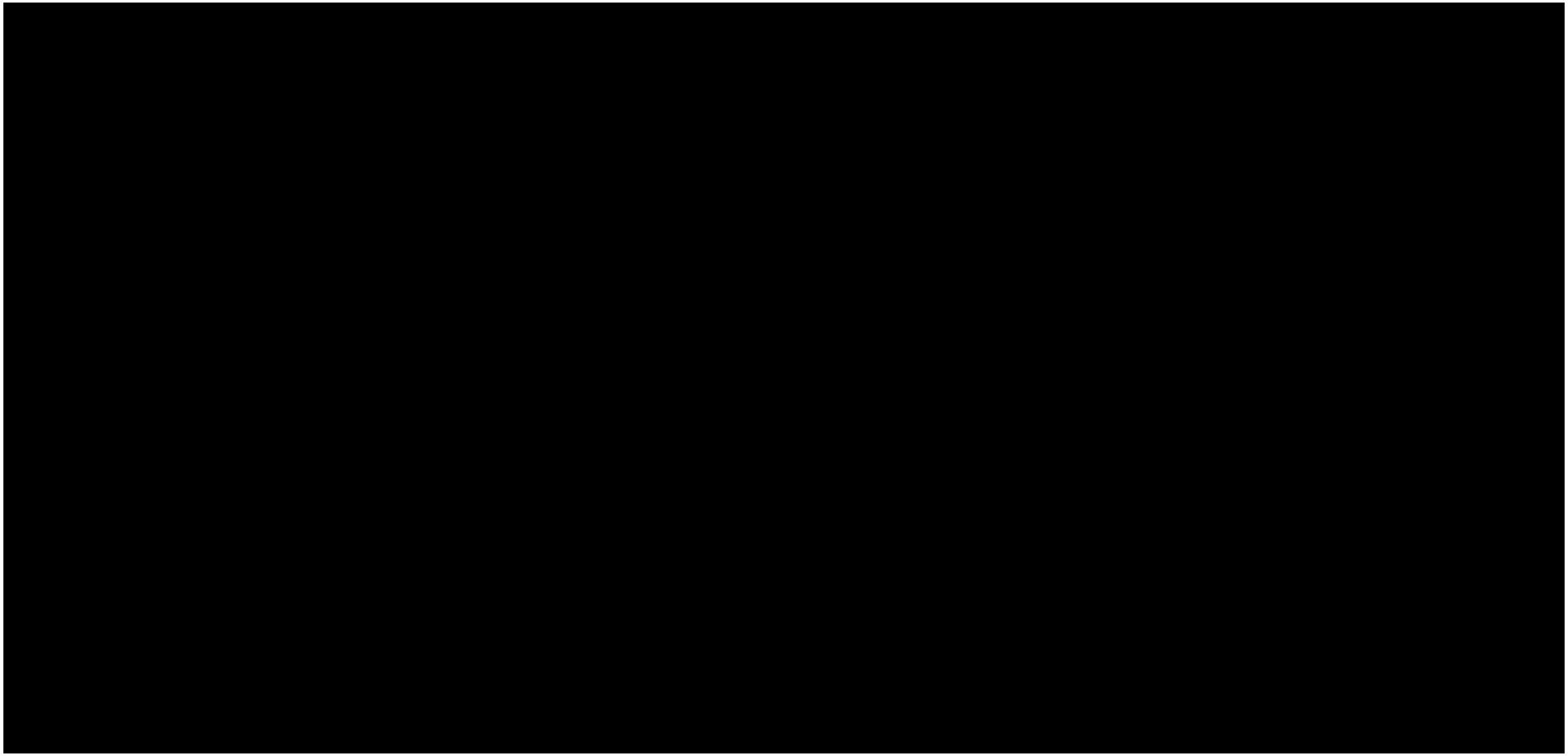
Table 42: Results of one-way sensitivity analyses versus risankizumab

Top 10 most influential variables		Incremental costs	
Rank	**Name**	**Lower**	**Upper**
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]

5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]

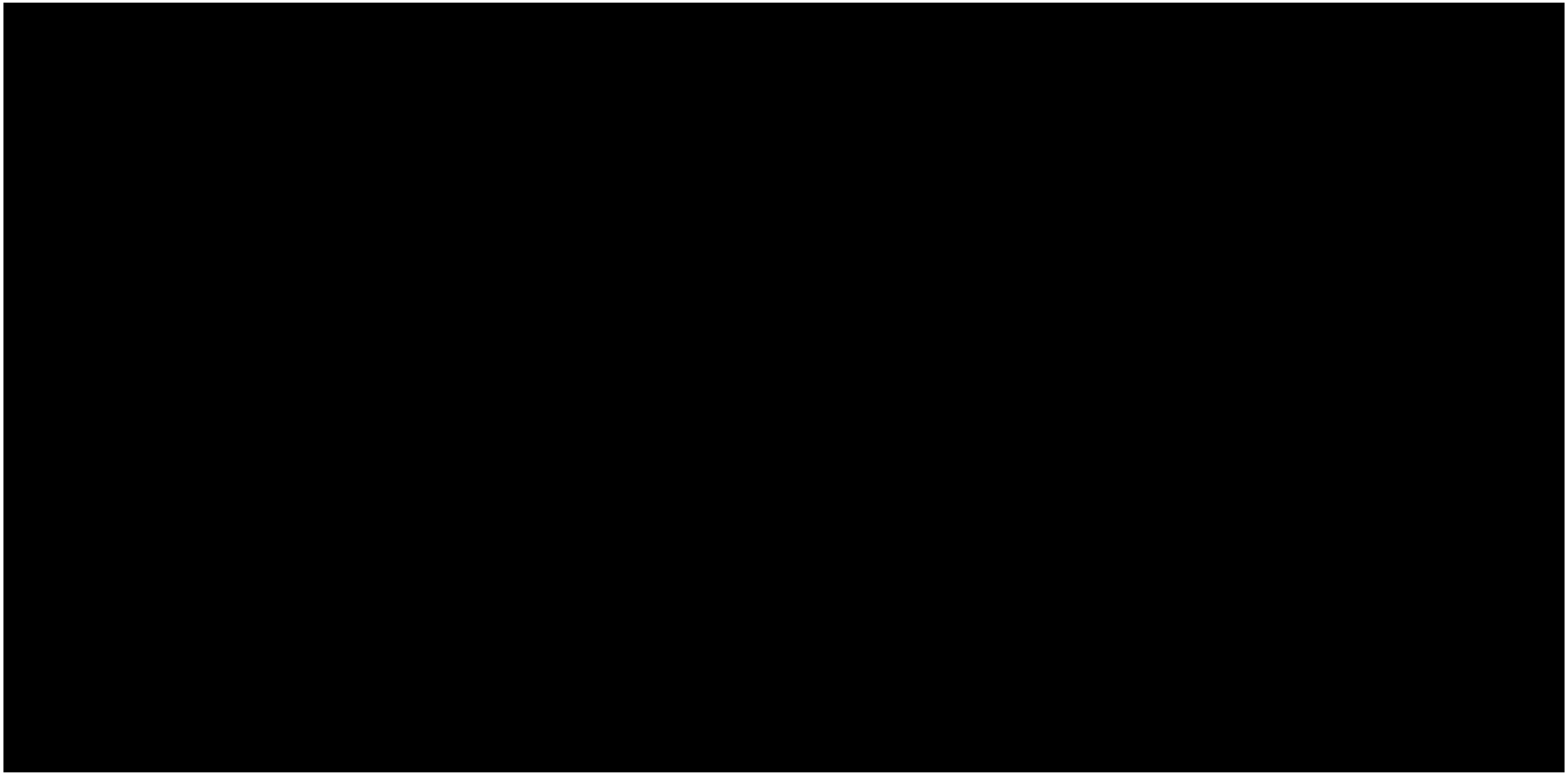
Key: GUS, guselkumab; IV, intravenous; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; SC, subcutaneous.

Figure 19: Tornado diagram of most influential parameters 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 20: Tornado diagram of most influential parameters versus risankizumab



Key: GUS, guselkumab; IV, intravenous; 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 43.

Table 43: 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

Exploratory scenario results are shown per comparator in Table 44 and Table 45. 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. Overall, guselkumab remains cost saving compared to vedolizumab and risankizumab.

Table 44: 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]
Key: GUS, guselkumab; SC, subcutaneous; IV, intravenous.		

Table 45: Results of scenario analyses versus risankizumab

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]
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 risankizumab in the treatment of adult patients with moderately to severely active CD who have had an inadequate response, lost response, or were intolerant to a biologic treatment under the assumption of equivalent efficacy. The analysis showed that guselkumab was cost saving versus vedolizumab and risankizumab, 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 risankizumab.

Overall, these results show that the implementation of guselkumab in the NHS would offer patients a valuable new treatment option with a 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.

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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 full patient population in which the medicine is expected to be licensed to treat (marketing authorisation). The patient population includes adults with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to a biologic treatment (henceforth, referred to as the "Bio-failure" population). Biologic therapies are usually antibodies or proteins that are taken as an injection or an infusion, e.g. a tumour necrosis factor (TNF)-inhibitor. This 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 Crohn's disease and is expected to be approved for use in Great Britain in 2025.

Guselkumab will be available for use as induction therapy either as an intravenous infusion in a hospital setting under medical supervision, or as an injection that can be taken at home/self-administered. In all people with Crohn's disease, long-term maintenance therapy will be approved as an injection that can be taken at home/self-administered.

Details of the proposed approval 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 patient groups 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)	£5000, 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	£4600 (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 Crohn's disease and what are the symptoms?

Crohn's disease is a chronic inflammatory bowel disease (IBD) where the immune system does not work properly and attacks the body, causing inflammation in the gut (also referred to as gastrointestinal [GI] tract), from mouth to anus.(1) This inflammation can affect different areas of the GI tract, with some parts being swollen, irritated and ulcerated, while others remain healthy and undamaged.(2-5) More severe forms of disease can lead to narrowing of part of the GI tract and ulcers that penetrate deeper into the GI wall, causing further damage and complications.(6) The most commonly affected areas are the small intestine and the large intestine (colon).(7, 8)

Crohn's disease is unpredictable; people commonly experience periods of active disease or flare-ups known as relapses, followed by short periods when the disease is inactive and the person is in good health known as remission.(9) During an active period, common symptoms are diarrhoea, abdominal pain, blood in stools (rectal bleeding) and extreme tiredness (fatigue).(10)

Crohn's disease is an incurable lifelong condition; without proper management it can cause long-term damage to the GI tract and issues in other parts of the body such as joint pain and the development of kidney/gall stones.(8, 9, 11) The goal of treatment is to reduce inflammation and control the symptoms of Crohn's disease.

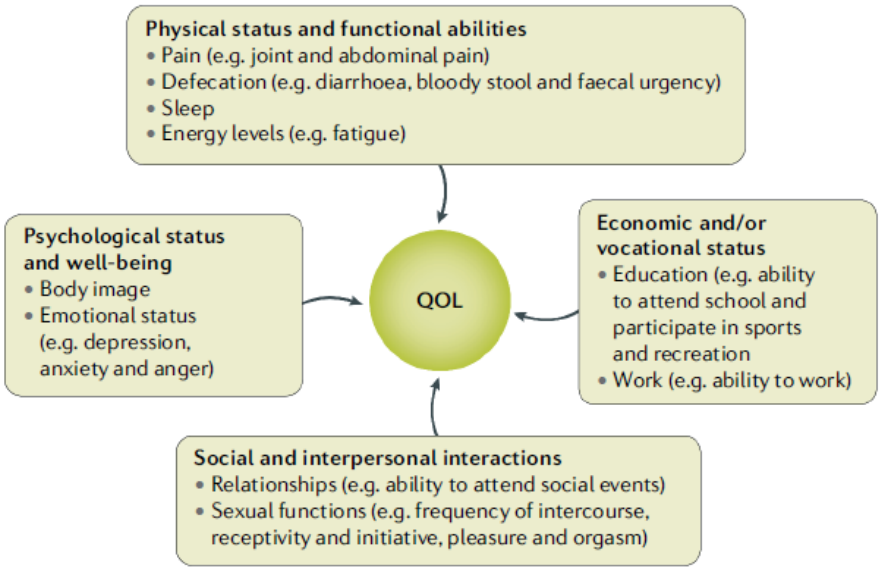
How many people in England are estimated to be living with Crohn's disease?

At least one in every 323 people in the UK are living with Crohn's disease.(12) Further research suggests that 40% of people have moderately to severely active Crohn's disease, and that up to 66% of people receiving biological therapy lose response to these treatments i.e. fail treatment with a biological therapy.(13, 14) Therefore, using Office for National Statistics population estimates for England and Wales, it is estimated that 49,000 people have moderately to severely active Crohn's disease and failed at least one biological therapy.(15) People typically start to show symptoms of Crohn's disease in early adulthood, most commonly between the ages of 20–29 years.

What is it like to live with Crohn's disease?

Crohn's disease has a significant impact on a person's well-being and overall health, described as health-related quality of life (HRQoL).(16) Most notably, the chronic and unpredictable symptom flare-ups that often begin in early adulthood impact people living with Crohn's disease. Symptoms can impact physical health and mental health, activities of daily living, work productivity and social relationships, as summarised in Figure 1.(17)

Figure 1: Factors that affect quality of life domains in Crohn's disease



Key: CD, Crohn's disease; QoL, quality of life.
Source: Roda et al. (2020).(17)

The quality of life of people with Crohn's disease is driven by the variable cycle of remission and active disease, but it is particularly affected during a period of active disease, which is made worse with more relapses per year.(16-21) People with moderately to severely active Crohn's disease have substantially lower HRQoL compared with people with mild symptoms.(18)

Symptoms are a major driver of poor HRQoL. People with Crohn's disease in multiple studies report that the most common and bothersome symptoms are abdominal pain, loose or liquid bowel movements, high frequency of bowel movements and fatigue/tiredness. Of these symptoms, abdominal pain and bowel movement urgency cause the most distress.(10, 22-24) These symptoms affect multiple elements of daily life as shown by interviews with people with Crohn's disease where participants reported effects to: activities of daily living (100% of people surveyed), work/school (92%), and emotional (94%), social (89%), and physical (78%) functioning with fatigue compounding these issues.(10, 25) Anxiety and depression are also drivers of poor HRQoL due to the

psychological impacts of the disease and symptoms.(26) People with Crohn's disease can feel anxiety, frustration, fear and anger, particularly due to the unpredictable onset of relapses.(12)

In addition to the symptom burden, treatment itself can drive poor HRQoL.(17) People treated with medication to suppress the immune system to reduce or prevent inflammation (flare-up), such as systemic steroids or azathioprine, as well as those who need surgery, often experience a decreased quality of life, This decline can be due to the side effects of the medication such as weight gain and problems sleeping, and adapting to life after surgery.(20, 27)

What is the impact on the family and carers of people with Crohn's disease?

Carers and family members also experience reduced quality of life due to caring for a person with Crohn's disease. Family carers report significantly worse mental health and depression and anxiety relative to healthy people.(26, 28) Research shows that family members see declines in emotional well-being, relationship with the patient, social life, work and finances, and leisure time; and partners experience strain due to a reduction in sexual functioning and romantic activities.(29) In a survey of patients and carers across 12 European countries, 32% required informal care during remission, and 48.6% required care during active disease. On average, family members and friends spend approximately 5.1 hours each week helping patients, which includes approximately 1.7 hours taken away from their jobs to provide support.(30)

What is the economic burden of Crohn's disease?

People with moderately to severely active Crohn's disease face higher costs compared with people with mild symptoms or those in remission.(18) These costs arise due to hospital stays, surgery and severity of symptoms.(31-36) Since Crohn's disease often affects people of working age, there are significant indirect costs due to missed work, lower productivity, unemployment, and caregiving responsibilities.(37)

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 Crohn's disease diagnosed?

Diagnosing Crohn's disease typically begins in primary care with a general practitioner (GP) who will assess their condition and may conduct some initial tests. If the GP suspects Crohn's disease, they will refer the person to a specialist, usually a gastroenterologist, for more detailed evaluation of their symptoms and treatment. This is part of secondary care, where advanced tests such as an endoscopy (flexible tube with a camera to look at the inside of the gut), a biopsy (removing a tiny piece of the bowel to check for signs of Crohn's disease), and scans or imaging are performed to examine the gut and confirm the diagnosis.(38) It is important for the person with Crohn's disease to understand that the journey to a diagnosis can sometimes be lengthy, and that they may face long waiting times for appointments and tests, which can be frustrating and stressful.

Commonly used measures for determining disease activity include the Crohn's Disease Activity Index (CDAI), the Harvey Bradshaw Index (HBI), Simple Endoscopic Score – Crohn's Disease (SES-CD) and other patient-reported outcome tools. CDAI values greater than 150 indicate active disease; values between 220-450 indicate moderately to severely active disease, and values greater than 450 indicate the most severe forms of disease

.(39) For HBI, a score of 0–4 indicates remission, 5–7 indicates mild disease and ≥ 8 indicates moderately to severely active disease.(40, 41) SES-CD grades ulcer size, ulcerated surface, affected surface and presence of narrowing/strictures in the bowel from an endoscopy, scores of 7–15 indicate moderate Crohn's disease and scores > 15 indicate severe disease.(42) Should guselkumab be approved for the treatment of people with moderately to severely active Crohn's disease, no additional diagnostic tests should be required if the consultant deems the patient to be eligible for this therapy.

Diagnosis and NHS waitlists:

Waiting lists for gastroenterology appointments in England are increasing and have nearly doubled over the past 5 years.(43) Waiting times directly impact the time taken 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 that may be required for many treatment options for moderately to severely active Crohn's disease, which results in significant burden for patients, caregivers and healthcare providers.

As detailed in the following sections, introducing treatments that can be self-administered at home from the start may provide an opportunity to reduce outpatient visits and hospitalisations, thereby alleviating the burden on patients and the healthcare system for the effective treatment of moderately to severely active Crohn's disease. 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 people with Crohn's disease?

Crohn's disease is an incurable, life-long condition.(8, 9, 11) The goal of treatment is to manage symptoms of the disease and keep them under control – i.e. to reduce inflammation, control symptoms during flare-ups, and induce and maintain remission.

The current treatment pathway for Crohn's disease includes conventional (i.e. steroids and some oral therapies or enemas) and advanced therapies (i.e. biologic therapies given by injection or infusion and oral therapies).

Conventional therapies(44):

Conventional therapies are typically offered to induce remission in people with Crohn's disease when they initially present or have one flare-up in a year. Initial conventional therapy includes glucocorticosteroids such as prednisolone, methylprednisolone or intravenous injections of (injection into the veins) hydrocortisone. An alternative steroid,

such as budesonide, can be given. However, this is not suitable for people with severely active Crohn's disease

If someone experiences two or more flare-ups in a year, add-on treatment with immunosuppressants may be recommended to induce remission – drugs specifically designed to suppress the activity of the immune system such as azathioprine or mercaptopurine

Advanced therapies

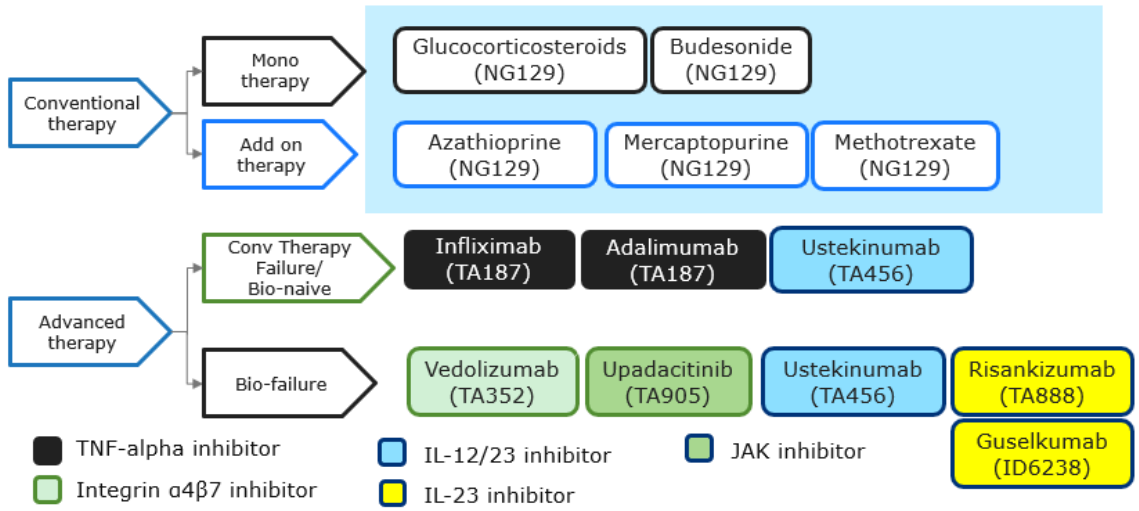
For some people, conventional therapies fail to control Crohn's disease flare-ups, or they are not tolerated (experience difficult or uncomfortable side effects or reactions) or contraindicated (should not be used because they could be harmful or unsafe). These people can be given advanced therapies, which target specific pathways in the immune system that cause flare-ups in Crohn's disease. These treatments include TNF-inhibitors (i.e. infliximab or adalimumab), anti-integrin antibodies (i.e. vedolizumab), JAK inhibitors (i.e. upadacitinib), IL-12/23 inhiitors (i.e. ustekinumab) or IL-23 inhibitors (i.e. risankizumab) (13, 45-48)

Figure 2 shows the uses of conventional therapy and advanced therapies in moderately to severely active Crohn's disease as recommended by NICE. Guidelines from the British Society of Gastroenterology (BSG) for people with moderately to severely active Crohn's disease are broadly the same as those provided by NICE.(49)

Proposed positioning of guselkumab

Guselkumab is positioned in moderately to severely active Crohn's disease where people have had an inadequate response, lost response to, or were intolerant to a biologic treatment. Guselkumab may also be suitable in some people with Crohn's disease for whom TNF-inhibitors are deemed unsuitable, similar to advanced therapies. Figure 2 provides an overview of the clinical pathway of care for people with Crohn's disease in England, including the proposed positioning of guselkumab. The accompanying submission to NICE uses vedolizumab and risankizumab as examples of drugs that may be considered as alternative treatments to guselkumab.

Figure 2: Clinical pathway of care for the management of Crohn's disease and anticipated positioning of guselkumab



Key: CD, Crohn's disease; IL, interleukin; JAK, Janus kinase; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; TNF, tumour necrosis factor.
Source: Based on NICE NG129, 2019 and TA187, TA456, TA352, TA905, TA456 and TA888.(13, 44-48)

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 Crohn's diseases on people's lives

The impact of uncontrolled Crohn's disease was shown in a survey carried out in adults with all forms of IBD in 2021 (n = 167).(50) The majority of respondents reported an impact on their ability to do tasks such as socialising, working/education, playing sports, travelling on public transport and maintaining their emotional wellbeing.

A 2024 Crohn's & Colitis UK report 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.(51) 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. The impacts increase anxiety and the likelihood of people with Crohn's disease being unable to freely travel and attend social and work events.(51)

Treatment preferences

A survey conducted between 2020–2021 in 360 people with Crohn's disease across seven European countries, including the UK, revealed important preferences for treatment.(52) The key findings were:

The most important factor for choosing a treatment was how the medication was given. Approximately 32% of respondents preferred oral tablets and subcutaneous (under the skin) injections over intravenous injections

Other important factors included the risk of serious side effects (28%), the chance of long-term remission (19%), achieving remission within a year (14%) and the risk of mild side effects (6%)

This study emphasises how important it is to provide personalised care and involve people in decision-making to ensure they get the most out of the treatments available for IBDs such as Crohn's disease and ulcerative colitis

In 2021, a global literature review examined studies on people with chronic immune diseases and their preference to receive treatment either by intravenous infusion or subcutaneous injection.(53) 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.

Limitations of current treatment options and the unmet need

Crohn's disease is incurable and many people with the disease experience multiple relapses per year accompanied by symptoms that can affect the entire body and have a high physical, functioning, social and psychological burden on patients and carers.(54) Current treatment options fail to control the disease and maintain remission in all patients. Where treatment fails on current biological therapies, there are limited options and 91% of people do not have personalised care plans. Furthermore, from an NHS perspective, treating people in relapse can cost up to six times more annually than maintaining remission.(54, 55)

People with Crohn's disease also may not be suitable for certain treatment options due to other conditions or specific risk factors:

TNF inhibitors are not suitable for patients with heart disease, at high risk of infections, recurrent infections, the elderly, and people with cancer(56)

JAK inhibitors should be used at the lowest dose possible and avoided in people with risk factors if alternatives are available due to safety concerns.(57) 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

Currently, the majority of injectable options for the BIO-failure population,(people who have failed to respond when taking a biological therapy) must initially be given in a hospital setting; this increases patient and carer burden as well as putting strain on hospital waiting lists and increasing healthcare resource use (HCRU) such as hospital outpatient visits, hospital stays, medication and surgery, in an NHS that is already under severe pressure.

There is a substantial unmet need for additional effective, better tolerated therapies that are convenient, sustain remission and improve outcomes of people with Crohn's disease. Addressing these unmet needs could limit the risk of further progression, complications, quality of life impairment, and costs associated with this debilitating disease.

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.(58) IL-23 is required for the normal functioning of the immune system; however, it is present at increased levels in people with Crohn's disease and plays an important role in causing the inflammation within the gut that is associated with Crohn's disease.(58) 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.(59, 60) Guselkumab has also been shown to induce and maintain clinical remission in some people with Crohn's disease – symptoms are under control, with minimal or no signs of inflammation in the colon, allowing them to live a more normal, symptom-free life.(59)

Guselkumab can be self-administered at home using an autoinjector or a pre-filled pen, which can provide greater convenience and flexibility for people with Crohn's disease as discussed below.(61)

Advantages of guselkumab

When starting treatment (induction phase), guselkumab has shown similar positive results when administered via intravenous infusion (injected into the vein) or when taken as an injection under the skin (subcutaneous injection).(58) 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 and NHS waiting lists as people with Crohn's disease do 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 with Crohn's disease do 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 in people with Crohn's disease at two different doses, which will be decided based on the judgement of the specialist gastroenterology clinical healthcare professional (see also Section 3c below).(59) This dose flexibility allows for a tailored approach for each patient, with the dosage being personalised to the patient's 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 Crohn's disease 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 rapidly reduce symptoms and induce remission, followed by the maintenance phase, which aims to maintain remission and control the disease.

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)(58):

- 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 the abdomen, thigh and upper arm. The subcutaneous injection dose is higher than the intravenous dose, in order 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 a person will receive based on clinical judgement:(58)

- 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 has the potential to reduce burden on people with Crohn's disease, carers and hospitals as people can take guselkumab at home and do not require professional supervision or trips to hospital. 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 Crohn's disease has been studies in three Phase III trials: GALAXI-2, GALAXI-3 and GRAVITI.(62-64) GALAXI-2 and GALAXI-3 are separate independent studies, but share an identical study design, were conducted at the same time and at the same locations. As a result, it is appropriate to report the combined data (pooled data) from GALAXI-2 and GALAXI-3 (see Table 2).

The data from GALAXI-2, GALAXI-3 and GRAVITI are provided as key trials in this submission. Information on the methodology of each trial is provided in Table 2.

Table 2: Summary of study design for GALAXI and GRAVITI trials

Clinical trial name	GALAXI-2/3	GRAVITI
Clinical trial number	NCT03466411	NCT05197049
Intervention	Induction: Guselkumab IV infusion Maintenance Guselkumab SC injection	Induction: Guselkumab SC injection Maintenance: Guselkumab SC injection
Locations	Sites across North American, South America, Europe and Asia-Pacific	Sites across North America, South America Europe and Asia-Pacific
Patient group size	730	347
Trial completion date	June 2030 (Estimated)	March 2025 (Estimated)
Key inclusion criteria	Have Crohn's disease or fistulizing Crohn's disease of at least 3 months duration (defined as a minimum of 12 weeks), with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography, histology, and/or endoscopy Have moderately to severely active Crohn's disease as assessed by CDAI, SF, and AP scores, and SES-CD Have screening laboratory test results within the protocol specified parameters A female participant of childbearing potential must have a negative urine pregnancy test result at screening and baseline Demonstrated intolerance or inadequate response to conventional or to biologic therapy for Crohn's disease	Diagnosis of Crohn's disease of at least 3 months in duration Have moderately to severely active Crohn's disease as assessed by CDAI, SF, and AP score, and SES-CD Demonstrated intolerance or inadequate response to conventional or to biologic therapy for Crohn's disease

Key exclusion criteria	Current diagnosis of ulcerative colitis or indeterminate colitis Have complications of Crohn's disease, such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation Unstable doses of concomitant Crohn's disease therapy Receipt of Crohn's disease approved biologic agents, investigational agents, or procedures outside of permitted timeframe as specified in the protocol Any medical contraindications preventing study participation	Current diagnosis of ulcerative colitis or indeterminate colitis Complications of Crohn's disease that require surgical intervention or confound efficacy assessments Unstable doses of concomitant Crohn's disease therapy

Key: AP, abdominal pain; CDAI, Crohn's disease activity index; IV, intravenous; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's disease; SF, stool frequency.
Sources: GALAXI-2/3 CSR; GRAVITI CSR; GALAXI-2/3 (NCT03466411) - Clinicaltrial.gov; GRAVITI (NCT05197049) - Clinicaltrial.gov.(62-67)

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 Phase III GALAXI-2/3 trials (62, 63)

GALAXI-2/3 Phase III studies successfully demonstrated consistent and robust efficacy for patients with moderately to severely active Crohn's disease

Data were provided from GALAXI-2 and GALAXI-3 combining the findings of both trials as a pooled set of results as explained above in section 3d. Guselkumab shows improved clinical efficacy relative to placebo across the whole population and the BIO-failure population of GALAXI-2/3 in the following endpoints highlighted in Table 3.(68, 69)

Table 3: Key endpoints in GALAXI-2/-3 compared with placebo

Primary endpoints	Clinical remission at Week 12 (disease activity based on symptom severity) Endoscopic response at Week 12 (how the colon appears through an endoscope, relative to people without Crohn’s disease)
Key secondary endpoints	Endoscopic remission at Week 12 Endoscopic response at Week 48 Corticoid-free clinical remission at Week 48 PRO-2 remission at Week 12

	Fatigue response at Week 12

Key: PRO-2, patient reported outcome-2
Source: J&J Innovative Medicine (Data on File, 2024a and 2024b).(68, 69)

Furthermore, compared with patients treated with ustekinumab in GALAXI-2/3, people treated with guselkumab showed improvements in endoscopic response/remission endpoints.(62, 63)

These successful results mean that guselkumab can noticeably improve symptom control, disease activity (clinical response) and leads to a normal appearance or mild disease of the gut.

Key results for the Phase III GRAVITI trial (64)

The results of the Phase III GRAVITI trial support the administration of guselkumab by subcutaneous induction for patients with moderately to severely active Crohn's disease.

Compared with placebo, guselkumab given as a subcutaneous injection in the whole trial population and BIO-failure patients achieved improved clinical efficacy in the endpoints presented in Table 4.(68, 69)

Table 4: Key endpoints in GRAVITI compared with placebo

Primary endpoints	Clinical remission at Week 12 Endoscopic response at Week 12
Key secondary endpoints	Clinical response at Week 12 Clinical remission at Week 24

Source: J&J Innovative Medicine (Data on File, 2024a and 2024b).(68, 69)

The successful results of GRAVITI reinforce the data from GALAXI-2/3, showing the efficacy advantage of guselkumab in two international Phase III trials.

The results of GRAVITI also support the use of subcutaneous injection of guselkumab in the induction phase of Crohn's disease treatment

Indirect treatment comparison/network meta-analysis

Guselkumab has not been directly compared with risankizumab and vedolizumab that are the comparators relevant to this submission .(70) In the absence of such comparisons, a network meta-analysis was performed to determine the relative treatment effect among patients with moderately to severely active Crohn's disease.(70)

The objective of the network meta-analysis was to evaluate the comparative effectiveness of guselkumab with risankizumab and vedolizumab for moderately to severely active Crohn's disease in induction and maintenance phases of treatment, where maintenance outcomes evaluate response at approximately 1 year in all enrolled patients.(71)

The results of network meta-analysis suggest that guselkumab is as effective or more efficacious than risankizumab and vedolizumab for Crohn's disease treatment based on clinical response, clinical remission, and endoscopic response outcomes, in patients who previously failed a biologic therapy.(70) Overall, guselkumab offers similar/more favourable outcomes for patients with Crohn's disease when compared with risankizumab or vedolizumab meaning guselkumab is suitable for a cost-comparison appraisal.(70)

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.
In the GALAXI trials, quality of life was assessed using three main tools: the Inflammatory Bowel Disease Questionnaire (IBDQ), Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29) and the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L).(59) The IBDQ is designed specifically for people with IBD and evaluates how bowel symptoms (like loose stools and abdominal pain), overall health (such as fatigue and sleep issues), social activities (like work attendance and cancelling social events), and emotional well-being (including feelings of anger, depression and irritability) are affected. Alternatively, the EQ-5D-5L is a general tool that looks at how people rate their mobility, self-care, daily activities, pain or discomfort, and feelings of anxiety or depression and the EQ-visual analogue scale (VAS). PROMIS-29 is a non-specific measure of pain intensity and seven health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance). The key symptoms of abdominal pain, stool frequency and fatigue were also measured.(59) The important highlights about the improvement in overall well-being from the guselkumab trials are summarised below. Further information can be found in the company submission Document B, Section B.3. When measured by IBDQ, EQ-5D-5L and PROMIS-29, HRQoL in patients treated with guselkumab had improved scores (meaning better HRQoL compared with placebo treated patients).(59) On symptom-specific HRQoL scales, patients treated with guselkumab in GALAXI-2/-3 showed an improvement in abdominal pain scores (meaning patients experienced less pain) and a reduction in stool frequency at Week 12 and Week 48 compared with placebo. Fatigue was measured using the PROMIS-Fatigue SF 7a score, and patients treated with guselkumab showed better scores (meaning less fatigue) compared with a placebo at Week 12 and Week 48.(59) In summary, guselkumab may provide much needed improvement in HRQoL for people impacted by the debilitating impact of Crohn's disease.(59) The proven efficacy of guselkumab, as shown in the GALAXI and GRAVITI studies, provides improved symptom control, which may lead to people feeling better physically and emotionally, and may help them lead a more fulfilling and active life. **Patient preference information** As stated in Section 2d, patient preference research has indicated that route of administration and, specifically, providing an oral or subcutaneous route of administration over an intravenous injection, is the most important factor to the majority of people with Crohn's disease in the UK and Europe(52) Guselkumab is unique amongst treatments that work within the interleukin-23 (IL-23) class, in providing a fully subcutaneous treatment schedule from the start of treatment

(induction) and during the maintenance phase, thereby helping to meet patient needs in terms of their administration preferences and decreasing the burden of having to travel to hospital for the person, their family and caregivers.(58)

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.

Possible side effects

Summary of safety data from GALAXI-2/-3 (60)

- The safety profile of guselkumab in the GALAXI-2 and GALAXI-3 trials show that it is well tolerated, with similar results to the placebo group and low numbers of severe adverse events and discontinuations
- For most participants who experienced an adverse event, this was only mild or moderate in intensity, requiring no treatment or on only local or non-invasive treatment.
- The rates of serious adverse events, severe adverse events, serious infections, and events leading to discontinuation were low (less than 5%) in the guselkumab group and comparable to those in the placebo group
- The rates of serious infections were similar across both treatment groups, and there were no reported deaths during the study

Summary of safety data from GRAVITI(64)

- The rates of severe adverse events and adverse events leading to treatment discontinuation were low in both guselkumab treatment groups through to Week 48, and the proportions of participants with serious adverse events in the guselkumab treatment groups were not higher than in the placebo group
- No differences in the rates of adverse events were found between the combined guselkumab subcutaneous treatment group and the placebo group through the 12-week induction period
- By Week 48, a higher proportion of participants in the guselkumab treatment groups reported at least one adverse event compared with the placebo group. However, when considering the follow-up time, the rates of adverse events per 100 subject years were not higher in the guselkumab treatment groups than in the placebo group

An overall summary of the side effect profile of guselkumab is provided Table 5. Like all medicines, guselkumab can cause side effects, although not everybody experiences them.

Table 5: List of guselkumab side effects

Type of side effect and risk	Signs and symptoms
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.(61)	

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 for their injection, 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 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 Crohn's disease 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 Crohn's disease
- **Efficiency for the NHS:** H home administration reduces NHS waiting times and healthcare resource utilisation by improving infusion suite capacity.(72) 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. 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 results of the GALAXI-2/-3 and GRAVITI trials show that guselkumab is similarly effective whether administered as an intravenous infusion or a subcutaneous injection for induction treatment, and it is effective as a maintenance dose of either 100 mg or 200 mg given subcutaneously.(59, 68, 69) Having control over the choice of injection and consistent efficacy, patients may experience relief from their symptoms with more consistent disease management and enjoy a more normal life.
- Guselkumab is generally well-tolerated with a favourable safety profile. Clinicians also have many years' experience 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 people 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 GALAXI-2/-3 and GRAVITI trials have shown that guselkumab is clinically effective, not all patients will respond to the treatment. However, these patients may still achieve a relief from symptoms. Additionally, some patients may experience side effects, but these are generally manageable, and the discontinuation rates are low. Physicians have extensive experience using guselkumab and managing side effects as guselkumab is approved for other conditions, such as psoriasis and psoriatic arthritis, and no new side effects have been identified in GALAXI-2/-3 and GRAVITI.

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 Crohn's disease?

The purpose of the model is to compare the costs of using guselkumab as an alternative to other treatment options available for Crohn's disease in NHS clinical practice. The model is designed to reflect the provision of care received by people with Crohn's disease who did not respond well to (had an inadequate response, lost response) or had side effects (were intolerant) to a biological therapy i.e. BIO-failure population 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 risankizumab were considered the most relevant comparators in the model. Both are recommended and used in clinical practice for the BIO-failure population, which is the same as the positioning of guselkumab in this submission. Furthermore, risankizumab and guselkumab are IL-23 inhibitors and have a similar mechanism of action. Consequently, in NHS clinical practice in England, guselkumab would be considered by clinicians as an alternative treatment to vedolizumab and risankizumab in the BIO-failure population of Crohn's disease.

In the absence of evidence directly comparing guselkumab with vedolizumab or risankizumab, statistical methods were applied to make indirect comparisons between these (a network meta-analysis). The network meta-analysis (Section 3e) demonstrated that guselkumab can provide similar or greater clinical benefits compared with vedolizumab and risankizumab. Therefore, the model focuses on cost outcomes and not clinical benefit as all three are assumed to be similar based on statistical analyses of the respective treatment studies.

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 risankizumab 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. Risankizumab is administered intravenously in the induction phase and subcutaneously in the maintenance phase.

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 risankizumab, 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 risankizumab (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. The introduction of guselkumab in clinical practice is not likely to increase the cost of treatment of Crohn's disease and may even result in cost savings to the NHS in England.

Uncertainty

The information used in the model could have some uncertainties. A tests was run (sensitivity analyses) to see how different factors 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 is likely to result in similar or lower costs in the treatment of Crohn's disease in the BIO-failure population. As the price of guselkumab was provided at the discounted price and was compared to vedolizumab and risankizumab 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 Crohn's disease who have not responded well to other treatments or had side effects. It has been shown to work well in clinical studies.

Unlike many other treatments for Crohn's disease recommended by NICE, guselkumab can be given at home as a convenient self-administered injection from the start; this means that the person may not need to go to the hospital for the initial treatment phase. This can have a significant positive impact and be a big relief for patients and their caregivers 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 a person needs to make to the hospital is also important to reduce the strain on an already stretched NHS. (73)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.(73)

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 Crohn's disease 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 Crohn's disease, as they do not qualify for the same benefits as people with other long-term illnesses.(74) 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).(75) 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 an invisible disability depending on the effect it has on a person's daily life.(76) 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.(77) 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.(78) Due to the unpredictable onset of flare-ups and symptoms, people can struggle to manage work/education/social life and even withdraw from engagements. People may be anxious about accidents or embarrassed by their condition and not share their condition with colleagues and friends. 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, allowing many to live a more normally life relative to someone without Crohn's disease. (79) The 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.(73)

Crohn's disease as a type of IBD is often called an invisible disability because it is not easy to see how it affects someone. People Crohn's disease 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 Crohn's disease:

Crohn's & Colitis UK(12): https://tinyurl.com/2dcyv778

IBDrelief(80): https://www.ibdrelief.com/

NICE guidance for Crohn's disease(44): https://www.nice.org.uk/guidance/ng129

Further information on GALAXI-2/3

Clinicaltrials.gov (NCT03466411)(66): https://clinicaltrials.gov/study/NCT03466411

Further information on GRAVITI:

Clinicaltrials.gov (NCT05197049)(67): https://clinicaltrials.gov/study/NCT05197049

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

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).

Clinical remission: where the 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 GI tract allowing people to live a more normal, symptom-free life. This is definition is based on the CDAI score.

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.

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: a procedure where a doctor uses a long, thin flexible tube called an endoscope with a tiny camera on the end to look inside the digestive tract.

Endoscopic remission: in Crohn's disease, this means that during an endoscopy, there are no signs of active inflammation in the intestines. It may mean that people may be experiencing fewer or no symptoms.

Endoscopic response: in Crohn's disease, this refers to the improvement of the disease as seen through an endoscopy. It may mean that the areas of the intestine that were swollen or damaged are healing.

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

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.

Inflammatory burden: the measure of inflammatory markers in the blood including C-reactive proteins and immune cells

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.

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.

4c) References

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison

Guselkumab for previously treated moderately to severely active Crohn's disease [ID6238]

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6238 Guselkumab CD_Clarification Response_CON_redacted	Final	Yes	25.03.25

Section A: Clarification on effectiveness data

Literature searches

A 1. Priority question: Searches for the both the clinical and cost effectiveness SLRs were last run in 2023 (July 2023 for the clinical effectiveness searches, and October 2023 for the cost effectiveness searches). Please re-run the searches to identify any new studies which may have been published since these dates.

Company response:

Clinical search update

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, Johnson & Johnson undertook a two-step approach as outlined below. The searches described below were conducted on 13th March 2025.

1. We first conducted a search on ClinicalTrials.gov to identify all Phase 2, 3, 4 trials in Crohn's disease (CD) that may be active or completed (Table 1). A total of 39 records were identified, of which 32 records were excluded due to study termination (n=4), population (n=10), intervention (n=4), outcomes (n=5), study design (n=5), withdrawn (n=4). The seven remaining records included six of those identified in the July 2023 SLR and included data that informed the NMAs presented in the company submission: ADVANCE, MOTIVATE, FORTIFY, GALAXI, GEMINI-2 and GEMINI-3. One remaining included record was identified relevant to this submission relating to the GRAVITI study. GRAVITI is a Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre, study to evaluate the efficacy and safety of guselkumab subcutaneous (SC) induction therapy in adult participants with moderately to severely active Crohn's disease.(1)

Table 1: Search strategy for ClinicalTrials.gov

Search strategy	Results
Crohn's disease | vedolizumab OR risankizumab OR Guselkumab | Active, not recruiting, Completed, Terminated, Enrolling by invitation, Suspended, Withdrawn, Unknown status studies | Phase: 2, 3, 4 | Interventional studies	39

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, 452 records were identified, of which 440 were excluded after screening due to: Population (n=154), Intervention (n=21), Outcomes (n=59), Study design (n=145), Duplicate (n=31), Publication type (n=30). Of the 12 included records, nine of these relate to, GALAXI 1, GALAXI 2, GALAXI 3 and FORTIFY, which were identified in the July 2023 SLR and included data that informed the NMAs presented in the company submission. The remaining three records identified are relevant to this submission and relate to a single study describing the Week-12 or week-48 outcomes from the GRAVITI trial, also identified in the search on ClinicalTrials.gov. as discussed above.

The results of these searches indicate that GRAVITI is the only new trial that is relevant to this submission as per the PICO criteria. Subsequently, the induction NMAs have been updated to include GRAVITI data and are presented as part of the response to question A6, part e. Maintenance NMAs have not been updated with GRAVITI data as the guselkumab 100mg SC Q8W and guselkumab 200mg SC Q4W dosing regimens are already included in the NMAs as part of the GALAXI trial programme data.

Table 2: PICO criteria used for the clinical TLR

Criteria	Include	Exclude
Population	• Adults and select adolescents (age ≥16 years) with moderately to severely active Crohn's disease (as defined by study)	• Any population not in inclusion criteria
Interventions	The following therapies alone or in combination with conventional therapy: • Guselkumab • Risankizumab • Vedolizumab	• Surgery • Non-pharmacological interventions
Comparators	• Active comparator or placebo	• Any other comparator
Outcomes	<u>Efficacy outcomes (as defined by study)</u> • Clinical remission • Clinical response • Endoscopic remission • Endoscopic response • Corticosteroid-free remission • PRO2-remission (*tracking only*) <u>Safety outcomes</u> • Serious infections • Serious adverse events (*tracking only*) <u>Quality of life outcomes</u> • 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	• Randomized, 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, case-control, and cross-sectional studies • Single-arm trials • Non-randomized trials
Publication type	• Full-text published articles or conference abstracts (proceedings from 2022 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[b]	• English	• Non-English

Date Limit	• Published articles: 2023 to present • Conference abstracts: 2023 to present	• Published articles: <2023 • Conference abstracts: <2023

[a] Systematic reviews were not included in the review, however, bibliographies of relevant systematic reviews in ulcerative colitis were reviewed to identify additional eligible citations
[b] Search captured all languages, but non-English citations were excluded during screening.
Abbreviations: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; EQ-5D-3L = EuroQol 5 Dimension 3 Level; EQ-5D-5L = EuroQol 5 Dimension 5 Level; IL = interleukin; JAK = Janus kinase; PICOS = Population, Intervention, Comparator, Outcomes, Study design; PRO-2 = Patient-Reported Outcome; RCTs = randomized controlled trials; SLR(s) = systematic literature review(s); TNF = tumor necrosis factor.

Table 3: PubMed search strategy and results for the clinical TLR

#	Searches	Results
1	"Crohn Disease"[mh] OR ((crohn* OR cleron) AND (disease* OR morbus OR colitis* OR colitides OR enteriti*)) OR ((regional* OR granulomatous OR terminal*) AND (colitis* OR colitides OR enteriti* OR ileitis OR ileitides OR ileocolitis OR ilea-colitis OR enterocolitis* OR entero-colitis*)) OR (inflammat* AND bowel* AND disease*) OR ((CD or IBD) AND (crohn* OR colitis* OR (inflammat* AND bowel*)))	134,689
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	Search: guselkumab*[tiab] or "Cnto-19S9"[tiab] or cnto1959[tiab] or Tremfya*2[tiab] or 089658A12D[tiab] or "1350289-85-S"[tiab] OR guselkumab[nm]	851
4	risankizumab*[tiab] or "abbv-066"[tiab] or abbv066 or "bi- 655066"[tiab] or bi655066[tiab] or skyrizi*[tiab] or 90ZX3Q3FR7[tiab] or "1612838-76-2"[tiab] or Risankizumab[nm]	664
5	#2 OR #3 OR #4	2,429
6	#1 and #5	1,140
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])	1,636,573
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]))	1,385,926

#	Searches	Results
9	#7 or #8	1,923,786
10	#6 and #9	265
11	(Child[mh] or Infant[mh] or Pediatrics[mh]} not ((Adult[mh] or Adolescent[mh]} and (Child[mh] or Infant[mh] or Pediatrics[mh])}	1,541,367
12	(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 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])})	3,015,093
13	(("Observational Study" [pt]} OR "Retrospective Studies" [mh]} NOT ("Randomized Controlled Trial" [pt] OR random*)	1,331,355
14	(Animals[mh] not (Animals[mh] and Humans[mh])}	5,316,311
15	#11 or #12 or #13 or #14	10,807,986
16	#10 NOT #15	249
17	#10 NOT #15 Filters: English	243
18	#10 NOT #15 Filters: English, from 2023/7/23 - 2025/3/13	61

Table 4: Embase search strategy and results for the clinical TLR

#	Searches	Results
1	'crohn disease'/syn	138902
2	(((crohn* OR cleron) NEAR/3 (disease* OR morbus OR colitis* OR colitides OR enteriti*)):ab,ti,kw) OR (((regional* OR granulomatous OR terminal*) NEAR/3 (colitis* OR colitides OR enteriti* OR ileitis OR ileitides OR ileocolitis OR 'ileo colitis' OR enterocolitis* OR 'entero colitis*')):ab,ti,kw) OR ((inflammat* NEAR/3 bowel* NEAR/3 disease*):ab,ti,kw) OR ((cd:ab,ti,kw OR ibd:ab,ti,kw) AND (crohn*:ab,ti,kw OR colitis*:ab,ti,kw OR ((inflammat* NEAR/3 bowel*):ab,ti,kw)))	191948
3	#1 OR #2	212157
4	'vedolizumab'/syn OR 'guselkumab'/syn OR 'risankizumab'/syn OR vedolizumab*:ab,ti,kw OR guselkumab*:ab,ti,kw OR risankizumab*:ab,ti,kw	14883
5	'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)	3115942

#	Searches	Results
6	#3 AND #4 AND #5	2748
7	('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)	1519845
8	(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)	3176643
9	('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)	8751085
10	'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	6137667
11	('child'/exp OR 'fetus'/exp) NOT (('adult'/exp OR 'adolescent'/exp) AND ('child'/exp OR 'fetus'/exp))	2262723
12	# OR #8 OR #9 OR #10 OR #11	20257712
13	#6 NOT #12	1783
14	#13 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	1094
15	#13 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2022-2025]/py	412
16	#14 NOT#15	682
17	#13 NOT #16	1101
18	#13 NOT #16 AND [23-07-2023]/sd	394
19	#13 NOT #16 AND [23-07-2023]/sd AND [english]/lim	391

Economic search update

In order to identify any additional relevant publications since October 2023, Johnson & Johnson conducted a TLR to identify economic evidence relevant to the UK setting. The TLR was restricted to the UK setting as a pragmatic approach to ensure that critical evidence was not missed, whilst working in the timeframe of response to clarification questions. The searches described below were conducted on 20th March 2025. The search strategy for the TLR was limited to the PICO described in

Table 5 and the searches conducted on PubMed and Embase electronic databases are presented in Table 6 and Table 7, respectively.

In total 1728 number of records were identified, of which 1691 were excluded after screening due to the study design not related to the United Kingdom, UK or England. Of the remaining 37 records, none were identified according to the PICO criteria and were excluded for the following reasons: population (n=12), intervention (n=0), comparator (n=0), outcome (n=12), study design (n=9), publication type (n=3), duplicate (n=1). As no additional relevant records were identified, it is suggested that the publications the original SLR remain the most relevant in informing the design of the economic model for the purposes of the UK setting.

Table 5: PICO criteria used for the economic TLR

	Inclusion criteria	Exclusion criteria
Population	Adults and select adolescents (age ≥ 16 years) with moderately to severely active Crohn's disease (as defined by study)	Any population not in inclusion criteria
Interventions	<u>The following therapies alone or in combination with conventional therapy:</u> <u>Biologics</u> • TNF-alpha inhibitors (i.e., adalimumab, infliximab, certolizumab pegol) • Integrin blockers (i.e., vedolizumab, natalizumab, etrolizumab) • IL-12/IL-23 inhibitors (ustekinumab) • IL-23 inhibitors (i.e., guselkumab, risankizumab, mirikizumab) <u>JAK inhibitors</u> • Upadacitinib • Tofacitinib • Filgotinib <u>Sphingosine l-phosphate receptor modulator</u> • Ozanimod • Etrasimod	• Surgery • Non-pharmacological interventions
Comparators	• Active comparator or placebo • No comparator	• Any other comparator
Outcomes	Economic outcomes: • Direct costs (e.g., medical, drug, resource use)	• Only clinical endpoints (e.g., efficacy, safety, or quality of life outcomes)

	Inclusion criteria	Exclusion criteria
	• Surgical outcomes including but not limited to: • Direct surgical costs • Indirect surgical costs (costs of complications, etc.) • Surgery utilities (pre- and post-surgery) • Rate of surgery uptake • Cost-effectiveness or cost-utility estimates (e.g., ICERs, ICURs, LYs, QALYs) • Indirect costs (e.g., opportunity cost, productivity loss, lost wages) • Reported utilities and disutilities by health state	
Study Design	• Any economic study or study with economic components • Cost-effectiveness, cost-utility, cost-minimisation, cost-consequence, cost-benefit analysis • Budget impact analysis • Burden/cost of illness, claims database analysis • Patient/physician/caregiver surveys • Published clinical trials (e.g., RCTs, non-randomised studies, observational studies [e.g., real-world evidence, registry, retrospective cohort study, cross-sectional, case-control, single-arm studies]) that report a cost analysis and/or health state utilities	• Case series, case reports, reviews, editorials, commentaries, opinion, perspective, protocols, and/or methodological articles • SLRs • Not related to the United Kingdom, UK or England
Language	English only	Non-English
Dates	• Published articles: 2013 to present • Conference abstracts: 2022 to present	• Published articles: < 2013 • Conference abstracts: < 2022
Key: ICER, incremental cost-effectiveness ration ; ICURs, Incremental Cost-utility Ratio; IL, interleukin; QALY, LY, life year; quality-adjusted life year; RCT, randomised controlled trial; SLR, systematic literature review.		

Table 6: PubMed search strategy and results for the economic TLR

#	Searches	Results
1	"Crohn Disease"[mh] OR ((crohn* OR cleron) AND (disease*OR morbus OR colitis* OR colitides OR enteriti*)) OR ((regional* ORgranulomatous OR terminal*) AND (colitis* OR colitides OR enteriti*OR ileitis OR ileitides OR ileocolitis OR ileo-colitis OR enterocolitis*OR entero-colitis*)) OR (inflammat* AND bowel* AND disease*) OR((CD or IBD) AND (crohn* OR colitis* OR (inflammat* AND bowel*)))	134,839
2	"costs and cost analysis"[mh] or costs[TIAB] or cost effective*[TIAB]	612,600
3	cost*[TIAB] or cost benefit analys*[TIAB] or health carecosts[TIAB]	899,233
4	Economics[mh] or "Costs and Cost Analysis"[mh] orEconomics, Nursing[mh] or Economics, Medical[mh] or Economics,Pharmaceutical[mh] or Economics, Hospital[mh] or Economics,Dental[mh] or "Fees and Charges"[mh] or Budgets[mh] or models,economic[mh] or markov chains[mh] or monte carlo method[mh] orDecision Theory[mh] or (economic*[TIAB] or cost[TIAB] orcosts[TIAB] or costly[TIAB] or costing[TIAB] or price[TIAB] orprices[TIAB] or pricing[TIAB] or pharmacoeconomic*[TIAB] orpharmaco-economic*[TIAB] or expenditure[TIAB] orexpenditures[TIAB] or expense[TIAB] or expenses[TIAB] orfinancial[TIAB] or finance[TIAB] or finances[TIAB] or financed[TIAB])or ((cost*[TIAB] AND (effective*[TIAB] or utilit*[TIAB] or benefit*[TIAB] or minimi*[TIAB] or analy*[TIAB] or outcome[TIAB] oroutcomes[TIAB])) or economic model*[TIAB]) or ((value[TIAB] AND(money[TIAB] or monetary[TIAB])) or markov[TIAB] or "monte carlo"[TIAB] or budget*[TIAB] or (decision*[TIAB] AND (tree*[TIAB] oranaly*[TIAB] or model*[TIAB]))))	2,234,763
5	economic*[tiab] or cost[tiab] or costs[tiab] or costly[tiab] orcosting[tiab] or price[tiab] or prices[tiab] or pricing[tiab] orpharmacoeconomic*[tiab] or pharmaco-economic*[tiab] orexpenditure[tiab] or expenditures[tiab] or expense[tiab] orexpenses[tiab] or financial[tiab] or finance[tiab] or finances[tiab] orfinanced[tiab]	1,389,889
6	#4 or #5	2,234,763
7	economics[mh] or exp "costs and cost analysis"[mh] oreconomics, dental[mh] or "economics, hospital"[mh] or economics,medical[mh] or economics, nursing[mh] or economics,pharmaceutical[mh] or (economic*[tiab] or cost[tiab] or costs[tiab]or costly[tiab] or costing[tiab] or price[tiab] or prices[tiab] orpricing[tiab] or pharmacoeconomic*[tiab] or (expenditure*[tiab] notenergy[tiab]) or (value[tiab] AND money[tiab]) or budget*[tiab] not ((energy[tiab] or oxygen[tiab]) AND cost[tiab]) or (metabolic[tiab]AND cost[tiab]) or ((energy[tiab] or oxygen[tiab]) ANDexpenditure[tiab]))	1,360,959
8	#2 or #3 or #6 or #7	2,267,866
9	#1 and #8	6,149
10	(Animals[mh] not (Animals[mh] and Humans[mh]))	5,318,515
11	(Child[mh] or Infant[mh] or Pediatrics[mh]) not ((Adult[mh]or Adolescent[mh]) and (Child[mh] or Infant[mh] or Pediatrics[mh]))	1,541,851
12	(address[pt] or autobiography[pt] or bibliography[pt] orbiography[pt] or comment[pt] or dictionary[pt] or directory[pt] oreditorial[pt] or "expression of concern"[pt] or festschrift[pt] orhistorical article[pt] or interactive tutorial[pt] or lecture[pt] or legalcase[pt] or legislation[pt] or news[pt] or newspaper article[pt] orpatient education handout[pt] or personal narrative[pt] orportrait[pt] or video-	3,016,424

#	Searches	Results
	audio media[pt] or webcast[pt] or (letter[pt]not (letter[pt] and randomized controlled trial[pt]))	
13	#9 not (#10 or #11 or #12)	5,498
14	#9 not (#10 or #11 or #12) Filters: from 2023/10/17 -2025/3/19	702

Table 7: Embase search strategy and results for the economic TLR

#	Searches	Results
1	'crohn disease'/syn OR (((crohn* OR cleron) NEAR/3 (disease* OR morbus OR colitis* OR colitides OR enteriti*)):ab,ti,kw) OR (((regional* OR granulomatous OR terminal*) NEAR/3 (colitis* OR colitides OR enteriti* OR ileitis OR ileitides OR ileocolitis OR 'ileo colitis' OR enterocolitis* OR 'entero colitis*')):ab,ti,kw) OR ((inflammat* NEAR/3 bowel* NEAR/3 disease*):ab,ti,kw) OR ((cd:ab,ti,kw OR ibd:ab,ti,kw) AND (crohn*:ab,ti,kw OR colitis*:ab,ti,kw OR ((inflammat* NEAR/3 bowel*):ab,ti,kw)))	212,333
2	cost:ab,ti OR costs:ab,ti	1,064,753
3	'economics'/exp OR 'cost'/exp OR 'health economics'/syn OR 'budget'/exp OR 'statistical model'/exp OR 'probability'/exp OR 'monte carlo method'/exp OR 'decision theory'/exp OR 'decision tree'/exp OR economic*:ab,ti OR cost:ab,ti OR costs:ab,ti OR costly:ab,ti OR costing:ab,ti OR price:ab,ti OR prices:ab,ti OR pricing:ab,ti OR pharmacoeconomic*:ab,ti OR 'pharmaco-economic*':ab,ti OR expenditure:ab,ti OR expenditures:ab,ti OR expense:ab,ti OR expenses:ab,ti OR financial:ab,ti OR finance:ab,ti OR finances:ab,ti OR financed:ab,ti OR ((cost* NEAR/2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)):ab,ti,kw) OR 'economic model*':ab,ti OR ((value NEAR/2 (money OR monetary)):ab,ti,kw) OR budget*:ab,ti,kw OR markov:ab,ti,kw OR 'monte carlo':ab,ti,kw OR ((decision* NEAR/2 (tree* OR analy* OR model*)):ab,ti,kw)	3,530,633
4	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or 'pharmaco-economic*' or expenditure or expenditures or expense or expenses or financial or finance or finances or financed):ab,ti	1,764,552
5	#3 OR #4	3,530,633
6	('health economics'/exp OR 'economic evaluation'/syn OR 'health care cost'/syn OR 'pharmacoeconomics'/syn OR econom*:ab,ti OR cost:ab,ti OR costs:ab,ti OR costly:ab,ti OR costing:ab,ti OR price:ab,ti OR prices:ab,ti OR pricing:ab,ti OR pharmacoeconomic*:ab,ti OR (expenditure*:ab,ti NOT energy:ab,ti) OR ((value NEAR/2 money):ab,ti) OR budget*:ab,ti) NOT (metabolic:ab,ti AND cost:ab,ti OR ((energy:ab,ti OR oxygen:ab,ti) AND cost:ab,ti) OR ((energy:ab,ti OR oxygen:ab,ti) AND expenditure:ab,ti))	2,240,630
7	#2 OR #5 OR #6	3,582,403
8	#1 AND #7	19,201
9	('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)	8,248,447
10	('child'/exp OR 'fetus'/exp) NOT (('adult'/exp OR 'adolescent'/exp) AND ('child'/exp OR 'fetus'/exp))	2,264,331

#	Searches	Results
11	(editorial:it or note:it or 'short survey':it or tombstone:it) or (letter:it not 'randomized controlled trial'/exp)	3,572,129
12	#8 not (#9 OR #10 OR #11)	17,268
13	#12 AND [18-10-2023]/sd	2,189
14	#13 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	1,026

A 2. Sections D.1.3.2 and F.1.3.2 state that grey literature searches of ClinicalTrials.gov and key clinical conferences were conducted. Please provide details of the search terms that were used for these resources

Company response:

The grey literature search strategies have been provided in Table 8 alongside contextual details regarding the searches.

Table 8: Grey literature search strategies for the original SLR conducted

Search strategy	Results	Date conducted
ClinicalTrials.gov		
Condition or disease: *Ulcerative colitis* Other terms: Country: Study type: *Study Phase: Phase 2, Phase 3, Phase 4* Study results: Status: Outcome Measure:	Retrieved 574 records	October 13, 2023
Condition or disease: *Ulcerative colitis* Other terms: Country: Study type: *Interventional* Study Phase: *NA* Study results: Status: Outcome Measure:	Retrieved 252 records	October 23, 2023
Digestive Disease Week (DDW) meeting 2023		
Online database: https://eposters.ddw.org/ Keywords: *ulcerative*, *colitis* Content type: Abstracts Event: DDW 2023	Retrieved 358 records	July 5, 2023

EMBASE includes a large number of clinical conferences, and details these within a publicly available listing. The following congress proceedings were not manually reviewed, given confirmation that they were already captured within the EMBASE database (and therefore included in the main electronic databases search):

- European Crohn's and Colitis Organisation (ECCO) meeting: 2022, 2023
- Digestive Disease Week (DDW) meeting: 2022
- American College of Gastroenterology (ACG) meeting: 2022
- United European Gastroenterology Week (UEGW) meeting: 2022
- Crohn’s and Colitis Congress meeting: 2022, 2023
- Advances in Inflammatory Bowel Diseases (AIBD) meeting: 2022

The following congress proceedings could not be reviewed as they were not publicly available when grey literature searching was undertaken:

- ACG 2023 meeting: hosted in late October 2023
- UEGW 2023 meeting: hosted in late October 2023
- AIBD 2023 meeting: hosted in mid-December 2023

Decision problem

A 3. Priority question. The decision problem (DP) population is stated in Table 1 of Document B to be narrower than that in the scope by excluding inadequate response or intolerance to conventional treatment, but it includes “*lost response*”, which is not mentioned in the scope.

a) **Please clarify that, despite the marketing authorisation, the company does not intends to exclude patients who have inadequate response or intolerance to conventional treatment from its submission.**

b) **Please clarify that "lost response" is outside of the NICE scope and therefore should not be included in the company's DP.**

Company response:

a) Johnson & Johnson confirm that patients who have inadequate response or intolerance to conventional treatment should not be excluded from the decision problem. According to NICE and BSG guidelines, patients who have failed conventional therapy are eligible for biologic treatments.(2, 3) While biosimilar anti-TNF therapies are generally recommended as the first-line biologic option due to cost, there are circumstances in which these may be deemed unsuitable by the treating clinician. For instance, a small proportion of patients with moderately-to-severely active Crohn's disease may be considered unsuitable for anti-TNF therapy due to contraindications, risk of intolerance, severe heart disease and those at high risk of infections, including the elderly.(4) In such cases, biologic treatments with alternative mechanisms of action may be considered as a first-line biologic agent. The rationale for treatment selection is made on an individual basis for patients depending on the reason for the ineligibility. Biologic treatments like guselkumab are anticipated to be appropriate alternatives in these circumstances, based on robust evidence from the GALAXI and GRAVITI trials presented in Document B, Section 3.5. However, it is anticipated that in the absence of factors that would lead to unsuitability of biosimilar anti-TNF therapy, that guselkumab would be used after an inadequate response, lost response or intolerance to a biosimilar anti-TNF.

b) Johnson & Johnson believe that patients who have "lost response" to conventional therapy should not be excluded from the decision problem. Similar to patients who have inadequate response or intolerance to conventional treatments, those that have lost response to conventional therapy would also be eligible for biologic treatment. This wording effectively encompasses patients with primary non-response, secondary loss of response or intolerance to a previous treatment which is wording

commonly used in Crohn's disease. This is in-line with the anticipated wording for the guselkumab SmPC and the wording in the existing risankizumab and vedolizumab SmPCs. Thus, depending on individual patient profiles, guselkumab could be a viable treatment option for these patients.

A 4. Priority question. The population in the DP states: *"…, including patients for whom TNFis are deemed unsuitable"* (Table 1, Document B).

a) Please clarify whether the patients for whom TNFis are unsuitable have also had an inadequate response, lost response or were intolerant to a biologic treatment or whether such patients might not have previously received any biologic treatment.

b) If the answer to (a) is 'no' then please justify the inclusion of this population given the anticipated marketing authorisation.

Company response:

a) For patients who are unsuitable for anti-TNF therapies and are eligible for biologic treatment (as discussed in question A3), initiation of a biologic therapy with an alternative mechanism of action is the standard pathway. The decision on the alternative mechanism of action will be based on individual patient factors and the reason for the unsuitability. There is not a standard sequential hierarchy for the treatment of CD. Therefore, there may be instances where some patients who are not suitable for anti-TNF therapy have not yet received any biologic treatment.

b) Johnson & Johnson believe that patients who are anti-TNF unsuitable and have not previously received biologic treatment should be considered in this decision problem. Guselkumab is anticipated to receive a marketing authorisation for [redacted] It is expected that patients who are unsuitable to anti-TNF treatments and are eligible for biologic therapy have already exhausted conventional therapy options. Therefore, aligned with the anticipated marketing authorisation, guselkumab therapy could be initiated for these patients.

In the GALAXI-2, GALAXI-3 and GRAVITI trials, the proportion of biologic-naïve patients in the guselkumab arms was reported as [redacted], [redacted] and [redacted] respectively. Among these patients, it is likely that some would be deemed unsuitable for anti-TNF therapies. The trial outcomes demonstrate that guselkumab is an efficacious therapy in these patients, as shown in the full analysis set (FAS) detailed in Document B, Section 3.5. It is also important to highlight that the comparators included in this submission are appropriate for treating patients who are unsuitable for anti-TNF therapies and are currently recommended by NICE for this population. As guselkumab has demonstrated comparable efficacy to vedolizumab and risankizumab, it is expected that guselkumab would also be an appropriate treatment option for patients that are considered anti-TNF unsuitable.

A 5. **Priority question. The company state in Table 1 of Document B that: *"Since relapse is defined as a loss of remission, clinical remission is indicative of relapse rates"*.**

a) Please explain how this is the case given that relapse is an event that follows remission and there seems to be no logical reason why the rates would be similar.

b) Please provide comparative efficacy in terms of relapse rates, as required by the NICE scope.

Company response:

a) While relapse rate could be an indicator of disease management, it is important to note that this is not an outcome typically used in Phase II-III clinical trials in CD. As such it would be considered exploratory in nature. Moreover, as it is not used in clinical studies, there is no standardised definition. As the perception of relapse is inherently subjective, influenced by both symptomatic assessments and clinical biomarkers, it is not an outcome considered in the GALAXI or GRAVITI clinical programmes or that of the comparators. Thus, relapse is inferred from patients who are not in clinical remission. However, as relapse is not defined or used standardly, interpretation could lead to inconsistencies in clinical assessment and reporting.

b) Achieving clinical remission is the primary objective of therapies for patients with Crohn's disease. While relapse rates are not often captured or considered an exploratory endpoint, the absence of a uniform definition presents challenges when evaluating the data associated. In the GALAXI and GRAVITI trials, as well as the comparator trials, data on relapse rates were not collected. Therefore, it is not feasible to perform NMAs concerning relapse rates.

It is important to note that the efficacy NMAs presented in the company submission (clinical remission, clinical response and endoscopic response) are frequently reported outcomes in clinical trials and align with NICE and BSG guidelines.

A 6. Priority question. The intervention is described in the DP in section B.1.1.2, document B 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. However, the trial evidence is subdivided by induction therapy with GALAXI-2/-3 using the 200mg IV dose and GRAVITI using the 400 mg SC dose, and only the former trials were included in the network meta-analysis (NMA).

a) Please explain how patients will be chosen in clinical practice to receive each of the dosing regimens. Specifically,

i. Are there distinct subgroups where one would get the IV and the other the SC induction regimen?

ii. Might there be sequential treatment such that a different regimen is given on failure of the first?

b) **If dosing in clinical practice is different to that observed in the trials, then please present evidence to demonstrate the effectiveness and safety of guselkumab at dosages used in clinical practice.**

c) **Please explain why GRAVITI was not included in the NMA to inform the effectiveness of the 400 mg SC dose.**

d) **Please include GRAVITI in the NMA to demonstrate the relative effectiveness of the 400 mg SC dose to that of the comparators.**

Company response:

ai) There are no distinct subgroups that necessitate one mode of administration over the other for guselkumab induction therapy. The purpose of offering both intravenous (IV) and subcutaneous (SC) administration during the induction phase is to provide flexibility for all patients. In clinical practice, healthcare professionals and patients can collaboratively determine which induction regimen is most appropriate based on individual needs and preferences. Additionally, the option of SC administration in the induction phase has the potential to alleviate some of the burden on the NHS by reducing waiting times linked to infusion clinic capacity and supports patients who encounter challenges attending the hospital for treatment infusions.

aii) The anticipated marketing authorisation for guselkumab induction does not consider sequential treatment between the IV and SC formulations; a binary decision is made at the onset of induction, where patients either receive guselkumab via IV or SC administration. Re-induction through either administration route was not explored in the GALAXI and GRAVITI trials. Therefore, in the absence of empirical evidence, it is not anticipated that re-induction or sequential treatment using either mode of administration would be practiced.

b) In clinical practice, the dosing schedule for guselkumab will be based on the recommendations outlined in the posology of the draft SmPC and the anticipated marketing authorisation. These recommendations are based on robust clinical data derived from the GALAXI and GRAVITI trials which were designed to assess the efficacy and safety of guselkumab in patients with moderately to severely active CD.

Consequently, any dosing regimens outside of the draft SmPC would be considered off-label.

c) GRAVITI was not included in the NMA at the time of the company submission as this was not identified by the SLR conducted at the time the search was performed. As a result of the TLR that was conducted as part of the response to question A1, the efficacy NMAs included in the submission (clinical response, clinical remission and endoscopic healing) have been updated to incorporate the GRAVITI trial. The outcomes from the NMAs are presented below in response to question part d.

d) Clinical remission, clinical response and endoscopic response induction NMAs have been conducted which include the guselkumab 400mg SC dose from the GRAVITI trial. The network for the clinical response and clinical remission NMAs are presented in Figure 1, the endoscopic response network presented in Figure 2 and Table 9 outlines the inputs used from the GRAVITI trial. Both random effect and fixed effect NMAs were conducted. The outcomes are presented as forest plots in the figures below. Similar to the discussions in Document B, Section 3.8, the random effects models were preferred a priori given differences in trial designs.

Figure 1: NMA network for clinical remission and response endpoints at induction, including GRAVITI

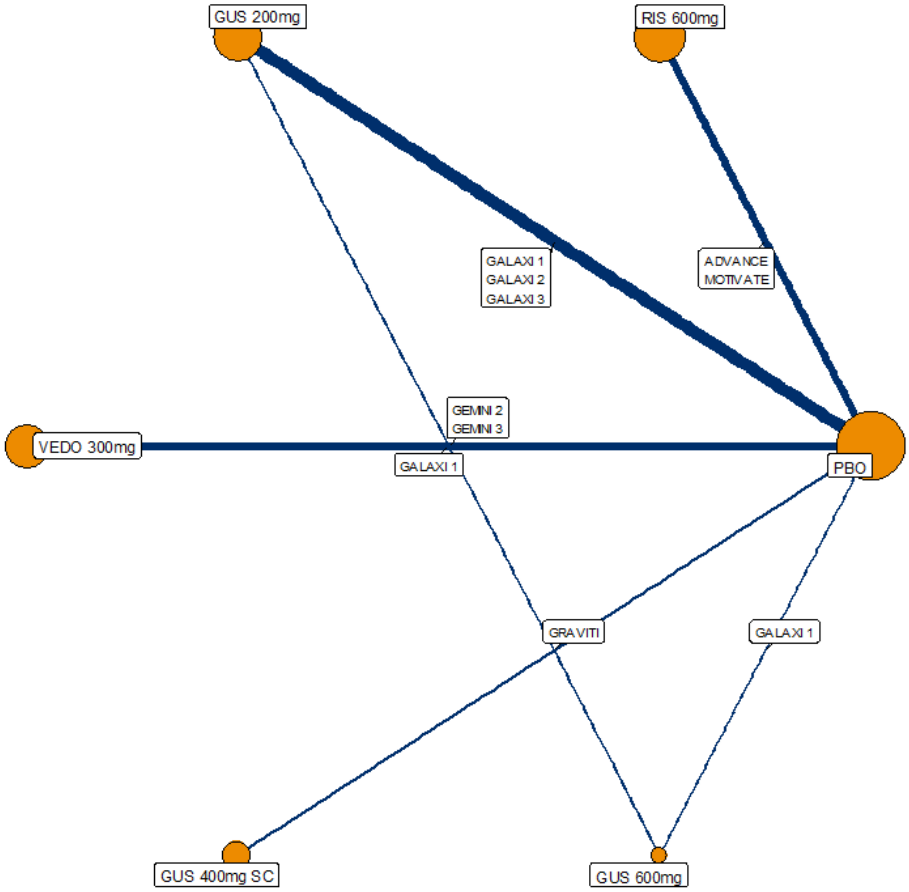


Figure 2: NMA network for the endoscopic response endpoints at induction, including GRAVITI

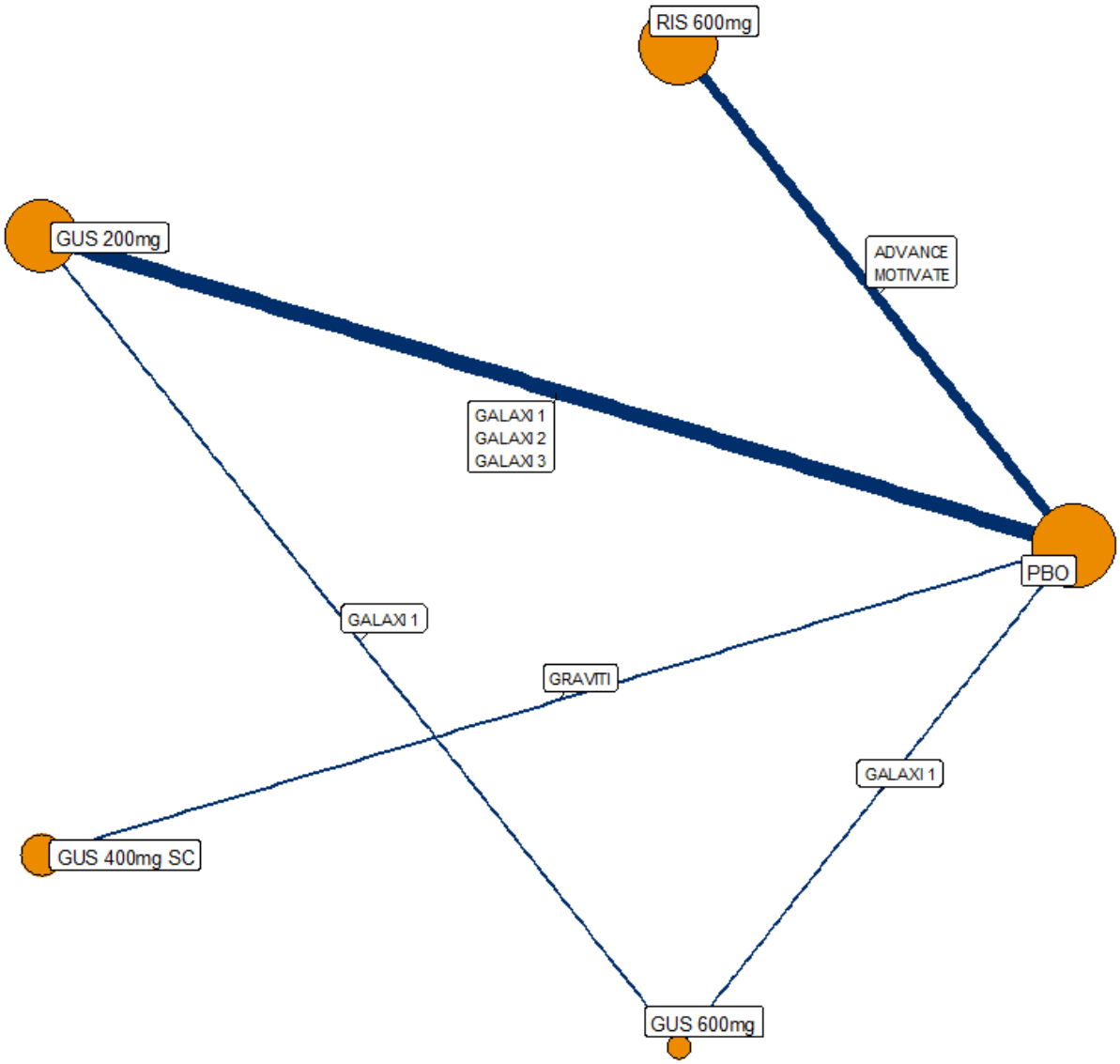


Table 9: GRAVITI data included in the induction NMAs

Trial	Arm	Outcome	Data for Induction NMA	Source
GRAVITI	PBO	Clinical response	15 / 53 = 28.3%	GRAVITI CSR, Table 15
GRAVITI	GUS 400mg SC	Clinical response	84 / 108 = 77.8%	GRAVITI CSR, Table 15
GRAVITI	PBO	Clinical remission	9 / 53 = 17.0%	GRAVITI CSR, Table 11
GRAVITI	GUS 400mg SC	Clinical remission	65 / 108 = 60.2%	GRAVITI CSR, Table 11
GRAVITI	PBO	Endoscopic response	6 / 53 = 11.3%	GRAVITI CSR, Table 19
GRAVITI	GUS 400mg SC	Endoscopic response	30 / 108 = 27.8%	GRAVITI CSR, Table 19

Induction NMAs- random effects

Overall, the outcomes from the NMAs show that guselkumab 400mg SC demonstrates comparable efficacy to vedolizumab and risankizumab for the clinical response, clinical remission and endoscopic response endpoints.

Figure 3: Forest plot for random-effects NMA of clinical response in the induction phase, BIO-failure population, including guselkumab 400mg SC from the GRAVITI trial

Figure 4: Forest plot for random-effects NMA of clinical remission in the induction phase, BIO-failure population, including guselkumab 400mg SC from the GRAVITI trial

Figure 5: Forest plot for random-effects NMA of endoscopic response in the induction phase, BIO-failure population, including guselkumab 400mg SC from the GRAVITI trial

Induction NMAs- fixed effects

Similar to the conclusions of the random effects NMAs, the outcomes from the fixed effect NMAs show that guselkumab 400mg SC demonstrates comparable efficacy to vedolizumab and risankizumab for the clinical response, clinical remission and endoscopic response endpoints.

Figure 6: Forest plot for fixed-effects NMA of clinical response in the induction phase, BIO-failure population, including guselkumab 400mg SC from the GRAVITI trial

Figure 7: Forest plot for fixed-effects NMA of clinical remission in the induction phase, BIO-failure population, including guselkumab 400mg SC from the GRAVITI trial

Figure 8: Forest plot for fixed-effects NMA of endoscopic response in the induction phase, BIO-failure population, including guselkumab 400mg SC from the GRAVITI trial

Systematic review

A 7. Section D.1.5 of appendix D states that *"Trial selection was conducted by duplicate reviewers who independently reviewed the citation titles and abstracts*". Please explain what this means, and how many reviewers performed title and abstract screening. Please also explain the same for full text screening.

Company response: Two researchers independently reviewed all citations retrieved from electronic database searches of EMBASE, MEDLINE® (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®), and Cochrane Central. In the first stage of selection, the two researchers reviewed citation titles and abstracts, and they excluded citations which were ineligible per the predefined eligibility criteria. Any discrepancies between the two reviewers were resolved by consensus or were resolved by a third independent reviewer. For citations which were not excluded in the first stage, full-text versions were retrieved (in this review, there were no full-text versions that could not be found). In the second stage of selection, the same process was used by researchers to determine eligibility of full-text versions.

A 8. Table 4 in Appendix D (PICOS criteria) indicates that non-English language publications without an English abstract were excluded from the systematic literature review (SLR).

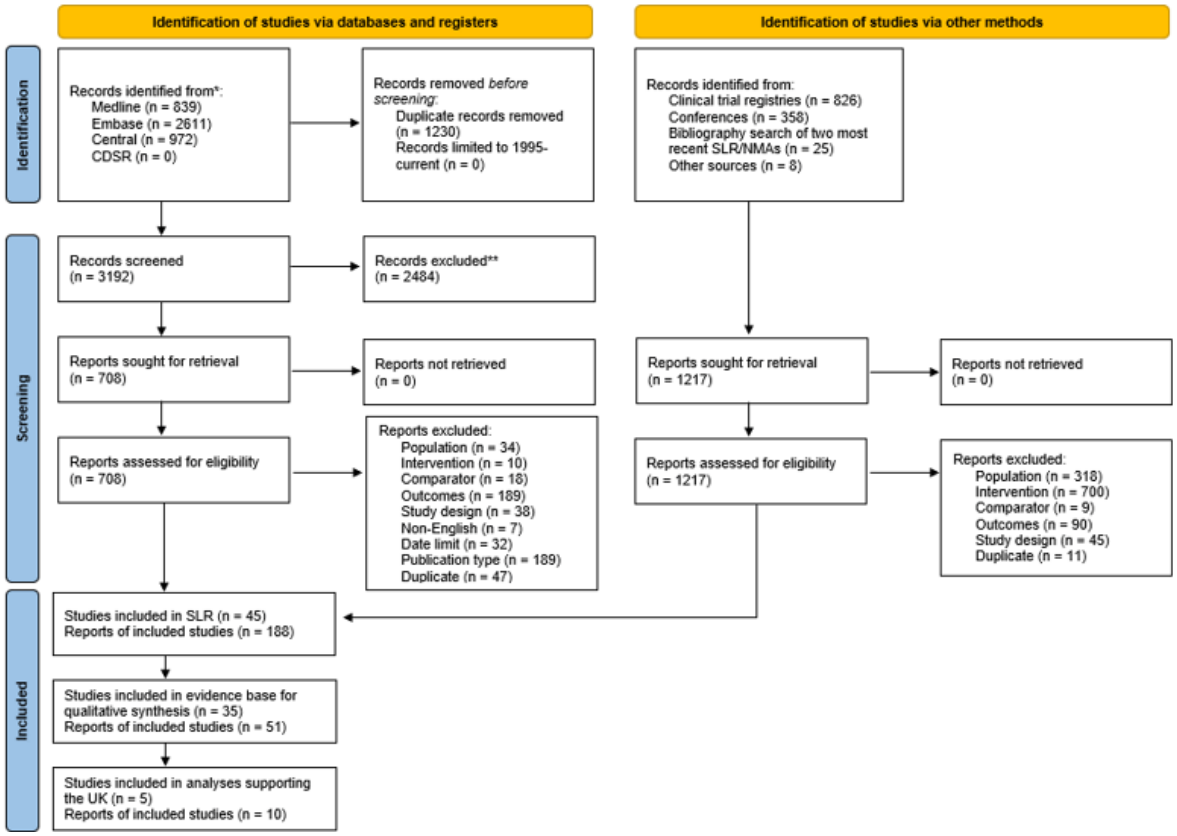
a) Please provide the number of relevant studies omitted from the SLR because of being published in non-English language without an English abstract.

b) Please clarify the impact of excluding studies published in non-English language without an English abstract on the estimates in the submission.

Company response:

a) Seven publications were excluded due to being non-English at the second screening stage, per the PRISMA flow diagram presented in Figure 9. To note, two records were also excluded in the first screening stage, (annotated in the diagram as (**)) due to publications being non-English, though these were not specifically labelled in the diagram due to volume of records excluded at that stage (n = 2,484).

Figure 9: PRISMA flow diagram from the original SLR



b) It should be noted that the searches conducted did not restrict based on abstract or publication language, and that all items retrieved from the database searching were reviewed. This was done to ensure that any potential mislabelling of publication language would not threaten the accuracy of applying our eligibility criteria. If a citation's abstract was not written in English, then it was further verified that an English-language full-text was unavailable before excluding.

The exclusion of non-English publications from our SLR is unlikely to impact the evidence networks pertaining to NMAs included in this submission. The population of interest includes UK patients, and we expect that publications written in languages other than English would primarily report data for patients with CD from single countries other than UK or North America.

Indirect treatment comparison (ITC)

A 9. Priority question. Given differences in trial design (e.g., treat-through vs. re-randomised maintenance), the company stated in D.1.8.3 and D.1.9.2.2 of Appendix D (also referred to in section B.3.8.5 of document B) that they performed a process referred to as 'normalisation', referring to NICE TA633. However, there is a lack of clarity in the details of the methodology, calculations, and data sources presented in the SLR report and appendices (referred to in the CS as Johnson & Johnson. [Data on file] Efficacy of guselkumab versus available biologic therapies for the maintenance treatment of moderate to severe Crohn's disease: A systematic review and meta-analysis. RF-XX2025). This is partly because the calculations are only shown in the data tables in Appendix L with references to other tables or trial names with no references.(5) Also, only one comparator trial is included in both the induction and maintenance phase networks i.e. GEMINI 2. GEMINI 3, ADVANCE and MOTIVATE are only in the induction NMA, and FORTIFY is only in the maintenance NMA.

a) **Please clarify that re-randomisation only affects the validity of outcomes at maintenance, and not those for induction up to the point of re-randomisation.**

b) **Please clarify that, although the company refers to ADVANCE and MOTIVATE as re-randomisation trials, given that they only report outcomes for the induction phase, they are not actually re-randomisation trials, and that the only trials that are re-randomisation trials are GEMINI 2 and FORTIFY.**

c) **Please conduct the induction NMA using only outcome data from the follow-up period immediately prior to re-randomisation.**

d) **Please provide a full exposition of the process of normalisation with calculations, which is presented outside of the data tables and includes references to all data sources.**

e) **Please provide all data sources used for normalisation.**

f) **Please provide an estimate of the risk and size of any residual bias following normalisation, making specific reference to the possibility of equivalence between guselkumab, and risankizumab and vedolizumab.**

Company response:

a) Johnson & Johnson confirm that re-randomisation affects the validity of outcomes during the maintenance phase only. This is because the data used for the induction NMAs are derived from outcomes reported at the end of the induction phase, prior to any re-randomisation conducted in the trials.

b) Johnson & Johnson would like to apologise for the mislabel of the ADVANCE and MOTIVATE trials as re-randomised trials and confirm that ADVANCE and MOTIVATE are induction-only trials.

c) Johnson & Johnson confirm that the induction NMA included in the original company submission fulfilled the criteria of using end-of-induction timepoints prior to re-randomisation. Therefore, a re-run of the NMA, as requested, is not necessary as it would yield identical results to those already provided.

d) A comprehensive description of the normalisation process alongside the 1-year NMA data and sources are presented below.

Trials in the CD setting have different designs that can lead to different populations by the end of maintenance evaluation. When indirectly comparing the efficacy of treatments across trials, such as in an NMA, these differences must be addressed to avoid bias (else, the estimated relative treatment effects could be reflecting the

differences in design rather than differences in efficacy of the treatments themselves). The largest difference is due to some trials being treat-through in nature (where patients are randomised into a treatment sequence at the beginning of induction and do not switch from that treatment sequence through till the end of maintenance evaluation) and some trials being re-randomised (where patients are initially randomised to an induction treatment, however, only patients who responded to that induction therapy go on to receive maintenance therapy).

A major disadvantage of the re-randomised trial is that end-of-maintenance results are only available for the induction responder population, which might differ greatly to the full population of induction responders plus induction non-responders (i.e., all patients, regardless of induction response) that are assessed in the treat-through design.

To address these differences, all trial data was normalised to reflect a standard treat-through design, where end-of-maintenance outcomes for each arm in each trial would reflect what would be expected if patients continued from induction through to the end of maintenance, on the planned treatment sequence, regardless of whether they responded at induction. We achieved this via imputation of maintenance outcomes among induction non-responders who were not reported in certain re-randomised trials (FORTIFY) or response-conditional placebo arms (those of GALAXI 1, 2, and 3); imputing from GEMINI 2, for which this was reported. Additionally, for re-randomised trials, the sample size needed to be imputed for each treatment arm as if they were designed as a treat-through trial (based on the induction sample size and the proportion re-randomised to each maintenance arm). Finally, in some cases, mixed population data was converted to bio-failure subgroup data when only mixed population data was available.

This normalisation approach was considered a great improvement over ignoring the trial design differences and the corresponding population differences. The data used for the 1-year NMAs have been reproduced with clearer sourcing and descriptions. These include all data used in the NMAs with sources indicating how the data was derived, whether it was as reported, imputed from another trial, converted from

mixed population data, or re-calculated (in the case of sample sizes for re-randomized trials). These are presented in Table 10, Table 11 and Table 12 for the clinical response, clinical remission and endoscopic response endpoints, respectively. To note, without delayed responder data has been highlighted in orange in the tables below to provide clarity on the calculations.

In summary, GEMINI 2 provided the only reliable source of maintenance outcome data among induction non-responders for a placebo arm, and this data was used to impute the data gaps in the FORTIFY and GALAXI trials. FORTIFY and GEMINI were the re-randomised trials and required sample size re-calculations. GEMINI 2 reported maintenance outcomes among induction non-responders directly, while FORTIFY reported maintenance outcomes among delayed responders through Week 24 and this was leveraged. GALAXI 1, 2, and 3 were treat-through trials and data was largely reported in the required format for 1-year NMAs both with and without delayed responders in the CSR or available through individual patient-level data (IPD).

Table 10: Calculations for 1-year NMA with and without delayed responders, clinical response

	Induction			Maintenance			1-year NMA			
Treatment arm	Induction responders (%) (A)	Induction non-responders (%) (B)	Delayed responders (%) (B2)	Maintenance clinical response in Induction responders (%) (C)	Maintenance clinical response in Induction non-responders (%) (D)	Maintenance clinical response in Delayed responders (%) (D2)	Without delayed responders 1 year % in Induction Responders (%) (A x C)	With delayed responders 1 year % in All Patients (%) (A x C) + (B x D), or (A x C) + (B x B2 x D2)	n*	N
FORTIFY										
Placebo	40.2[a]	59.8	-	31.2[c]	4.3[e]	-	12.5	15.1	43	284[g]
RIS 180 mg SC Q8W	61.9[a]	38.1	75.7[b]	63.8[c]	-	50.9[f]	39.5	54.2	70	129.0[g]
RIS 360 mg SC Q8W	61.9[a]	38.1	75.0[b]	58.7[d]	-	69.6[f]	36.3	56.2	65	116.5[g]
GALAXI 1										
Placebo	20.0[h]	80.0[h]	-	50.0[h]	4.3[e]	-	10.0	13.4	4	30
GUS 100mg Q8W	-	-	-	-	-	-	53.1[h]	68.8[h]	22	32
GUS 200mg Q4W	-	-	-	-	-	-	57.1[h]	77.1[h]	27	35
GALAXI 2										
Placebo	30.8[h]	69.2[h]	-	50.0[h]	4.3[e]	-	15.4	18.4	7	39
GUS 100mg Q8W	-	-	-	-	-	-	45.5[h]	64.9[h]	50	77
GUS 200mg Q4W	-	-	-	-	-	-	53.4[h]	68.5[h]	50	73
GALAXI 3										
Placebo	15.4[h]	84.6[h]	-	83.3[h]	4.3[e]	-	12.8	16.5	6	39
GUS 100mg Q8W	-	-	-	-	-	-	55.3[h]	71.1[h]	54	76
GUS 200mg Q4W	-	-	-	-	-	-	48.6[h]	68.9[h]	51	74
GEMINI 2										
Placebo	28.6[i]	71.4	-	42.0[j]	4.3[k]	-	12.0	15.1	11	70[l]
VEDO 300mg Q8W	35.2[i]	64.8	-	29.3[i]	16.6[k]	-	10.3	21.1	8	36[l]

* n was calculated from unrounded values and used for NMA. Orange values were directly imputed from other trials.
FORTIFY – see details in later tables dedicated to FORTIFY:
[a] Source: Values reported in Figure in D'Haens et al., 2022 (6): P544 Patients with moderate to severe Crohn's disease with and without prior biologic failure demonstrated improved clinical outcomes with risankizumab: Results from phase 3 induction and maintenance trials, Journal of Crohn's and Colitis, Volume 16, Issue Supplement_1, January 2022, Page i491, https://doi.org/10.1093/ecco-jcc/jjab232.671
[b] Source: Values converted from mixed population reported in Table 30 from Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022).
[c] Source: Values converted from mixed population reported Figure in Atreya et al., 2023 (7): P548 Efficacy outcomes of placebo maintenance treatment in patients with moderate to severe Crohn's disease who responded to placebo induction therapy: Post-hoc analysis of the Phase 3 ADVANCE, MOTIVATE, and FORTIFY Risankizumab Studies, Journal of Crohn's and Colitis, Volume 17, Issue Supplement_1, February 2023, Pages i675–i677
[d] Source: Value reported in Figure by D'Haens et al., 2022 (6): P544 Patients with moderate to severe Crohn's disease with and without prior biologic failure demonstrated improved clinical outcomes with risankizumab: Results from phase 3 induction and maintenance trials, Journal of Crohn's and Colitis, Volume 16, Issue Supplement_1, January 2022, Page i491, https://doi.org/10.1093/ecco-jcc/jjab232.671
[e] Source: Value imputed from GEMINI 2 (8).
[f] Source: Values converted from mixed population reported in Table 1 from Ferrante et al., 2022 (9): S715 Clinical and Endoscopic Improvements With Risankizumab Induction and Maintenance Dosing versus Placebo Are Observed Irrespective of Number of Prior Failed Biologics. American Journal of Gastroenterology. 117. e498-e499. 10.14309/01.ajg.0000859500.54469.44.
[g] Source: Values re-calculated by sample sizes in re-randomised FORTIFY. (10)
GALAXI 1, 2, 3:
[h] Source: Values reported in GALAXI 1, 2, 3 CSR tables or obtained from IPD; 1-year NMA with delayed responders data were reported for active arms directly in CSR and from IPD.
GEMINI 2 – see details in later tables dedicated to GEMINI 2:
[i] Source: Values reported in Supplementary Table 2 of Sands et al., 2017 (11): Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naïve to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy. Inflamm Bowel Dis. 2017 Jan;23(1):97-106. doi: 10.1097/MIB.0000000000000979.
[j] Source: Value imputed using GALAXI-2/3 and IM-UNITI IPD.
[k] Source: Value converted from mixed population reported in Table 4-36 of the German benefit assessment dossier for Vedolizumab, published 2014 Oct 10.
[l] Source: Values re-calculated by sample sizes in re-randomised GEMINI 2.(8)

Table 11: Calculations for 1-year NMA with and without delayed responders, clinical remission

	Induction			Maintenance			1-year NMA			
Treatment arm	Induction responders (%) (A)	Induction non-responders (%) (B)	Delayed responders (%) (B2)	Maintenance clinical remission in Induction responders (%) (C)	Maintenance clinical remission in Induction non-responders (%) (D)	Maintenance clinical remission in Delayed responders (%) (D2)	Without delayed responders 1 year % in Induction Responders (%) (A x C)	With delayed responders 1 year % in All Patients (%) (A x C) + (B x D), or (A x C) + (B x B2 x D2)	n*	N
FORTIFY										
Placebo	40.2[a]	59.8	-	18.3[c]	4.3[e]	-	7.3	9.9	28	284[g]
RIS 180 mg SC Q8W	61.9[a]	38.1	75.7[b]	48.7[d]	-	49.0[f]	30.1	44.3	57	129.0[g]
RIS 360 mg SC Q8W	61.9[a]	38.1	75.0[b]	48.0[d]	-	61.2[f]	29.7	47.2	55	116.5[g]
GALAXI 1										
Placebo	20.0[h]	80.0[h]	-	50.0[h]	4.3[a]	-	10.0	13.4	4	30
GUS 100mg Q8W	-	-	-	-	-	-	46.9[h]	59.4[h]	19	32
GUS 200mg Q4W	-	-	-	-	-	-	51.4[h]	62.9[h]	22	35
GALAXI 2										
Placebo	30.8[h]	69.2[h]	-	50.0[h]	4.3[a]	-	12.8	15.8	6	39
GUS 100mg Q8W	-	-	-	-	-	-	39.0[h]	54.5[h]	42	77
GUS 200mg Q4W	-	-	-	-	-	-	52.1[h]	64.4[h]	47	73
GALAXI 3										
Placebo	15.4[h]	84.6[h]	-	83.3[h]	4.3[a]	-	12.8	16.5	6	39
GUS 100mg Q8W	-	-	-	-	-	-	52.6[h]	67.1[h]	51	76
GUS 200mg Q4W	-	-	-	-	-	-	47.3[h]	63.5[h]	47	74
GEMINI 2										
Placebo	28.6[i]	71.4	-	37.8[j]	4.3[k]	-	10.8	13.9	10	70[l]
VEDO 300mg Q8W	35.2[i]	64.8	-	28.0[i]	12.3[k]	-	9.9	17.9	6	36[l]

Legend: '-' means not required for calculation. Orange values were directly imputed from other trials.
FORTIFY – see details in later tables dedicated to FORTIFY:

[a] Source: Values reported in Figure by D'Haens et al., 2022 (6): P544 Patients with moderate to severe Crohn's disease with and without prior biologic failure demonstrated improved clinical outcomes with risankizumab: Results from phase 3 induction and maintenance trials, Journal of Crohn's and Colitis, Volume 16, Issue Supplement_1, January 2022, Page i491, https://doi.org/10.1093/ecco-jcc/jjab232.671.
[b] Source: Values converted from mixed population in Table 30 from Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022).
[c] Source: Value converted from mixed population in a Figure from Atreya et al., 2023(7): P548 Efficacy outcomes of placebo maintenance treatment in patients with moderate to severe Crohn's disease who responded to placebo induction therapy: Post-hoc analysis of the Phase 3 ADVANCE, MOTIVATE, and FORTIFY Risankizumab Studies, Journal of Crohn's and Colitis, Volume 17, Issue Supplement_1, February 2023, Pages i675–i677, https://doi.org/10.1093/ecco-jcc/jjac190.0678.
[d] Source: Values reported in Table 46 from Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022)
[e] Source: Value imputed from GEMINI 2.(8)
[f] Source: Values converted from mixed population in Table 1 from Ferrante et al., 2022 (9): S715 Clinical and Endoscopic Improvements With Risankizumab Induction and Maintenance Dosing versus Placebo Are Observed Irrespective of Number of Prior Failed Biologics. American Journal of Gastroenterology. 117. e498-e499. 10.14309/01.ajg.0000859500.54469.44.
[g] Source: Values re-calculated by sample sizes in re-randomised FORTIFY.(10)
GALAXI 1, 2, 3:
[h] Source: Values reported in GALAXI 1, 2, 3 CSR tables or obtained from IPD; 1-year NMA with delayed responders data were reported for active arms directly in CSR and from IPD.
GEMINI 2 – see details in later tables dedicated to GEMINI 2:(8)
[i] Source: Values reported in Supplementary Table 2 of Sands et al., 2017: Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naïve to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy. Inflamm Bowel Dis. 2017 Jan;23(1):97-106. doi: 10.1097/MIB.0000000000000979.
[j] Source: Value imputed using GALAXI-2/3 and IM-UNITI IPD.
[k] Source: Value converted from mixed population reported in Table 4-36 of the German benefit assessment dossier for Vedolizumab, published 2014 Oct 10.
[l] Source: Values re-calculated by sample sizes in re-randomized GEMINI 2.

Table 12: Calculations for 1-year NMA with and without delayed responders, endoscopic response

	Induction			Maintenance			1-year NMA			
Treatment arm	Induction responders (%) (A)	Induction non-responders (%) (B)	Delayed responders (%) (B2)	Maintenance Endoscopic response in Induction responders (%) (C)	Maintenance Endoscopic response in Induction non-responders (%) (D)	Maintenance Endoscopic response in Delayed responders (%) (D2)	Without delayed responders 1 year % in Induction Responders (%) (A x C)	With delayed responders 1 year % in All Patients (%) (A x C) + (B x D), or (A x C) + (B x B2 x D2)	n*	N
FORTIFY										
Placebo	40.2[a]	59.8	-	13.3[c]	2.4[e]	-	5.3	6.8	19	284[g]
RIS 180 mg SC Q8W	61.9[a]	38.1	75.7[b]	40.7[d]	-	34.6[f]	25.2	35.2	45	129.0[g]
RIS 360 mg SC Q8W	61.9[a]	38.1	75.0[b]	44.1[d]	-	42.9[f]	27.3	39.6	46	116.5[g]
GALAXI 1										
Placebo	20.0[h]	80.0[h]	-	0[h]	2.4[e]	-	0	1.9	1	30
GUS 100mg Q8W	-	-	-	-	-	-	34.4[h]	40.6[h]	13	32
GUS 200mg Q4W	-	-	-	-	-	-	31.4[h]	42.9[h]	15	35
GALAXI 2										
Placebo	30.8[h]	69.2[h]	-	16.7[h]	2.4[e]	-	5.1	6.8	3	39
GUS 100mg Q8W	-	-	-	-	-	-	36.4[h]	44.2[h]	34	77
GUS 200mg Q4W	-	-	-	-	-	-	26.0[h]	45.2[h]	33	73
GALAXI 3										
Placebo	15.4[h]	84.6[h]	-	33.3[h]	2.4[e]	-	5.1	7.2	3	39
GUS 100mg Q8W	-	-	-	-	-	-	35.5[h]	42.1[h]	32	76
GUS 200mg Q4W	-	-	-	-	-	-	36.5[h]	48.6[h]	36	74

* n was calculated from unrounded values and used for NMA. Orange values were directly imputed from other trials.
FORTIFY – see details in later tables dedicated to FORTIFY::
[a] Source: Values reported in Figure by D'Haens et al., 2022 (6): P544 Patients with moderate to severe Crohn's disease with and without prior biologic failure demonstrated improved clinical outcomes with risankizumab: Results from phase 3 induction and maintenance trials, Journal of Crohn's and Colitis, Volume 16, Issue Supplement_1, January 2022, Page i491, https://doi.org/10.1093/ecco-jcc/jjab232.671

[b] Source: Values converted from mixed population reported in Table 30 from Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022).
[c] Source: Values converted from mixed population reported in a Figure from Atreya et al., 2023(7): P548 Efficacy outcomes of placebo maintenance treatment in patients with moderate to severe Crohn's disease who responded to placebo induction therapy: Post-hoc analysis of the Phase 3 ADVANCE, MOTIVATE, and FORTIFY Risankizumab Studies, Journal of Crohn's and Colitis, Volume 17, Issue Supplement_1, February 2023, Pages i675–i677, https://doi.org/10.1093/ecco-jcc/jjac190.0678.
[d] Source: Values reported in Table 46 from Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022)
[e] Source: Value imputed from GEMINI 2.(8)
[f] Source: Values converted from mixed population reported in Table 1 from Ferrante et al., 2022 (9): S715 Clinical and Endoscopic Improvements With Risankizumab Induction and Maintenance Dosing versus Placebo Are Observed Irrespective of Number of Prior Failed Biologics. American Journal of Gastroenterology. 117. e498-e499. 10.14309/01.ajg.0000859500.54469.44.
[g] Source: Values re-calculated by sample sizes in re-randomized FORTIFY.(10)
GALAXI 1, 2, 3:
[h] Source: Values reported in GALAXI 1, 2, 3 CSR tables or obtained from IPD; 1-year NMA with delayed responders data were reported for active arms directly in CSR and from IPD.

Approach to calculations for re-randomized trials FORTIFY and GEMINI 2:

As noted in the footnotes of the above tables, certain values for FORTIFY and GEMINI 2 depended on converting data from a reported mixed population to what would have been expected to be reported for the bio-failure population. The approach to converting from the mixed populations is described below.

We start with the following relationship between probabilities in mixed and subgroup populations:

$$P(out|mixed) = P(out|biofail) * P(biofail) + P(out|confail) * P(confail)$$

where:

- $P(out|mixed)$ is the probability of an outcome in the mixed population
- $P(out|biofail)$ is the probability of an outcome in the bio-failure population
- $P(out|confail)$ is the probability of an outcome in the con-failure population
- $P(biofail)$ is the probability of being in the bio-failure population
- $P(confail)$ is the probability of being in the con-failure population
- … and $P(biofail) + P(confail) = P(mixed) = 1$

We then solve for $P(out|biofail)$ as follows:

$$P(out|biofail) = \frac{P(out|mixed)}{P(biofail) + \frac{P(confail)}{RR}}$$

where $RR = \frac{P(out|biofail)}{P(out|confail)}$ is the relative risk of an outcome in the bio-failure versus con-failure population that must be estimated as $\widehat{RR} = \frac{\hat{P}(out|biofail)}{\hat{P}(out|confail)}$ from an alternative source, since we don't have these quantities for the trial and population of interest. These RRs and sources are provided in the tables below.

Additionally, since FORTIFY and GEMINI 2 are re-randomised trials, the sample size for treatment arms converted to treat-through design requires estimation based on proportions of patients re-randomised into maintenance arms. These re-calculated Ns are already presented below.

1-year NMA calculations for FORTIFY:

Re-calculation of sample size:

Table 13: Re-calculation of ITT sample size for FORTIFY

Treatment Sequence	Population	Induction ITT N[a]	Maintenance N (re-randomized induction responders)[b]	% maintenance N of the total re-randomized	Re-calculated ITT N for treatment sequence
Risankizumab 600 mg IV to placebo	Bio-failure	386	123	NA	NA
Risankizumab 600 mg IV to Risankizumab 180 mg SC Q8W	Bio-failure		113	113 / 338 = 33.4%	33.4% X 386 = 129.0
Risankizumab 600 mg IV to Risankizumab 360 mg SC Q8W	Bio-failure		102	102 / 338 = 30.2%	30.2% X 386 = 116.5
Total	Bio-failure		338	NA	NA

*Intermediate values rounded for display but only final values rounded in calculation or re-calculated ITT N
Sources: [a] Table 1 (ADVANCE 1 MOTIVATE, Week 12) – 945-Ferrante-2022; [b] Table 46 - Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022)

Conversion of mixed to subgroup data

Several RRs were estimated from different populations or outcomes to be used in the conversion from mixed formula described above. A RR between bio-failure and con-failure subgroups was estimated for the clinical response at the end of induction, and RRs were estimated for each of clinical response, remission, and endoscopic response from FORTIFY's induction responder population.

Table 14: RR for converting mixed to subgroup data for FORTIFY

Population	Treatment	Response	Remission	Endoscopic Response	Description
Bio-failure	Risankizumab 600 mg IV	58.9%[a]	-	-	Pooled MOTIVATE and ADVANCE Induction
Con-failure	Risankizumab 600 mg IV	61.8%[a]	-	-	
RR	-	0.95	-	-	
Bio-failure	Risankizumab 360 mg SC Q8W	58.7%[b]	48.0%[c]	44.1%[c]	FORTIFY maintenance outcomes among induction responders
Con-failure	Risankizumab 360 mg SC Q8W	69.2%[b]	64.1%[c]	53.8%[c]	
RR	-	0.85	0.75	0.82	

[a] Source: Table 46 – Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022). [b] Source: Figure (FORTIFY): FORTIFY poster by SG. [c] Source: Figure from Atreya et al., 2023. P548 https://doi.org/10.1093/ecco-jcc/jjac190.0678.

Table 15: Conversion of mixed to subgroup for FORTIFY

Treatment	Population	Outcome	N	% split	Outcome in mixed population (%)	Outcome in subgroup (%)
Risankizumab 180 mg SC Q8W	Bio-failure	Delayed induction response	22	74.3	76.7[a]	75.7
Risankizumab 180 mg SC Q8W	Con-failure	Delayed induction response	8	25.7		79.4
Risankizumab 360 mg SC Q8W	Bio-failure	Delayed induction response	22	74.3	75.9[a]	75.0
Risankizumab 360 mg SC Q8W	Con-failure	Delayed induction response	7	25.7		78.6
Placebo	Bio-failure	Clinical response at maintenance in placebo responders who continued on placebo	76	72.6	32.7[b]	31.2
Placebo	Con-failure	Clinical response at maintenance in placebo responders who continued on placebo	29	27.4		36.7

Risankizumab 180 mg SC Q8W	Bio-failure	Clinical response at maintenance in induction responders	239	72.6	66.9[b]	63.8
Risankizumab 180 mg SC Q8W	Con-failure	Clinical response at maintenance in induction responders	90	27.4		75.2
Risankizumab 180 mg SC Q8W	Bio-failure	Clinical response at maintenance in delayed responders	22	73.4	53.3[c]	50.9
Risankizumab 180 mg SC Q8W	Con-failure	Clinical response at maintenance in delayed responders	8	26.6		60.0
Risankizumab 360 mg SC Q8W	Bio-failure	Clinical response at maintenance in delayed responders	24	73.4	75.8[c]	69.6
Risankizumab 360 mg SC Q8W	Con-failure	Clinical response at maintenance in delayed responders	9	26.6		92.8
Risankizumab 180 mg SC Q8W	Bio-failure	Clinical remission at maintenance in delayed induction responders	22	73.4	53.3[c]	49.0
Risankizumab 180 mg SC Q8W	Con-failure	Clinical remission at maintenance in delayed induction responders	8	26.6		65.3
Risankizumab 360 mg SC Q8W	Bio-failure	Clinical remission at maintenance in delayed induction responders	24	73.4	66.7[c]	61.2
Risankizumab 360 mg SC Q8W	Con-failure	Clinical remission at maintenance in delayed induction responders	9	26.6		81.7
Risankizumab 180 mg SC Q8W	Bio-failure	Endoscopic response at maintenance	22	73.4	36.7[c]	34.6

		in delayed induction responders				
Risankizumab 180 mg SC Q8W	Con-failure	Endoscopic response at maintenance in delayed induction responders	8	26.6		42.3
Risankizumab 360 mg SC Q8W	Bio-failure	Endoscopic response at maintenance in delayed induction responders	24	73.4	45.5[c]	42.9
Risankizumab 360 mg SC Q8W	Con-failure	Endoscopic response at maintenance in delayed induction responders	9	26.6		52.4
Values in orange have been imputed Sources: [a] Table 30 - Skyrizi Risankizumab CHMP assessment report on group of extensions of marketing authorisation (2022); [b] CD - FORTIFY - P548_ECCO2023; [c] Table 1 - 945-Ferrante-2022						

Calculations for GEMINI 2:

Re-calculation of sample size:

Table 16: Re-calculation of ITT sample size for GEMINI 2

Treatment Sequence	Population	Induction ITT N	Maintenance N (re-randomized induction responders)[b]	% maintenance N of the total re-randomized	Re-calculated ITT N for treatment sequence
Vedolizumab 300 – Placebo	Bio-failure	105[a]	70[a]	NA	NA
Vedolizumab 300 – Vedolizumab 300 Q8W	Bio-failure		36[a]	36 / 106 = 34.0%	34.0% X 105 = 35.7
Total	Bio-failure		106	NA	NA
Vedolizumab 300 – Placebo	Con-failure	115[a,b]	78[a,b]	NA	NA
Vedolizumab 300 – Vedolizumab 300 Q8W	Con-failure		37[a,b]	37 / 115 = 32.2%	32.2% X 115 = 37.0
Total	Con-failure		115	NA	NA
*Intermediate values rounded for display but only final values rounded in calculation or re-calculated ITT N Sources: [a] 2509-Sands-2017; [b] 3371-Sandborn-2013					

Conversion of mixed to subgroup data

Table 17: RR for conversion of mixed to subgroup for GEMINI 2

Population	Treatment	Response	Remission	Description
Con-failure	Placebo	-	26.5%[a]	Maintenance response in induction responders
Bio-failure	Placebo	-	12.4%[a]	Maintenance response in induction responders
RR (non fail vs fail)	-	-	0.468	Maintenance response in induction responders
Con-failure	Vedolizumab Q8W	-	51.5%[b]	Maintenance response in induction responders
Bio-failure	Vedolizumab Q8W	-	28.0%[b]	Maintenance response in induction responders
RR (non fail vs fail)	-	-	0.54	Maintenance response in induction responders
Sources: [a] VIVID-1 – end of maintenance placebo induction responders; [b] Supplementary Table 2: 2509-Sands-2017				

Table 18: Conversion of mixed to subgroup data for GEMINI 2

Treatment	Population	Outcome	N	% split	Outcome in mixed population (%)	Outcome in subgroup (%)
Placebo	Bio-failure	Clinical response at maintenance in induction non responders	28[a,b]	40.0	7.2[b]	4.3
Placebo	Con-failure	Clinical response at maintenance in induction non responders	42 [a,b]	60.0		9.2
Placebo	Bio-failure	Clinical remission at maintenance in induction non responders	28 [a,c]	40.0	7.2[c]	4.3
Placebo	Con-failure	Clinical remission at maintenance in induction non responders	42 [a,c]	60.0		9.2
Vedolizumab Q8W	Bio-failure	Clinical response at maintenance	130[a,b]	37.1	25.4[b]	16.6

		in induction non responders				
Vedolizumab Q8W	Con-failure	Clinical response at maintenance in induction non responders	221 [a,b]	62.9		30.5
Vedolizumab Q8W	Bio-failure	Clinical remission at maintenance in induction non responders	130 [a,c]	37.1	18.8[c]	12.3
Vedolizumab Q8W	Con-failure	Clinical remission at maintenance in induction non responders	221 [a,c]	62.9		22.6
Values in orange have been imputed Sources:[a] Supplementary Table 2 - 2509-Sands-2017; [b]Tabelle 4-36: 2014-07-10_Modul4B_Vedolizumab; [c] Tabelle 4-27: 2014-07-10_Modul4B_Vedolizumab						

e) The data sources have been provided as part of the response to part d, as detailed above.

f) Johnson & Johnson believe the risk and size of residual bias following the normalisation approach is low. The normalisation approach is intended to correct for a critical difference between trials. There were only select instances where direct cross-trial imputation was required, and these are unlikely to be very influential. Notably, the maintenance response/remission among induction non-responders in the placebo arm was imputed from GEMINI 2 for every trial in the network, therefore we would not expect this choice to influence relative treatment effects between active comparators. In addition, the results from the 1-year NMA without delayed responders, (a different normalisation process), lead to the same conclusion of comparable efficacy between treatments. This indicates that the conclusions of the NMAs are insensitive to the choice of normalisation process.

A 10. Priority question. On page 79 of document B, the company states that there was residual heterogeneity in the NMA.

a) How was heterogeneity across trials assessed and managed, particularly in terms of placebo response rates, baseline disease severity, and prior biologic exposure?

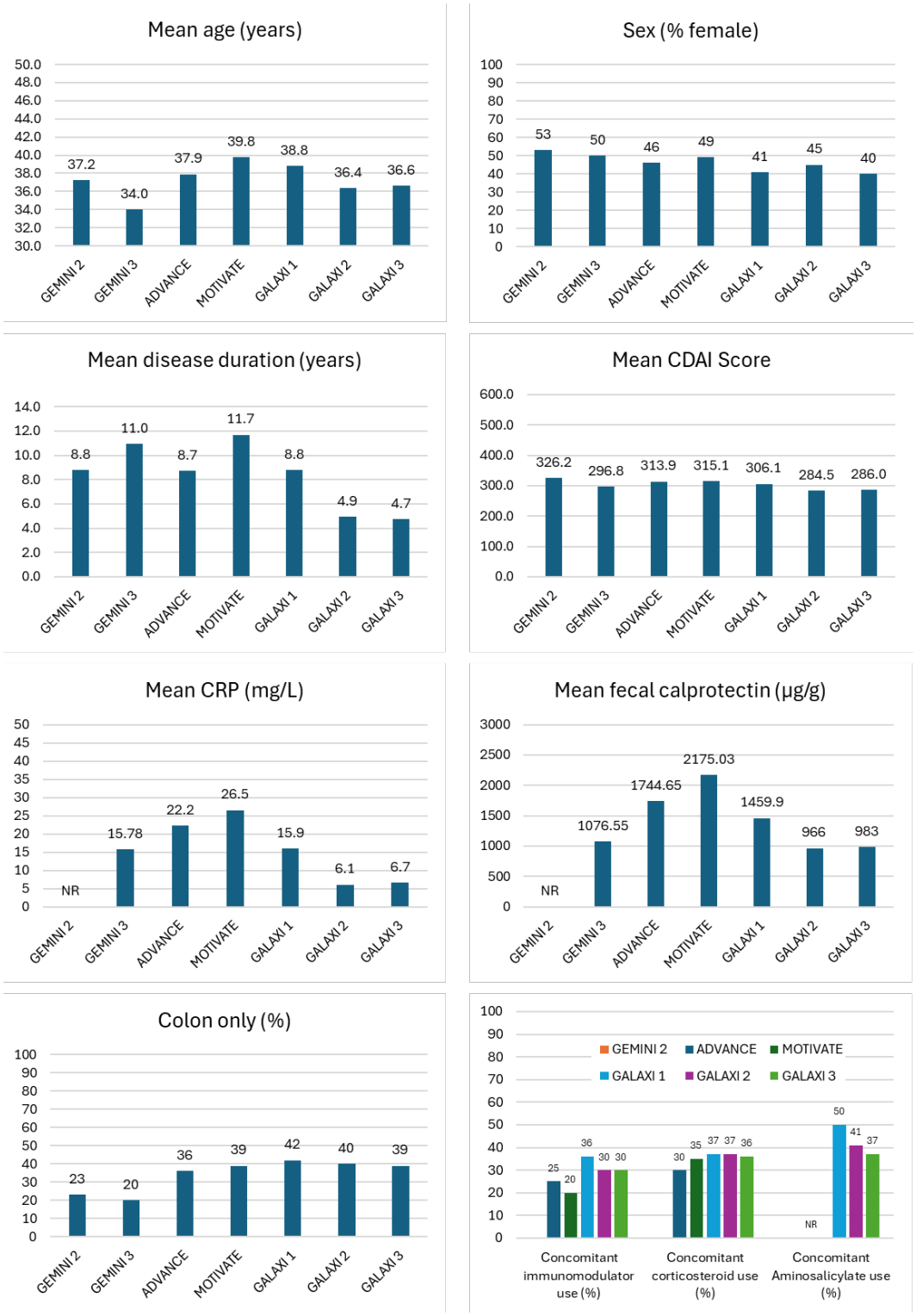
b) Please provide an estimate of the risk and size of any biases in the indirect treatment comparisons as a result of this residual heterogeneity, making specific reference to the possibility of equivalence between guselkumab, and risankizumab and vedolizumab.

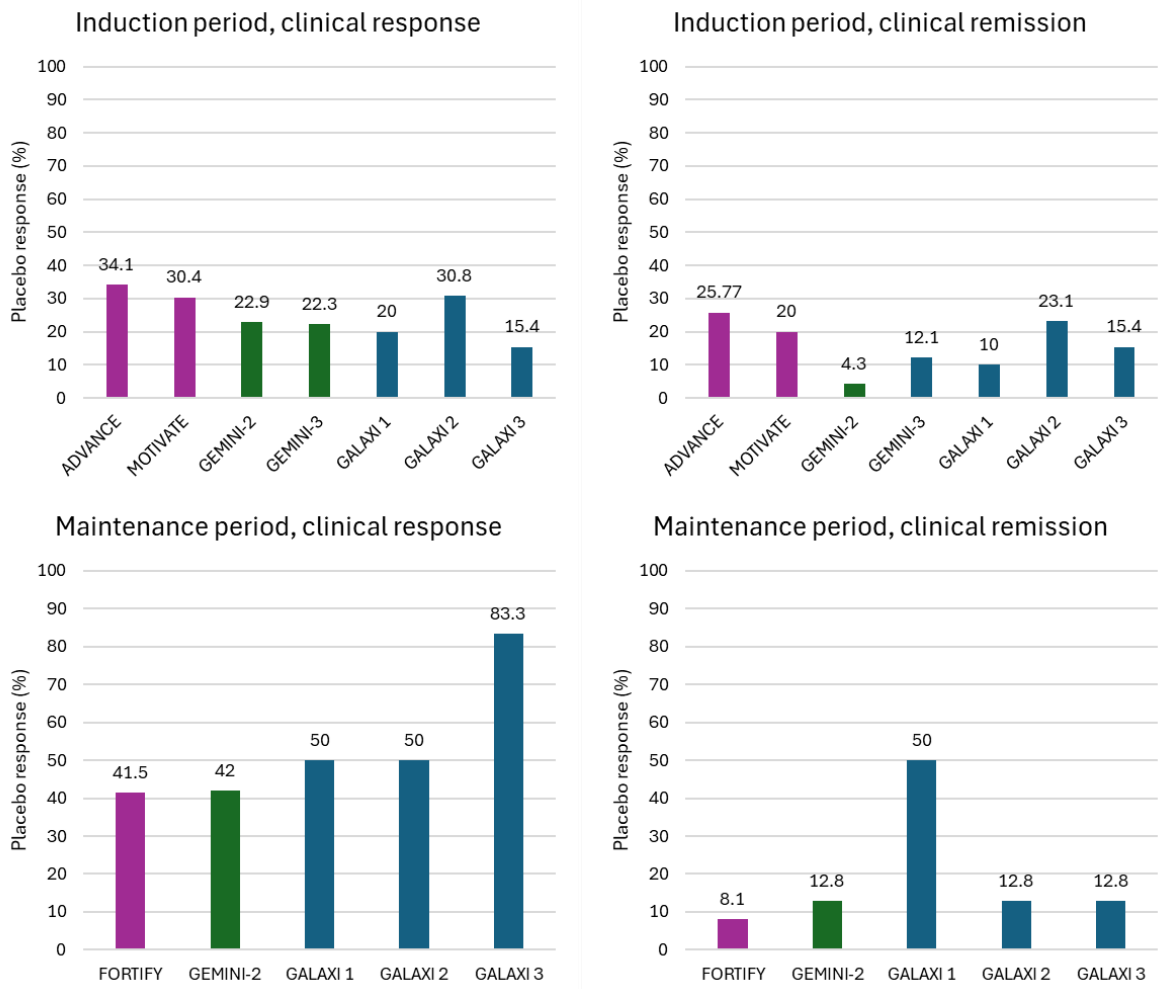
Company response:

a) The analyses conducted were restricted to only patients who had previously failed biologic therapy, and we expect that this addresses a major source of cross-trial heterogeneity across the different evidence networks.

Cross-trial heterogeneity was assessed through a detailed qualitative assessment of key patient baseline traits, placebo response (or baseline risk) and outcome definitions (presented in appendix K of the accompanying NMA report) . Heterogeneity in placebo response rates was noted for the induction phase, and more substantially for the maintenance phase on clinical response. Bar charts outlining the patient baseline traits (for induction periods) and placebo response (for both induction and maintenance periods) are provided in Figure 10, however the reported baselines traits pertain to full analysis sets. Broad similarity was noted across several traits. Heterogeneity in disease duration and laboratory measurements suggested that GALAXI 2 and GALAXI 3 patients may have had less severe disease. Outcome definitions were similar across all trials included in the NMAs for clinical remission (all specifying CDAI score < 150 points), and for clinical response (all specifying at least 100-point reduction in CDAI score from baseline).

Figure 10: Patient characteristics across all trials included in the NMAs, in the full population





For analyses of the induction phase, the quantity of data permitted the conduct of network meta-regression as recommended by Cameron et al.(12) This adjustment can correct for multiple observed and unobserved effect modifiers, allowing for more clinically relevant interpretations of results. Although this was not feasible for 1-year analyses, we expect that the normalisation of trial designs addresses some cross-trial heterogeneity.

b) The most commonly used heterogeneity measure, I^2, provides an estimate of the proportion of variability in a meta-analysis that is explained by differences between the included trials above and beyond sampling error. However, it should be noted that analyses containing a limited number of trials, such as these NMAs, may yield uncertain or uninformative I^2 estimates, limiting the conclusions which can be drawn.(13) Instead, a global test involving a decomposition of heterogeneity was

used to produce Chi-square Q statistics and associated P-values to evaluate total, within-design, and between-design heterogeneity.(14, 15)Results showed there was little heterogeneity in the whole network (P = 0.947). Indeed, residual heterogeneity not accounted for can introduce bias to results, impacting the direction and/or significance of treatment effect estimates between guselkumab and comparator agents. However, our diagnostics did not suggest an extent of heterogeneity that would threaten analysis validity, and given this, we expect there is low likelihood that the compared CD therapies are not equivalent in their levels of efficacy.

Table 19: 1-year analysis, clinical response

Type	[redacted]	Q	df	Pval
Total	[redacted]	[redacted]	[redacted]	
Within designs	[redacted]	[redacted]	[redacted]	
Between designs	[redacted]	[redacted]	[redacted]	

Abbreviations: df= degrees of freedom; Q- Cochran's Q statistic; Pval= P-value

Table 20: 1-year analysis, clinical remission

Type	[redacted]	Q	df	pval
Total	[redacted]	[redacted]	[redacted]	
Within designs	[redacted]	[redacted]	[redacted]	
Between designs	[redacted]	[redacted]		

Abbreviations: df= degrees of freedom; Q- Cochran's Q statistic; Pval= P-value

Table 21: 1-year analysis, endoscopic response

Type	[redacted]	Q	df	pval
Total	[redacted]	[redacted]	[redacted]	
Within designs	[redacted]	[redacted]	[redacted]	
Between designs	[redacted]	[redacted]		

Abbreviations: df= degrees of freedom; Q- Cochran's Q statistic; Pval= P-value

Adverse events

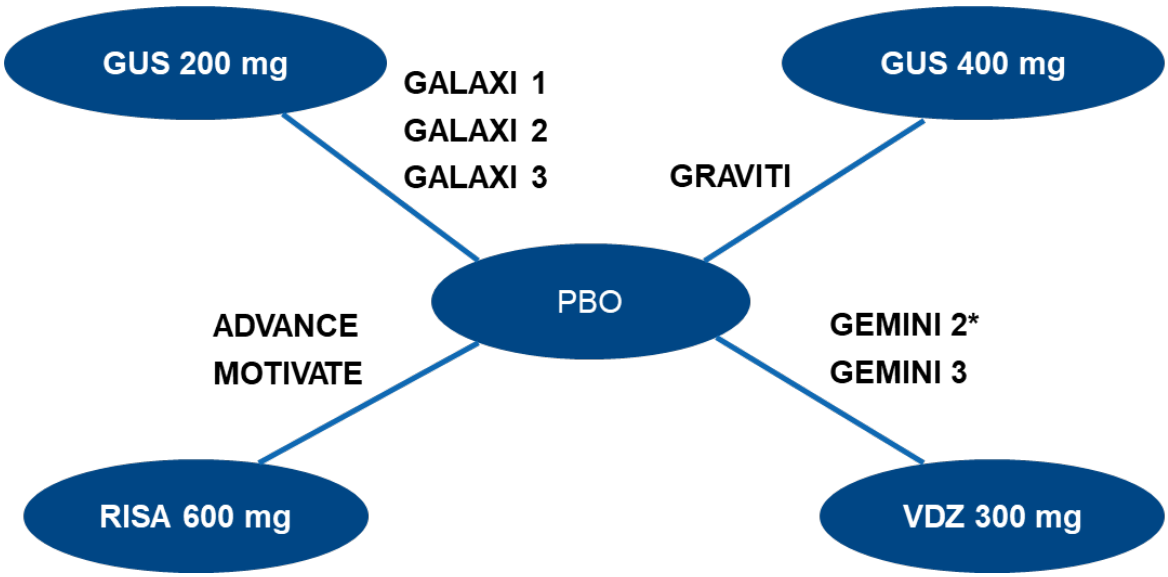
A 11. Priority question. The company states: *"Additionally, the safety of guselkumab appears to be broadly similar to the identified comparators."* (p. 103 of document B). However, there is no NMA of any adverse event (AE) data to demonstrate this. In contrast, the appraisal of upadacitinib for the same indication states: *"The company presented network meta-analyses for induction and maintenance treatment to compare the adverse event outcomes of upadacitinib with ustekinumab and vedolizumab. The results showed that for both induction and maintenance treatment, serious adverse events were comparable between arms, with the credible intervals spanning the line of no effect for all comparisons."* (p. 15) Please therefore conduct NMAs for serous AEs and discontinuation due to AEs to test whether outcomes are similar.

Company response: NMAs for safety outcomes (serious adverse events [SAEs] and adverse events [AEs] leading to discontinuation) were conducted between guselkumab and its comparators in the induction phase and included publicly available data for licensed doses of these therapies. The network for the safety NMAs is shown in Figure 11 and inputs are provided in Table 22. It should be noted that data for AEs leading to discontinuation was not available in the public domain for GEMINI-2 and therefore this safety endpoint is informed by the GEMINI-3 trial only.

Unfortunately, it is not feasible for Johnson & Johnson to conduct the maintenance safety NMAs in the timeframe of clarification response. However, it is important to highlight that guselkumab has a well-characterised safety profile in the treatment of psoriasis and psoriatic arthritis. In a pooled analysis of 4,399 guselkumab-treated psoriatic patients with 10,787 years of exposure, rates of AEs were similar between guselkumab- and placebo-treated patients and consistent throughout long-term guselkumab treatment.(16) In CD, no new safety concerns were identified from the GALAXI and GRAVITI trials and the overall AE profile was considered consistent with the known profile of guselkumab from the psoriasis and psoriatic arthritis studies. The NMAs presented below demonstrate comparable safety among

guselkumab, vedolizumab and risankizumab during the induction phase and we anticipate this to remain consistent in the maintenance phase.

Figure 11: NMA network diagram for serious adverse events and adverse events leading to discontinuation



Notes: *data for AEs leading to discontinuation was not available in the public domain for GEMINI-2 and therefore this safety endpoint is informed by the GEMINI-3 trial only

Table 22: Inputs used to inform the induction safety NMAs conducted

			Adverse events leading to discontinuation			Serious adverse events		
Trial	**Treatment**	**N**	**Source**	**Time point**	**% (events/ N)**	**Source**	**Time point**	**% (events/ N)**
GALAXI-1	PBO	70	CSR(17)	12	2.9% (2/70)	CSR(17)	12	5.7% (4/70)
GALAXI-1	GUS 200	73	CSR(17)	12	1.4% (1/73)	CSR(17)	12	4.1% (3/73)
GALAXI-2	PBO	76	CSR(18)	12	2.6% (2/76)	CSR(18)	12	2.6% (2/76)
GALAXI-2	GUS 200	289	CSR(18)	12	0.7% (2/289)	CSR(18)	12	2.4% (7/289)
GALAXI-3	PBO	72	CSR(19)	12	6.9% (5/72)	CSR(19)	12	9.7% (7/72)
GALAXI-3	GUS 200	293	CSR(19)	12	3.1% (9/293)	CSR(19)	12	3.1% (9/293)
GRAVITI	PBO	117	CSR(20)	12	2.6% (3/117)	CSR(20)	12	7.7% (9/117)
GRAVITI	GUS 400	230	CSR(20)	12	0.4% (1/230)	CSR(20)	12	2.2% (5/230)
GEMINI 3	PBO	207	Sands et al. 2014 (21)	10	3.9% (8/207)	Sands et al. 2014(21)	10	7.7% (16/207)
GEMINI 3	VDZ 300	209	Sands et al. 2014(21)	10	1.9% (4/209)	Sands et al. 2014(21)	10	6.2% (13/209)
GEMINI 2	PBO	148	-	NR	NR	Sanborn et al. 2013(8)	6	6.1% (9/148)
GEMINI 2	VDZ 300	220	-	NR	NR	Sanborn et al. 2013(8)	6	9.1% (20/220)
ADVANCE	PBO	186	D'Haens et al. 2022 (22)	12	7.5% (14/186)	D'Haens et al. 2022(22)	12	15/1% (28/186)
ADVANCE	RISA 600	373	D'Haens et al. 2022(22)	12	2.4% (9/373)	D'Haens et al. 2022(22)	12	7.2% (27/373)
MOTIVATE	PBO	207	D'Haens et al. 2022(22)	12	8.2% (17/207)	D'Haens et al. 2022(22)	12	12.6% (26/207)
MOTIVATE	RISA 600	206	D'Haens et al. 2022(22)	12	1.0% (2/206)	D'Haens et al. 2022(22)	12	4.9% (10/206)

Abbreviations: PBO= placebo; GUS= guselkumab; VDZ= vedolizumab; RISA= risankizumab

The NMAs for safety outcomes were performed using a similar approach as the clinical response, clinical remission and endoscopic response NMAs, in line with the NICE TSD 2 guidelines.(23, 24) 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.

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 200mg IV was comparable to guselkumab 400mg SC, vedolizumab and risankizumab, with the credible intervals overlapping with an OR of 1. The forest plots of both the RE and FE model are presented in the figures below.

Figure 12: Forest plot for random effect NMA of AEs leading to discontinuation in the induction phase of guselkumab 200mg IV versus comparators, full population

Figure 13: Forest plot for fixed effect NMA of AEs leading to discontinuation in the induction phase of guselkumab 200mg IV versus comparators, full population

Serious adverse event NMA for the induction phase

In the random and fixed effect NMAs of serious adverse events, safety for guselkumab 200mg IV was comparable to guselkumab 400mg SC, vedolizumab and risankizumab, with the credible intervals overlapping with an OR of 1. The forest plots of both the RE and FE model are presented in the figures below.

Figure 14: Forest plot for random effect NMA of serious adverse events in the induction phase of guselkumab 200mg IV versus comparators, full population

Figure 15: Forest plot for fixed effect NMA of serious adverse events in the induction phase of guselkumab 200mg IV versus comparators, full population

Section B: Clarification on cost-effectiveness data

Population

B 1. Please discuss the representativeness of the modelled population for the UK patient population and provide supporting evidence.

Company response: The population considered in the model is reflective of the GALAXI trial program. The GALAXI studies were conducted at multiple centres worldwide, including two sites in the United Kingdom. In general, the baseline CD characteristics and medical histories observed in the GALAXI clinical trial programme reflect the moderately-to-severely active CD population. Both the GALAXI and GRAVITI studies included a high proportion of patients who had failed or were intolerant to a biologic therapy, which represents the anticipated population that would be treated with guselkumab in UK clinical practice. Additionally, the proportion of patients identified as bio-failure in the GALAXI and GRAVITI trials was comparable to that seen in the relevant trials for risankizumab and for vedolizumab, which served as the basis of empirical evidence for their recommendation for use within the NHS.

Model assumptions

B 2. Priority question: Are the primary and delayed / secondary response assessment in line with evidence and in line with clinical practice for guselkumab and all comparators? Please provide supporting evidence and clinical expert opinion. Please also provide a scenario where a secondary response assessment is not possible.

Company response: The primary and secondary response assessment modelled in this submission is structured according to the dosing regimens and formulations specified in the draft SmPC for guselkumab and the SmPCs for vedolizumab and risankizumab. The relevant text from Section 4.2 of the draft summary of product characteristics (SmPC) for guselkumab is presented below.(25)

[redacted]

Response assessments have been modelled to align with the draft SmPC which will inform the clinical use of guselkumab. Alternative response assessment and clinical decision-making concerning primary and delayed response with guselkumab would be considered inconsistent with product label.

The timing of response assessment and dosing regimens, according to their respective SmPCs, are detailed below for vedolizumab and risankizumab:

- Vedolizumab: dosed at 300 mg intravenously (IV) at weeks 0, 2, and 6, followed by maintenance doses every 8 weeks thereafter. The SmPC states the option for patients to have an additional dose at week 10 if they have not shown a response at week 6.(26)
- Risankizumab: a dosing regimen of 600 mg IV at weeks 0, 4, and 8, followed by 360mg SC starting at week 12 and every 8 weeks thereafter. The SmPC recommends considering treatment discontinuation in patients who have shown no evidence of therapeutic benefit by week 24. Therefore, delayed responders (patients that do not respond at week 12) receive 360mg SC at weeks 12 and 20 followed by response assessment at week 24.(27)

The modelling of primary and secondary/delayed response assessments presented in this submission aligns with all product SmPCs which would be expected to be followed in clinical practice. Furthermore, the publication by Panaccione et al, 2025 provides evidence supporting the secondary/delayed response assessment for risankizumab at week 24, based on the MOTIVATE and ADVANCE clinical trials.(28) This publication indicates that delayed responders may be treated with either risankizumab IV (1200 mg at weeks 12, 16, or 20) or SC (180 mg or 360 mg at weeks 12 and 20). It is important to note that the economic model developed by Johnson & Johnson only considers the 360mg SC dose of risankizumab at weeks 12 and 20 for delayed responders as this is the licensed dose for Crohn's disease according to the respective SmPC.(27)

While primary and secondary/delayed response assessments are typically undertaken in clinical practice, a scenario is provided below Table 23 where only primary responders are considered (week 12 responders for guselkumab and risankizumab and week 6 responders for vedolizumab). The outcomes of the scenario show that the incremental costs decrease by [redacted] and [redacted] versus vedolizumab and risankizumab respectively. This reduction is attributable to the discontinuation of treatment by all non-responders following the primary response assessment.

Table 23: Scenario results without secondary response assessment

Treatment	Induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	Inc costs versus GUS	Inc costs versus GUS (base case)	Difference versus base case
GUS	[redacted]	[redacted]	[redacted]	-	-	-
VDZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: GUS= guselkumab, VDZ= vedolizumab, RIS= risankizumab; Inc= incremental						

B 3. The treatment discontinuation rate is assumed to be constant, which may not align with clinical practice. In the CS, treatment discontinuation was applied in the maintenance phase only.

a) Please provide further evidence on long-term treatment discontinuation in practice. Please also show the impact of alternative assumptions on the cost comparison results using scenario analyses, such as increasing / decreasing rates over time.

b) Please explain whether there could be cases of treatment discontinuation during the induction phase in clinical practice, and how this would affect the cost comparison results.

c) If there is likely to be an impact of treatment discontinuation during the induction phase in clinical practice, please provide a scenario where treatment discontinuation occurs both in the induction and maintenance phase. Please apply the same or a newly sourced treatment discontinuation rate for the induction phase, whatever deemed more plausible.

Company response:

a) 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 48 time point as

longer-term data is unavailable to suggest any changes in the discontinuation rate over time. 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 over time are not expected to impact the overall outcomes and conclusion. This approach is also consistent with the methods in a recent cost comparison NICE appraisal in IBD, where a constant discontinuation rate was modelled over a 10-year horizon.(29)

b) In clinical practice, while some patients may discontinue treatment during the induction phase, this occurrence is likely to be uncommon. As a chronic inflammatory disease, it is anticipated that it will take time to see response from the initiation of drug therapy. While some symptomatic improvements may start to be reported as early as one week after initiation of treatment, harder to achieve outcomes such as clinical or endoscopic remission would not be anticipated until at least 12-weeks and even then, not in all patients. As such, it is routine practice to await the completion of the induction period before fully evaluating response. Furthermore, as the most severe patients (those with a CDAI of 450-600) who would be likely to need emergency surgery are excluded from clinical trials, this leads to low discontinuation rates during induction phases.

This is supported by data from the GALAXI-3 trial where [redacted] patients [redacted] discontinued treatment on guselkumab during the induction phase.(19) Given the low discontinuation rates observed, the impact on the model results is expected to be minimal. Additionally, discontinuation during the induction phase is directly accounted for during the response assessment at week 12, as patients who do not complete induction therapy will not proceed to maintenance treatment.

c) Given the discussions above, a simplifying assumption was made where discontinuation was not modelled in the induction phase, consistent with previous appraisals across IBD.(29-31) However, a scenario has been conducted where discontinuation in the induction phase is informed by the data observed in the GALAXI-3 trial. In this scenario, an assumption has been applied where by [redacted] of patients do not receive induction treatment, to demonstrate the maximum impact of

discontinuation during the induction phase. The outcomes presented in Table 24 show that the inclusion of all-cause discontinuation during the induction phase has negligible impact on the results and conclusions.

Table 24: Scenario results including discontinuation during the induction phase [redacted] based on GALAXI-3 data

Treatment	Induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	Inc costs versus GUS	Inc costs versus GUS (base case)	Difference versus base case
GUS	[redacted]	[redacted]	[redacted]	-	-	-
VDZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: GUS= guselkumab, VDZ= vedolizumab, RIS= risankizumab; Inc= incremental						

Costs and resource use

B 4. Priority question. Guselkumab and vedolizumab have intravenous (IV) and subcutaneous (SC) administration options. Guselkumab was assumed to have a 20% share for IV during induction and all patients receive SC treatment during maintenance. Vedolizumab is administered via IV during induction and a 50% patient share was assumed eligible for SC during maintenance. Moreover, during maintenance 30% of patients treated with vedolizumab were assumed to escalate dosing based on expert advice and TA888.

a) For guselkumab during induction, consulted clinical experts agreed upon a patient share of 20% receiving IV. Please provide further information on the derivation of this estimate. Please provide a scenario where the vedolizumab shares for IV and SC, i.e. only IV during induction, and 50% SC during maintenance are applied for guselkumab.

b) For vedolizumab during maintenance, the EAG was unable to retrieve the 50% share from the referenced TA888. Please provide the page

number for verification. If sourced from expert feedback, please provide further supporting evidence to verify this assumption. Please update the health economic model or provide a scenario if another potential share is identified.

c) **Please provide additional evidence on current UK clinical practice to justify the patient share assumed eligible for vedolizumab dose escalation, besides TA888. Please also clarify whether dose escalation was also possible in the vedolizumab trials.**

Company response:

a) During the individual interviews with the four healthcare professionals (HCPs), Johnson & Johnson presented an assumption of the plausibility for 80% of patients to receive SC induction and 20% to receive IV induction on guselkumab in clinical practice. The feedback from the four HCPs was varied with one clinician discussing that a 90% SC and 10% IV split should be considered and another suggesting a 50% split. The mixed feedback was based on the variability in infusion waiting times across the country and NHS burden. However, the remaining two HCPs considered the base case assumption of 80% SC and 20% IV to be reasonable.(32)

The scenario requested by the EAG of presenting 100% of patients on guselkumab IV induction and 50% of patients on guselkumab IV maintenance is not feasible as IV maintenance therapy has not been investigated in the GALAXI or GRAVITI trials and consequently is not considered in the anticipated marketing authorisation. However, two alternative scenarios are explored: the first assumes 100% of patients will receive IV induction to align with the EAG's request, while the second estimates that 50% of patients will receive IV induction to correspond with vedolizumab maintenance assumptions. These scenarios are presented in Table 25 and Table 26, respectively. The outcomes of the scenarios show that guselkumab remains cost saving with a small impact in overall outcomes over a 10-year time horizon.

Table 25: Scenario results where 100% of guselkumab patients receive IV induction

Treatment	Induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	Inc costs versus GUS	Inc costs versus GUS (base case)	Difference versus base case
GUS	[redacted]	[redacted]	[redacted]	-		-
VDZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: GUS= guselkumab, VDZ= vedolizumab, RIS= risankizumab; Inc= incremental						

Table 26: Scenario results where 50% of guselkumab patients receive IV induction

Treatment	Induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	Inc costs versus GUS	Inc costs versus GUS (base case)	Difference versus base case
GUS	[redacted]	[redacted]	[redacted]	-		-
VDZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: GUS= guselkumab, VDZ= vedolizumab, RIS= risankizumab; Inc= incremental						

b) The 50% share of IV/SC administration for vedolizumab during the maintenance phase is detailed on page 17 of the company submission, which corresponds to page 33 of the PDF.(33) Since this share was previously assessed and accepted in the risankizumab cost comparison appraisal (TA888) and additional information has not been identified, scenarios exploring the maintenance proportions of vedolizumab via IV and SC routes have not been conducted.

c) Johnson & Johnson were unable to identify any new evidence, specific to current UK clinical practice on the proportion of patients eligible for vedolizumab dose escalation. However, outcomes from a global SLR and meta-analysis conducted by Peyrin-Biroulet et al, provide relevant insights on the incidence rate of loss of response to vedolizumab maintenance therapy in patients with CD. From the seven patient cohorts that contributed data to the meta- analysis, a random effect estimate of 47.9 loss of response per 100 person-years of follow up was reported.

Furthermore, four studies reported data on the efficacy of vedolizumab dose intensification, with a random effects model estimating a pooled efficacy of 53.8%.(34) These findings suggest that the model assumptions regarding vedolizumab loss of response and dose escalation are reasonable.

It should be noted that dose escalation for vedolizumab was possible in the GEMINI-2 clinical trial. In the patient population that had failed TNF-a therapy, 27% of patients received escalated vedolizumab dosing in the maintenance phase (300mg every 4 weeks).(26) This proportion of patients is similar to the estimated proportion that is currently modelled (30%). A scenario has been conducted assuming that 27% of patients are eligible for vedolizumab dose escalation in the maintenance phase as per the GEMINI-2 trial and is presented in Table 27. The outcomes show that the incremental costs between guselkumab and vedolizumab decreases by [redacted] over a 10-year time horizon, aligning with the conclusions of the base case results.

Table 27: Scenario results assuming 27% of patients receive dose escalation for vedolizumab in maintenance therapy as per the GEMINI-2 trial

Treatment	Induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	Inc costs versus GUS	Inc costs versus GUS (base case)	Difference versus base case
GUS	[redacted]	[redacted]	[redacted]	-	-	-
VDZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: GUS= guselkumab, VDZ= vedolizumab, RIS= risankizumab; Inc= incremental						

B 5. IV administration costs were based on NHS reference costs 2022/23 for non-admitted face-to-face attendance for a follow-up visit.

a) Please comment on why first-time visit IV costs were not included, and assess the plausibility of this approach.

b) Please provide a scenario, using a separate unit cost for first-time IV visits for all applicable treatments, in the health economic model.

Company response:

a) In the model, a simplifying assumption was adopted whereby first-time IV costs were excluded. This was based on the expectation that these costs would have minimal impact on overall outcomes, as they are incurred equally across all treatment arms.

b) As requested, a scenario has been conducted that incorporates the cost of the first-time IV visit, amounting to £219.88. This value is based on the weighted average of a consultant and non-consultant led, non-admitted face-to-face fist appointment (code WF01B), derived from the NHS reference costs for 2022/23.(35) The outcomes of this scenario are presented in Table 28 and the impact on the overall results is found to be minimal.

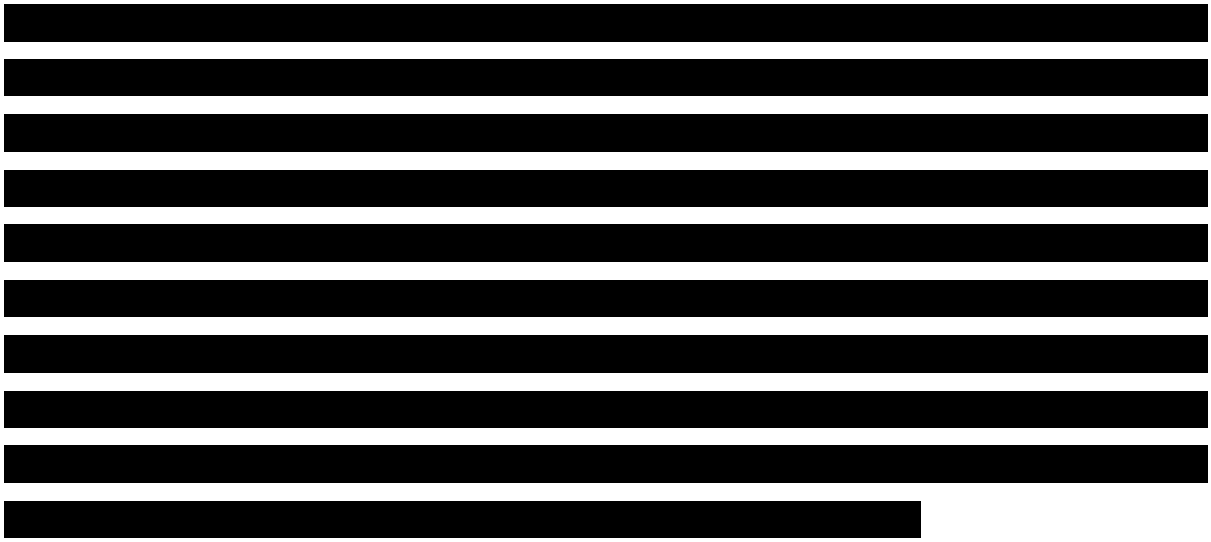
Table 28: EAG Scenario results with separate unit costs for the first IV visits

Treatment	Induction costs (£)	Maintenance costs (£)	Total treatment costs (£)	Inc costs versus GUS	Inc costs versus GUS (base case)	Difference versus base case
GUS	[redacted]	[redacted]	[redacted]	-		-
VDZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: GUS= guselkumab, VDZ= vedolizumab, RIS= risankizumab; Inc= incremental						

B 6. Priority question: During maintenance, guselkumab is available as a subcutaneous injection in 100 mg or 200 mg dosing. Page 106 of document B notes that "all primary responders (week 12) receive the 100 mg dosing, and all delayed (secondary responders at week 24) receive the 200 mg dose" but does not consider the impact on health outcomes. The draft SmPCs (Appendix C) state that increased dosing "may be" considered. Could there be instances where primary responders receive the higher dosing, or delayed responders receive the smaller dosing? Please provide clinical expert opinion, and conduct scenarios of alternative assumptions.

Company response: The decision tree for guselkumab maintenance dosing has been modelled to reflect the anticipated use of guselkumab in clinical practice and is

based on the draft SmPC for guselkumab as described in question B.2.(25) The recommendations outlined in the in posology of the draft SmPC are based on robust clinical data derived from the GALAXI and GRAVITI trials which were designed to assess the efficacy and safety of guselkumab in patients with moderately to severely active CD.(1, 36)



B 7. In the company model, vedolizumab maintenance for responders starts from week 10 onwards, with an equal share receiving either IV every 8 weeks or SC every 2 weeks (Table 30, 33 of document B). Extended induction delays maintenance for non-responders. However, in the 'Calc_VDZ' trace of the health economic model (column N until W), responders are not accounted for at week 10. Also sheet 'Dosing inputs' reports week 14 as the regular maintenance start. Please explain this inconsistency, and provide an updated health economic model.

Company response: Johnson & Johnson apologise for the typographical error in Table 30 and Table 33 presented in Document B. The tables should read as vedolizumab maintenance treatment starting at week 14, as per its SmPC (detailed below).(26) The revised tables are reproduced as Table 29 and Table 30 below.

According to the posology section of the vedolizumab SmPC, the recommended regimen for vedolizumab 300 mg IV is administration at weeks 0, 2, and 6, followed by every 8 weeks thereafter. Additionally, it is advised that patients who have not shown a response may benefit from a dose of IV vedolizumab at week 10, with therapy being continued every 8 weeks from week 14 in responding patients. Thus, whether patients respond to vedolizumab after receiving standard induction (last dose at week 6) or extended induction (last dose at week 10), all responders initiate maintenance treatment at week 14. Furthermore, since the SmPC indicates that the first SC maintenance dose should be administered 'in place of the next scheduled intravenous dose,' the SC vedolizumab dosing regimen for the maintenance phase also starts at week 14. The model is therefore consistent with the guidance provided in the SmPC, and no updates to the model are necessary.

Table 29: 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	6	300 mg IV	10	14
Risankizumab	600 mg IV	0, 4, 8	12	360 mg SC	12, 20	24
Key: IV, intravenous; SC, subcutaneous.						

Table 30: Acquisition costs of the intervention and comparator technologies

	Guselkumab	Risankizumab	Vedolizumab
Pharmaceutical formulation	200 mg solution for injection in pre-filled syringe (2 mL) 200 mg concentrate for solution for infusion vial (20 mL) 100 mg solution for injection in pre-filled pen (1 mL) 200 mg PushPen solution for injection in pre-filled pen (2 mL)	600 mg concentrate for solution for infusion vial (10 mL) 360 mg solution for injection in cartridge (2.4 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 price: £2,250.00 per 100 mg SC dose £[redacted] per 200 mg SC dose	List price: £3.326.09 per 600 mg injection List price £3.326.09 per	List price: £2,050.00 per 300 mg infusion List price: £512.50 per 108 mg injection

	Guselkumab	Risankizumab	Vedolizumab
	£[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	360 mg injection	
Method of administration	• **Induction**: SC or IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC	• **Induction**: IV • **Maintenance**: SC or IV
Doses	• **Induction**: 400 mg SC or 200 mg IV per administration • **Maintenance**: 100 mg SC per administration or 200 mg SC per administration	• **Induction**: 600 mg IV per administration • **Maintenance**: 360 mg SC per administration	• **Induction**: 300 mg IV per administration • **Maintenance**: 300 mg IV or 108 mg SC
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 14 and then every 8 weeks (IV) or every 2 weeks (SC)
Dose adjustments(extended induction, dose escalation)	None	• Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by Week 24	**Induction:** • Patients with Crohn's disease, who have not shown a response may benefit from a dose of IV vedolizumab at week 10 **Maintenance:**

	Guselkumab	Risankizumab	Vedolizumab
			• Patients receiving 300 mg IV vedolizumab every 8 weeks may be considered to receive treatment every 4 weeks if there is a decrease in response • There is no dose adjustment for 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.			

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B 8. No adverse events costs were included in the model. The CS stated on page 103 that the “safety of guselkumab appears to be broadly similar to the identified comparators”. Contrary to the CS, differential adverse event rates were used in the company submission for TA888 to account for treatment-specific risks and their costs. The EAG for TA888, however, set all adverse event frequencies equal in their exploratory analyses, since adverse events were sourced from several observational trials and questions of comparability arose.

a) Please provide a table with all adverse events, their absolute and relative frequency for each intervention and comparators; irrespective of severity grade and frequency. Please also provide references.

b) If equal safety is not supported by the evidence, please include the adverse events, their costs, and potential downstream differences in the health economic model.

Company response:

a) Adverse events for guselkumab, vedolizumab and risankizumab are presented in Table 31. The adverse events presented for guselkumab align with those available in the public domain for comparator trials; however, full safety data for guselkumab are available in the GALAXI and GRAVTI CSRs. Generally, the rates of adverse events are similar between guselkumab, vedolizumab and risankizumab. This is further supported by the publications of Fanizza et al and Bourgonje et al, where the safety of IL-23s were found to be generally favourable with no notable increases in serious adverse events and elevation in the risk of infections, as observed in clinical trials.(37, 38)

Table 31: Adverse events for guselkumab, vedolizumab and risankizumab

	Guselkumab				Vedolizumab		Risankizumab		
Adverse events, n (%)	**GRAVITI (20) (N=274)**	**GALAXI-1(17) (N=220)**	**GALAXI-2(18) (N=289)**	**GALAXI-3(19) (N=293)**	**GEMINI 2(8) (N=814)**	**GEMINI 3 (21) (N=209)**	**ADVANCE (22) (N=373)**	**MOTIVATE (22) (N=206)**	**FORTIFY (10) (N=184)**
AEs	220 (80.3)	163 (74.1)	221 (76.5)	228 (77.8)	706 (87)	117 (56)	210 (56)	98 (48)	135 (73)
SAEs	25 (9.1)	16 (7.2)	24 (8.3)	9 (3.1)	199 (24.4)	13 (6)	27 (7)	10 (5)	23 (13)
AEs leading to treatment discontinuation	8 (2.9)	13 (5.9)	14 (4.8)	9 (3.1)	NR	4 (2)	9 (2)	2 (1)	6 (3)
Serious infection	4 (1.5)	5 (2.3)	3 (1.0)	0	45 (5.5)	2 (<1)	3 (1)	1 (<1)	7 (4)
Malignancy	1 (0.4)	2 (0.9)	0	1 (0.3)	4 (0.5)	NR	0	0	0
Abdominal pain	27 (9.9)	5 (2.3)	20 (6.9)	13 (4.4)	79 (9.7)	9 (4)	8 (2)	5 (2)	13 (7)
Anaemia	10 (3.6)	11 (5.0)	18 (6.2)	12 (4.0)	NR	5 (2)	11 (3)	5 (2)	8 (4)
Aphthous stomatitis/ulcer	1 (0.4)	2 (0.9)	0	2 (0.7)	NR	4 (2)	NR	NR	NR
Arthralgia	11 (4.0)	15 (6.8)	27 (9.3)	20 (6.8)	110 (13.5)	10 (5)	15 (4)	8 (4)	20 (11)
Back pain	4 (1.5)	12 (5.5)	11 (3.8)	7 (2.4)	38 (4.7)	NR	NR	NR	NR
CD exacerbation/worsening	17 (6.2)	15 (6.8)	25 (8.7)	26 (8.9)	164 (20.1)	6 (3)	10 (3)	8 (4)	32 (17)
Diarrhoea	10 (3.6)	9 (4.1)	10 (3.5)	6 (2.0)	NR	NR	2 (1)	3 (1)	10 (5)
Dizziness	3 (1.1)	3 (1.4)	4 (1.4)	2 (0.7)	NR	5 (2)	NR	NR	NR
Fatigue	7 (2.6)	4 (1.8)	6 (2.1)	3 (1.0)	53 (6.5)	6 (3)	NR	NR	NR
Headache	17 (6.2)	22 (10.0)	5 (1.7)	17 (5.8)	97 (11.9)	11 (5)	24 (6)	11 (5)	11 (6)
Infection	125 (45.6)	81 (36.8)	122 (42.2)	146 (49.8)	359 (44.1)	NR (19)	NR	NR	NR
Infusion reaction	NR	NR	NR	1 (0.3)	33 (4.1)	4 (2)	4 (1)	1 (<1)	NA
Injection site reaction	3 (1.1)	1 (0.5)	1 (0.3)	NR	NA	NA	NA	NA	9 (5)
Musculoskeletal pain	NR	2 (0.9)	NR	NR	NR	4 (2)	NR	NR	NR
Nasopharyngitis	11 (4.0)	25 (11.4)	17 (5.9)	15 (5.1)	100 (12.3)	9 (4)	22 (6)	8 (4)	24 (14)
Nausea	6 (2.2)	7 (3.2)	9 (3.1)	8 (2.7)	90 (11.1)	12 (6)	17 (5)	5 (2)	13 (7)

Pyrexia	11 (4.0)	13 (5.9)	17 (5.9)	17 (5.8)	103 (12.7)	7 (3)	NR	NR	NR
Upper respiratory tract infection	2 (0.7)	13 (5.9)	26 (9.0)	56 (19.1)	54 (6.6)	9 (4)	NR	NR	NR
Urinary tract infection	3 (1.1)	3 (1.4)	6 (2.1)	4 (1.4)	NR	6 (3)	NR	NR	NR
Vomiting	6 (2.2)	5 (2.3)	5 (1.7)	8 (2.7)	49 (6.0)	9 (4)	NR	NR	NR

Abbreviations: AE= adverse events; SAE= serious adverse events; NR= not reported

b) The induction safety NMAs conducted and presented in question A11 demonstrate that guselkumab has comparable safety to vedolizumab and risankizumab. As a result, the costs associated with adverse events are anticipated to be similar across these treatments, leading to a neutral impact on overall costs. Therefore, costs related to adverse events have not been included in the model. This is aligned with the approaches of previous cost comparison appraisals in IBD.(29, 33, 39, 40)

B 9. Priority question: The CS did not take subsequent treatments into account.

a) Please explain why these were not included in the cost comparison.

b) Please explain whether subsequent treatment lines are expected in clinical practice after treatment with guselkumab in the different possible settings, explain what treatments would likely be used, and compare this to subsequent treatments after vedolizumab and risankizumab.

c) If there are differences in subsequent treatment lines after guselkumab in different settings and between guselkumab and vedolizumab and risankizumab, please include subsequent treatments for each intervention and comparators in the health economic model, clearly noting the source of the data.

Company response:

a) As guselkumab is the third interleukin-23 (IL-23) inhibitor to be appraised via the cost comparison route, the cost comparison model was designed to include the most relevant and necessary information pragmatically, whilst reducing unnecessary complexity. Consistent with the premise of the cost comparison approach, the model developed provides insights into the anticipated economic outcomes of guselkumab displacing the comparators considered in this submission, within the current

treatment pathway for CD. Subsequent treatments were not modelled as the costs associated with these are anticipated to be similar across the treatments in this submission. In clinical practice, when a patient fails on treatment, another treatment is typically initiated based on individual patient needs. Additionally, it is important to note that subsequent therapies are not sequential in the CD treatment pathway, thus, the treatment options offered after guselkumab are likely to be similar to those for risankizumab and vedolizumab (discussed further in part b). This would result in overall costs for subsequent treatments being similar across the treatments, leading to minimal or no impact on cost differences, should guselkumab replace the comparators. The exclusion of subsequent treatments is consistent with previously accepted cost comparison appraisals in IBD including TA888 and TA905.(29, 33, 39, 40)

b) In clinical practice, patients who do not respond or lose response to guselkumab as well as to the comparators included in this submission, are likely to discontinue treatment and transition to a new therapy. In CD, the first line of therapy is usually a biosimilar anti-TNF, as recommended by the NICE and BSG guidelines.(2, 3) However, the choice of treatment for the bio-failure population, is tailored to individual patient needs, considering patient preferences, disease phenotype, co-morbidities and therefore there is no typical algorithm for subsequent lines of therapy, as per BSG and NICE guidelines.(2, 3) Consequently, patients who fail on guselkumab are likely to be offered similar subsequent treatments as those who do not respond to vedolizumab or risankizumab, since guselkumab is expected to occupy the same position in the treatment pathway. This parity in treatment positioning would likely lead to comparable subsequent treatment costs across all therapies.

c) As discussed in responses a and b above, Johnson & Johnson do not anticipate any significant differences in the subsequent treatment options available to patients following failure on guselkumab, vedolizumab, or risankizumab. The incurred costs associated with these subsequent treatments are expected to have a neutral impact on overall costs, therefore, subsequent treatments have not been included in the economic analysis.

B 10. The CS did not include additional or miscellaneous unit costs since they were not considered relevant. Please provide supporting evidence and expert opinion on why these were deemed irrelevant. If potential additional costs are identified, please provide evidence for these and include them in the health economic model.

Company response: Additional costs such as monitoring or miscellaneous unit costs were not included in the model as treatment monitoring is deemed to be similar across the treatments in this appraisal. According to the draft SmPC, guselkumab does not require any additional monitoring compared with vedolizumab and risankizumab.(25-27) Therefore, it is anticipated that there will be no impact on cost differences and aligns with recent cost comparison appraisals in CD.(33, 39)

B 11. In CS Table 33, risankizumab dosing frequency during maintenance was reported with every 4 weeks after week 12. Please clarify whether this is an error, as SmPCs and the health economic model report an 8-week frequency after week 12.

Company response: Johnson & Johnson apologise for the error and confirm that the maintenance frequency for risankizumab after week 12 is every 8 weeks, as stated in its SmPC.(27) The correct dosing regimen (risankizumab 360mg every 8 weeks) is accurately reflected in the model submitted as part of this submission.

Results

B 12. Priority question: Please provide more explanation on the drivers of the cost comparison over time.

a) Please illustrate incremental costs of guselkumab versus all comparators over time in year 1 in a figure, highlighting the time points of primary and delayed / secondary response assessments for all comparators.

b) Please clarify the effects of a longer time horizon and also illustrate incremental costs over time in a figure with a 10 year time horizon.

c) **Please explain the implications of shorter versus longer time horizons and discuss why a longer, i.e. 5-year or 10-year, time horizon is important to capture differences between guselkumab and its comparators.**

d) **Please explain what drives differences in costs between guselkumab and its comparators in each phase, i.e. for induction costs, maintenance costs in year 1 and maintenance costs in subsequent years. Please also elaborate on the assumptions that contribute to these cost drivers.**

Company response:

a) The incremental costs over time of guselkumab versus vedolizumab and risankizumab are shown in Figure 16. The incremental cost saving increases gradually over time, with no major changes in incremental costs at any of the response assessment timepoints. Since guselkumab is cost-saving in both the induction and maintenance phase versus all comparators, incremental costs are expected to increase over time in all treatment phases.

Figure 16: Incremental costs over time of guselkumab versus vedolizumab and risankizumab in year 1

Abbreviations: Gus= guselkumab; RZB= risankizumab; VDZ= vedolizumab.

b) Figure 17 shows the incremental costs over time for the full 10-year time horizon of the model. Similar to Figure 16, the incremental cost savings continue to increase throughout the time horizon, slowing over time. This is driven by treatment discontinuation, where approximately [redacted] of patients are assumed to remain on treatment by year 10. As seen in Figure 17, the additional cost-savings are smaller in year 10 compared to year 1.

Figure 17: Incremental costs over time of guselkumab versus vedolizumab and risankizumab in over the full 10-year time-horizon

Abbreviations: Gus= guselkumab; RZB= risankizumab; VDZ= vedolizumab.

c) As shown in Figure 17, the incremental cost savings continue to increase over the full 10-year time horizon of the model. The increase in cost saving slows throughout the time horizon as patients discontinue treatment over time. However, considering that approximately [redacted] of patients are modelled to remain on treatment by the end of year 5 compared to approximately [redacted] by the end of year 10, we believe a time

horizon of 10 years is more appropriate to capture the relevant cost differences between treatments in CD.

d) For both the induction and maintenance phases, the main factor driving cost savings associated with guselkumab is the difference in drug acquisition costs. This is largely attributed to the patient access scheme (PAS) discount applied to guselkumab, while list prices are used for comparator treatments due to confidentiality. These cost savings are further influenced by the frequency of drug administration. In the induction phase, guselkumab is the only treatment that provides SC induction, which results in cost savings related to administration compared to vedolizumab and risankizumab.

Another key driver is the proportion of patients responding in the primary and secondary response assessments. These assessments inform the proportion of patients who continue treatment from the induction phase through the maintenance phase, up until the end of the model time horizon. Additionally, all-cause discontinuation affects the proportion of patients remaining on treatment from the beginning of the maintenance phase onward. Including all-cause discontinuation mirrors real-world clinical practice, where patients may discontinue treatment due to loss of response or adverse events.

B 13. Please investigate and explain the difference in administration costs for subcutaneous use of guselkumab and risankizumab during the maintenance phase in the health economic model.

Company response: The total SC administration costs during the maintenance phase are lower for guselkumab compared to risankizumab, as the model considers costs for the first SC dose only. In the model base case, it is assumed that 80% of guselkumab patients receive SC induction, while all risankizumab patients undergo IV induction, as per its SmPC.(27) For the 80% of guselkumab patients receiving SC induction, the cost of the initial SC administration is already factored into the induction phase. Consequently, the total SC administration costs during the maintenance phase are 80% lower for guselkumab compared to risankizumab.

Validation

B 14. Please share the minutes from the meetings with the four UK clinical experts, in addition to the summary, which has already been provided. For guselkumab IV / SC proportions, and vedolizumab IV / SC proportions as well as dose escalation, please elaborate on how the resulting estimates were arrived at and what the individual responses were.

Company response: The summary of the calls with the four UK clinical experts provided by Johnson & Johnson alongside the submission documents represent the full meeting minutes. These notes were validated with the clinicians to ensure accurate representation of the discussions.

As discussed in question B4 part a, an assumption of 80% of patients to receive SC induction and 20% to receive IV induction on guselkumab in clinical practice was suggested. The clinicians had opportunities to provide their feedback in which two HCPs found the assumption to be reasonable.

Regarding the proportions of patients receiving IV/SC vedolizumab maintenance and dose escalation, the previously accepted proportions from prior IBD appraisals (TA888 and TA925) were presented to the clinicians in the absence of additional data. Overall, there was variability in the feedback regarding the proportions of patients on IV/SC vedolizumab maintenance, as well as for those experiencing dose escalation. This variation was attributed to differing practices across trusts. Consequently, Johnson & Johnson adopted a 50% IV/SC vedolizumab maintenance split based on TA888 and a 30% dose escalation rate from TA925 for the model base case. (29, 33)

As guselkumab is being appraised in parallel for patients with moderately to severely active ulcerative colitis (ID6237), efforts were made to capture validations that reflect clinical practice accurately, whilst being consistent with precedence across the recent cost comparisons in IBD.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guselkumab for treating moderately to severely active Crohn's disease [ID6238]

NICE medicines optimisation briefing

July 2024

Key issues

- The specific licensed indication for guselkumab in Crohn's disease 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 (risankizumab 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 become 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 Crohn's disease whose condition has responded inadequately to conventional or biologic treatment, or in whom these have not been tolerated. Guselkumab is also currently being assessed by NICE for treating moderately to severely active ulcerative colitis (ID6237).

Context

Crohn's disease is a chronic, relapsing-remitting inflammatory condition that may affect any part of the gastrointestinal tract. For treating moderately to severely active Crohn's disease, NICE has assessed:

- 2 TNF-alpha inhibitors: infliximab and adalimumab (TA187).
- 3 monoclonal antibodies: risankizumab (TA888), ustekinumab (TA456) and vedolizumab (TA352).
- the Janus Kinase (JAK) inhibitor upadacitinib (TA905).

Another monoclonal antibody, mirikizumab, is currently being assessed for treating moderately to severely active Crohn's disease (ID6244).

Table 1: Characteristics of guselkumab compared with other medicines used for treating moderately to severely active Crohn's disease in adults at a similar point in the treatment pathway

	Guselkumab	Ustekinumab	Risankizumab	Vedolizumab	Adalimumab Infliximab	Upadacitinib
Mechanism of action	Monoclonal antibody (IL-23 inhibitor)	Monoclonal antibody (IL-12 and IL-23 inhibitor)	Monoclonal antibody (IL-23 inhibitor)	Monoclonal antibody (alpha-4-beta-7 integrin blocker)	TNF-alpha inhibitors	JAK inhibitor
Indication	Moderately to severely active Crohn's disease with inadequate response, contraindication or intolerance to conventional treatment (details to be confirmed when the marketing authorisation is granted)	Moderately to severely active Crohn's disease with inadequate response, lost response, contraindication or intolerance to conventional or TNF-alpha inhibitor (Ustekinumab SPC)	Moderately to severely active Crohn's disease with inadequate response, lost response, contraindication or intolerance to conventional or a biologic treatment (Risankizumab SPC)	Moderately to severely active Crohn's disease with inadequate response, lost response, contraindication or intolerance to conventional treatment or TNF-alpha inhibitor (Vedolizumab SPC)	Moderately to severely active Crohn's disease with inadequate response, contraindication or intolerance to conventional treatment (Adalimumab SPC) (Infliximab SPC)	Moderately to severely active Crohn's disease with inadequate response, lost response or intolerance to conventional or a biologic treatment (Upadacitinib SPC)
Technology appraisal recommendation	Not applicable	Moderately to severely active Crohn's disease in adults who have had an inadequate response with, lost response to	Moderately to severely active Crohn's disease in people 16 years and over, only if the disease has not responded	Moderately to severely active Crohn's disease only if a TNF-alpha inhibitor has failed (that is, the disease has responded	Severe active Crohn's disease in adults whose disease has not responded to conventional therapy (including	Moderately to severely active Crohn's disease in adults, only if the disease has not responded well enough or lost

		or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies (TA456)	well enough or lost response to a previous biological treatment, or a previous biological treatment was not tolerated, or TNF-alpha inhibitors are not suitable (TA888)	inadequately or has lost response to treatment) or a TNF-alpha inhibitor cannot be tolerated or is contraindicated (TA352)	immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional treatment (TA187)	response to a previous biological treatment, or a previous biological treatment was not tolerated, or TNF-alpha inhibitors are contraindicated (TA905)
Dosage and route of administration	Dosage and route to be confirmed when the marketing authorisation is granted	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	600 mg IV infusion at weeks 0, 4 and 8 then 360 mg by SC injection at week 12 repeated every 8 weeks	300 mg IV infusion at weeks 0 and 2, then either 300 mg by IV infusion at week 6 repeated every 8 weeks, or 108 mg by SC injection at week 6 repeated every 2 weeks	**Adalimumab**: 80 mg by SC injection at week 0 and 40 mg at week 2, (or if needed, 160 mg at week 0 and 80 mg at week 2) then 40 mg every 2 weeks (increased if needed to 40 mg weekly or 80 mg every 2 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	45 mg once daily orally for 12 weeks, then 15mg or 30 mg once daily orally

					at week 6 then every 2 weeks	
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 self-administered at home after training)	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 self-administered at home after training)	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 self-administered at home after training)	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 self-administered at home after training)	Oral treatment: convenient, non-invasive, lower service delivery costs than injections
Abbreviations: IV, intravenous; SC, subcutaneous						

Current practice

Medicines for treating moderately to severely active Crohn's disease in adults are commissioned by integrated care boards. Local treatment pathways for initial management follow NICE guidance.

The NICE guideline on the management of Crohn's disease (NG129) recommends treatment according to disease presentation and severity, as well as individual patient factors. Conventional treatment for moderately to severely active Crohn's disease includes:

- corticosteroids or aminosalicylates for induction of remission
- azathioprine, methotrexate or mercaptopurine as add-on therapy for induction or as monotherapy for maintaining remission.

If conventional treatment is not effective, or is contraindicated or not tolerated, the treatment pathway becomes complex and system intelligence indicates that current practice varies. Specialist treatment with biologics (TNF-alpha inhibitors or monoclonal antibodies) or the JAK inhibitor upadacitinib, can be considered. Individual patient factors affect choice, such as route and frequency of administration, severity of disease, extraintestinal manifestations, presence of fistulising disease, contraindications, comorbidities (such as cancer risk, co-existence of autoimmune disease) and age.

TNF-alpha inhibitors (infliximab or adalimumab; TA187) are usually the first-choice biologics for moderately to severely active disease; adalimumab and infliximab (IV only) are available as biosimilars. Adalimumab and infliximab are licensed as subcutaneous injections for maintenance therapy, which can be delivered by homecare services and self-administered at home. Infliximab is also licensed as an infusion which, when administered in specialist settings, is likely to increase service delivery costs (clinic costs and healthcare professionals' time).

The monoclonal antibodies risankizumab (TA888), ustekinumab (TA456) and vedolizumab (TA352) are used in practice if TNF-alpha inhibitors are not effective, or if they are contraindicated or not tolerated. There is variation between centres with some locations preferring certain monoclonal antibodies and positioning one ahead of others, while others position all equally. The patent for ustekinumab is nearing expiry; this may affect acquisition cost and as a result the positioning of ustekinumab if biosimilars become available.

Vedolizumab has traditionally been given as an IV infusion in secondary care but is now available as a subcutaneous injection allowing for greater convenience and is likely to reduce service delivery costs. Ustekinumab and risankizumab used as maintenance treatment are also given as a subcutaneous injection, allowing people to administer at home.

System intelligence suggests that the JAK inhibitor upadacitinib (TA905) is sometimes used before monoclonal antibodies, if TNF-alpha inhibitors are not effective, for younger people with lower cardiovascular risk factors.

Guselkumab is likely to be used after the TNF-alpha inhibitors, as an alternative to other monoclonal antibodies and upadacitinib. It has the same mechanism of action as risankizumab so may be a direct alternative to this option. The choice of treatment is likely to depend on:

- individual patient factors (including comorbidities, contraindications, potential adverse effects, route of administration and preference)
- acquisition cost and overall cost of treatment (including delivery costs and monitoring), and
- local treatment pathways (including availability of infusion facilities and therapeutic drug monitoring).

Patient centred factors

Most treatments used for active Crohn's disease 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 inhibitor upadacitinib is an oral medicine. 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

Crohn's disease most commonly presents in adolescence and early adulthood, but can develop at any age. It occurs equally in men and women. Although not identified by name as a disability, people who have Crohn's disease 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 previously treated moderately to severely active Crohn's disease [ID6238].

Patient Organisation Submission

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Crohn's & Colitis UK
3. Job title or position	Policy Lead
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	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.

comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; and • research - our own and that of external organisations.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The symptoms of Crohn's disease, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, blood or mucus in stools, abdominal pain and fatigue, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships.[1] [2] The inflammation in Crohn's disease may lead to strictures (narrowing) of the bowel resulting in abdominal pain caused by partial blockage. Severe cases may lead to life-threatening complications such as complete blockage or perforation of the bowel. At least 50% of people with Crohn's disease may require surgery within ten years of diagnosis and 70-80% during their lifetime. Due to the nature of Crohn's disease and the fact that it can occur anywhere in the gastrointestinal tract, having surgery once does not preclude the potential need to have surgery again. For patients with moderate to severe Crohn's disease, the condition is more challenging, frequently overwhelming and detrimentally life-altering. This cohort is likely to experience more severe flares, weight loss, fever and constitutional symptoms. **Comorbidities** Patients with Crohn's disease are at a higher risk of mortality and more likely to experience several comorbidities including diabetes, hypertension, atrial fibrillation, angina, stroke, rheumatoid arthritis, asthma, chronic obstructive pulmonary disorder and chronic liver disease.[3] **Mortality** Research suggests that people with Crohn's disease are at a higher risk of mortality particularly from intestinal cancer, intestinal failure, perioperative complication and amyloidosis.[4] **Quality of Life** Education, employment, personal relationships, social and family life may all be disrupted by the unpredictable occurrence of Crohn's disease flare-ups. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect self-esteem and social functioning, particularly among the young and newly-diagnosed. Emotional wellbeing can be significantly affected by difficulty in coping with personal lives and feelings of embarrassment, frustration, sadness and fears of needing surgery or developing cancer.[5] Stigma and lack of wider understanding of the condition exacerbates the impact. Anxiety, depressive episodes and depressive disorders are higher in people with

	Crohn's disease, at least in part as a consequence of the condition itself and its medical treatment (e.g., corticosteroid therapy).[6] Additionally, much research has shown that stress can be involved in triggering flares.[7] Social functioning can be impaired leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. Research shows that young people aged 16-25 with Crohn's disease who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. The experience of caring for someone with Crohn's disease can be especially difficult given that it is an invisible condition, the unpredictable nature of the symptoms, which many also find extremely uncomfortable to talk about, and the effects of treatment. For parents of young people, there are challenges around providing support, while enabling independence and seeing lives and aspiration affected by their child's condition. *"Crohn's disease blights my life. I am an experienced teacher and a trustee of a local charity but my ability to work and contribute to my community, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12-18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge."* **Quote from a person living with Crohn's disease** *"I'm an active divorced 60 year old woman now who feels the impact of my symptoms have precluded me from having a regular social life and finding a partner. On the surface I'm a confident outgoing woman but emotionally I'm crying inside and feel completely isolated. This terrible disease has robbed me of my life in many ways and at times I have felt living on into my even older age is pointless. Nobody truly understands what it's like to have Crohn's unless they themselves are patients. My friends can't comprehend why a 'woman like me never remarried'. It's easy, I'm too embarrassed to even contemplate sharing a house with a man. The psychological effects keep me in like a hermit crab at the weekends."* **Quote from a person living with Crohn's disease**

[1] Crohn's and Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards.
[2] IBD UK (2019) IBD Standards.
[3] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *Evidence-based mental health*, **24**(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.
[4] Yasukawa, S., Matsui, T., Yano, Y. *et al.,* (2019). Crohn's disease-specific mortality: a 30-year cohort study at a tertiary referral center in Japan. *Journal of gastroenterology*, **54**(1), 42–52. https://doi.org/10.1007/s00535-018-1482-y.
[5] Cosnes J, et al., (2011). Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*, **140** (6), 1785-94.
[6] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *Evidence-based mental health*, **24**(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.
[7] Sun, Y., Li, L., Xie, R., et al., (2019). Stress Triggers Flare of Inflammatory Bowel Disease in Children and Adults. *Frontiers in pediatrics*, **7**, 432. https://doi.org/10.3389/fped.2019.00432

	"I am 23 years old and I have had to leave my university place studying Mental Health Nursing three times due to my Crohn's disease. My life has been on hold for years due to this illness and I have lost 3 years of income, which has been a great burden." **Quote from a person living with Crohn's disease** *"My wife states that I have changed since being diagnosed, I never thought I had, but looking back, she is right. We are battling this illness together ... it's not just me it affects, It's everyone, my wife, work and family".* **Quote from a person living with Crohn's disease**

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The 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 (56%) 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. **Steroids** Corticosteroids are commonly used a first line treatment. However, there are significant short and long-term side effects with these, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis.[9] Therefore they do not represent a therapeutic option as a maintenance treatment. The BSG guidelines set out clear stipulations on the best practice of prescribing steroid therapies given their diminishing returns, harsh side effects and risk of dependency.[10] *"My 'moon face' from the constant use of prednisolone was depressing and because of my ill health my hair became really thin. Prednisolone also affected my mood. I was so angry and unhappy. This also kept me awake at night, so I took sleeping pills."* **Quote from a person living with IBD** **Surgery** For many patients with Crohn's disease, the prospect of surgery is one they face with considerable anxiety, and it can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. Clinical outcomes after pouch surgery remain variable and fertility in women can be significantly affected by any pelvic surgery. *"Personally I'm not prepared for the drastic surgery of having my colon removed*." **Quote from a person living with IBD** *"I'd had enough of being ill and hospital admissions and blood transfusions and requested surgery to remove my colon. The surgeon said it disintegrated as he was taking it out it was in such a bad state. I now have a j-pouch and while life is a lot better it isn't the cure that was promised and it impacts on my life considerably."* **Quote from a person living with IBD**

[8] IBD UK, 2024 IBD UK Report: The State of IBD Care in the UK, 2024 IBD UK Report: The State of IBD Care in the UK | IBD UK
[9] Blackwell J, Selinger C, Raine T, *et al* (2021). Steroid use and misuse: a key performance indicator in the management of IBD. *Frontline Gastroenterology* , **12**, p.207-213.
[10] BSG (2019) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html

8. Is there an unmet need for patients with this condition?	There is currently no medical or surgical cure for Crohn's disease. Current available treatments are aimed at inducing and maintaining remission and improving quality of life. The range of options available for treating Crohn's disease remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies. **Immunosuppressants** Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them.[11] [12] 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. [13] [14] **Anti-TNFs** These are increasingly being used earlier in the treatment pathway and can have a significant and positive effect on quality of life for patients. However, up to 40% of patients treated with anti-TNF therapy do not respond to induction therapy.[15] In the approximately one-third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time.[16] Overall, there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with Crohn's disease to resume their lives and restore their quality of life. *"I am well aware that these drugs have a very significant cost but without them, the last 12 years would have been very different for me. Even with them I have had to have 2 lots of surgery to remove scarred bowel but without them I think I would have had to have more extensive surgery and possibly not even be here to send this email. I am also well aware that I am on my last chance here with current available drugs having taken everything the NHS has to offer; if the vedo stops working then I have nowhere else to go with medication. New drugs and options for medication will be vital for my health going forward."* **Quote from a person living with IBD, in which drug treatments have not been effective.**

[11] Fraser, A.G, Orchard, T.R, Jewell, D.P. (2002). The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut*, **50**: 485–9.
[12] Candy, S, Wright, J, Gerber, M, *et al.,* (1995) A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut*, **37**: 674–8.
[13] Siegel, C.A, Marden, S.M, Persing, S.M, *et al.,* (2009). Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*, **7**:874–881

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 Crohn's disease, in England, are shown to contribute to economic disadvantage, which can impact adherence and lead to complications and increased cancer risks and cost to the NHS. 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.

[14] Jorquera, A, Solari, S, Vollrath, V. et al., (2012). Phenotype and genotype of thiopurine methyltransferase in Chilean individuals. *Rev Med Chil*, **140**:889–895
[15] Rutgeerts, P, Van Assche, G, Vermeire S. (2004). Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology*, **126**(6):1593-610.
[16] Roda, G. (2016). Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*, **7** (1), e135.

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 Crohn's disease, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, blood or mucus in stools, abdominal pain and fatigue, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships.[17] [18] • There is significant unmet need for people with moderate to severe Crohn's disease. 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.

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[17] Crohn's and Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards.
[18] IBD UK (2019) IBD Standards.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guselkumab for previously treated moderately to severely active Crohn's disease ID6238

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society of Gastroenterology – IBD committee
3. Job title or position	Consultant pharmacist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society of Gastroenterology is focused on the promotion of gastroenterology and hepatology. It has over four thousand members drawn from the ranks of physicians, surgeons, pathologists, radiologists, scientists, nurses and AHPs (https://www.bsg.org.uk/). Not for profit.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	J&J is an industry partner of the BSG and therefore we have received funds from them in the last 12 months. They have paid for a stand as an exhibitor at BSG Live.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Induce and maintain clinical, steroid-free and endoscopic remission in Crohn's Disease (CD), so improving patients symptoms/quality of life and may reduce the risk/need for surgery and its associated costs.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	CDAI scores of below of 150. Normalisation of biomarkers e.g. FCPL and CRP. Patient reported outcomes improvements (both bowel and/or extra intestinal manifestations if present). Endoscopic and/or MRI improvement. Histological improvement. Corticosteroid-free remission.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. CD is a chronic condition, without cure, and so life-long management is required. Surgery cannot enable a cure in CD (unlike UC), as it can represent in remaining parts of the GIT. There are only a distinct number of therapies available. Current therapies are not 100% effective (depending on trials this can range from approx. 25-75%) and so treatment failure occurs. All of the current therapies have contra-indications.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Medications:

	• Corticosteroids • Immunomodulators: - Thiopurines (azathioprine & mercaptopurine) - Methotrexate • Advanced therapies: - Biologic medicines (anti-TNFs; adalimumab, infliximab. Integrin inhibitor; vedolizumab. IL-23; ustekinumab & risankizumab) - JAK inhibitor (upadacitinib) • 5ASA are sometimes used but the evidence for this is lacking and is often historical Surgery (but not curative) and medications are needed afterwards. Nutrition
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE BSG 2019 (new update due imminently) ECCO
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	For moderate to severe CD, first line anti-TNF is well established (as long as not contra-indicated due to comorbidities). Thereafter, which advanced therapies are to be used in which sequence is not set and usually depends on patients co-morbidities, symptoms, preference, service capacities and contract costs.
9c. What impact would the technology have on the current pathway of care?	Additional medicine option as post anti-TNF treatment option (unless C/I).

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	Nil
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Hospital and homecare (secondary care)
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	That level of long-term data is not available
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Lacking information for paediatrics, elderly, renal impairment, hepatic impairment and pregnancy/breastfeeding, however, experience with other IL23 could be useful to enable clinician-patient discussion for an informed decision.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Similar to other current medications used.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Severity of CD = must be moderate to severe as per clinical imaging and/or symptoms. Patient review (symptoms, biomarkers, imaging, biopsy), will determine if effective after loading dose period and beyond if effective, can continue with yearly follow-up, if not effective, to be stopped. Once achieved remission, discussions can be had for treatment breaks.

	Any intolerable side effects or reactions would cause drug stop.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	No
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes; increases the pool of medications available, which currently is small, especially when considering chronicity of CD needing life-long management.
17. How do any side effects or adverse effects of the technology affect the management of the	The side effect profile is favourable and comparable to other medications already used and the community are experienced in managing them. They include:

condition and the patient's quality of life?	• Common: - diarrhoea - liver transaminases increased – mostly transient and didn't alter treatment • Uncommon: - herpes simplex infections – vaccination could be provided in riskier groups i.e. over 50 years of age and on this medication - gastroenteritis - neutropenia – mostly transient and didn't alter treatment

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	That level of long-term data is not available, but not expected when considering other drugs in same class (IL23)
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
21. How do data on real-world experience	Not been used outside of trial

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Service/homecare capacity to enable prescribing and administration ICB may restrict services to only one type of drug per class
22b. Consider whether these issues are different from issues with current care and why.	No

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• CD is life-long condition without cure. • Number of CD treatments are limited. • Maximal options are required to enable life-long treatment. • IBD community have vast experience in these types of medications to enable safe and effective use.

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Guselkumab for previously treated moderately-to-severely active Crohn's disease [ID6238]

Produced by

Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre+ (UMC+)

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Contributions of authors:

Nigel Armstrong acted as project lead and health economist/reviews manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Mubarak Patel and Xiaoyu Tian acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Teresa Holly acted as health economist on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Huiqin Yang critiqued the company's definition of the decision problem and the network meta-analysis, contributed to the writing of the report and jointly led the project.

Abbreviations

AE	Adverse event
AP	Abdominal pain
BIO-failure	Biologic experienced
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CON	Confidential
CrI	Credible interval
CS	Company submission
DARE	Database of Abstracts of Reviews of Effects
DP	Decision problem
EAG	External Assessment Group
EED	Economic Evaluation Database
EUR	Erasmus University Rotterdam
GUS	Guselkumab
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
iMTA	Institute for Medical Technology Assessment
IV	Intravenous
KSR	Kleijnen Systematic Reviews Ltd
MA	Marketing authorisation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	Netherlands
NMA	Network meta-analysis
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PRO	Patient-reported outcome
PROMIS-Fatigue SF	Patient-Reported Outcomes Measurement Information System-Fatigue Short Form
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
RCT	Randomised controlled trial
RIS	Risankizumab
RISA	Risankizumab
RoB	Risk of bias
SAE	Serious adverse events
SC	Subcutaneous
SE	Standard error
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	Stool frequency
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
SUCRA	Surface under the cumulative ranking curve
TA	Technology Appraisal

TNFs	Tumour necrosis factors
UK	United Kingdom
UMC+	University Medical Centre+
VEDO	Vedolizumab
VDZ	Vedolizumab

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1. Summary of the External Assessment Group's view of the company's cost-comparison case

The External Assessment Group (EAG) believes that the company has shown that in the biologic experienced (BIO-failure) population equivalence in efficacy had been demonstrated between two induction dosing regimens of guselkumab and both risankizumab and vedolizumab. These regimens are the 200 mg intravenous (IV) dose and the 400 mg subcutaneous (SC) dose, each followed by 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 (MA). The evidence supporting this is from a set of network meta-analyses (NMAs), which include the GALAXI-2/3 trials, and, in response to clarification request, the GRAVITI trial, which used the 400 mg SC induction dose. The company also demonstrated similarity in safety in the form of serious adverse events (SAEs) and discontinuation due to adverse events (AEs), also in response to clarification request, although only for the induction phase in the primary analysis population, which the company explained was due to time constraints. It should be noted that, although the 95% credible interval (CrI) overlapped the point of no difference i.e. 1, the point estimate for the odds ratio (OR) for the 200 mg IV dose was over 3 versus the 400 mg SC dose for AEs leading to discontinuation.

It should also be noted that there is more doubt regarding equivalence for the maintenance phase given the need to include re-randomisation trials, FORTIFY and GEMINI 2, which informed comparisons with risankizumab and vedolizumab respectively. Unlike the company's trials, which are referred to as 'treat-through', patients who respond following induction in the re-randomisation trials are re-randomised to the intervention or placebo. The outcomes of placebo non-responders were only available for GEMINI 2. The company argued that the outcomes of interest in the maintenance phase were those relating to the initial randomisation i.e. at the start of induction, as opposed to those conditional on response at the end of induction i.e. treat-through trials are superior to re-randomisation trials. The company therefore performed what they called 'normalisation', in order to impute outcomes for both the responders to induction who continued to respond and the non-responders to induction who had a delayed response at 1-year post-start of induction. The EAG agrees that this is the case for this appraisal i.e. in order to inform a decision whether to initiate induction with one of the treatments, as opposed to whether to continue treatment given response to induction. The EAG therefore agrees with the attempt to 'normalise' the data. However, a major limitation is that the outcomes for placebo non-responders from GEMINI 2 was used without any transformation to impute the outcomes for the placebo arms of all other trials.

The main limitation of the evidence provided is that it is confined to the BIO-failure population, whereas the company have extended the decision problem (DP) population to include the biologic naïve/ conventional only experienced population.

2. Critique of the decision problem in the company's submission

The population in the National Institute for Health and Care Excellence (NICE) scope is:[1]
Adults with moderately to severely active CD who have had an inadequate response to or demonstrated intolerance to either conventional therapy or biologic treatment.

The population in the company's decision problem (DP), as stated in Table 1 of the company submission (CS), was:[2]
Adult patients with moderately to severely active CD who have had an inadequate response, lost response or were intolerant to a biologic treatment, including patients for whom TNFis are deemed unsuitable.

The intervention in the NICE scope is simply described as guselkumab.[1] However, the anticipated marketing authorisation (MA) is for one of two administration routes at induction and two dosing regimens at the maintenance phase:[2]

- *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)*
- *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).*

EAG comment: The External Assessment Group (EAG) noticed that the DP population was stated in Table 1 of the CS to be narrower than that in the scope by excluding inadequate response or intolerance to conventional treatment, but it includes "*lost response*", which is not mentioned in the scope. The company were therefore asked to:[3]

a) clarify that, despite the MA, the company does not intend to exclude patients who have inadequate response or intolerance to conventional treatment from its submission; and

b) clarify that "lost response" is outside of the NICE scope and therefore should not be included in the company's DP.

The EAG also noticed that the population in the DP states: *"..., including patients for whom TNFis are deemed unsuitable"* (Table 1, CS). In the clarification letter the company were therefore asked to:[3]

a) clarify whether the patients for whom TNFis are unsuitable have also had an inadequate response, lost response or were intolerant to a biologic treatment or whether such patients might not have previously received any biologic treatment; and

b) if the answer to a) is 'no' then please justify the inclusion of this population given the anticipated MA.

They responded that they do want to include the biologic naïve/conventional only experienced population.[4] The EAG notes that the network meta-analysis (NMA; see Section 3.3) is, however, limited to the biologic experienced (BIO-failure) population, and this includes the update provided in the clarification letter response to allow the inclusion of the GRAVITI trial.

With regards to the intervention, the EAG noticed that the trial evidence is subdivided by induction therapy with GALAXI-2/-3 using the 200 mg IV dose and GRAVITI using the 400 mg SC dose, and

only the former trials were included in the NMA. Therefore, in the clarification letter the company were asked:[3]

a) to explain how patients will be chosen in clinical practice to receive each of the dosing regimens. Specifically:
    i. are there distinct subgroups where one would get the IV and the other the SC induction regimen?
    ii. might there be sequential treatment such that a different regimen is given on failure of the first?
b) if dosing in clinical practice is different to that observed in the trials, then please present evidence to demonstrate the effectiveness and safety of guselkumab at dosages used in clinical practice.
c) to explain why GRAVITI was not included in the NMA to inform the effectiveness of the 400 mg SC dose.
d) to include GRAVITI in the NMA to demonstrate the relative effectiveness of the 400 mg SC dose to that of the comparators.

The company responded that there are no subgroups and that the different modes of administration are to provide choice.[4] They stated that GRAVITI was excluded because it: *"... was not identified by the SLR conducted at the time the search was performed."* As part of the response, they then incorporated GRAVITI to inform the 400 mg SC dose in the efficacy NMAs (clinical response, clinical remission and endoscopic healing) have been updated to incorporate the GRAVITI trial (see Section 3.3.2).

3. Summary of the External Assessment Group's critique of clinical effectiveness evidence submitted

3.1 Systematic literature review methods

3.1.1 Searches

Clinical effectiveness searches were conducted to identify randomised controlled trials (RCTs) in the target indication of Crohn's disease (CD). The search combined facets for CD with named specific therapeutic regimens for guselkumab and its comparators.

The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 4, 5] Searches were conducted on 27 July 2023 and covered a broad range of resources including MEDLINE (including In-Process & Other Non-Indexed Citations, Epub Ahead of Print and MEDLINE® Daily), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR), all via the OvidSP interface. Searches were limited to data published from 1995 onwards, and no language limit was applied. Sensitive study design filters were applied to limit the searches to RCTs in MEDLINE and Embase. Grey literature searches were carried out for six conference proceedings held between 2022-2023 and on ClinicalTrials.gov. These searches were conducted between July-October 2023. In response to clarification, additional searches were conducted on 13 March 2025 on ClinicalTrials.gov, PubMed and Embase for recent clinical trials. For full details please see the CS, Appendix D and response to clarification.[2, 4, 5]

EAG comment: Searches were transparent and reproducible, and comprehensive strategies were used. The systematic literature review (SLR) may have benefited from searches of additional grey literature resources, such as Health Technology Assessment (HTA) agency and governmental websites. Overall, the EAG has no major concerns regarding the literature searches conducted.

3.1.2 Inclusion screening

The study eligibility criteria for the SLR are broadly aligned with the domains presented in the NICE Final Scope and the company's DP.

Identified trials were assessed for eligibility at both the title and abstract screening and full-text review stages by duplicate reviewers independently. Discrepancies were resolved through consensus or by a third independent reviewer. Data extraction was conducted by one reviewer and validated by a second independent reviewer to ensure accuracy, with any disagreements resolved through consensus or by a third independent reviewer. Assessment of risk of bias (RoB) was performed by one reviewer and validated by a second independent reviewer to confirm accuracy. Any discrepancies in RoB judgments or their justifications were resolved through consensus or by a third independent reviewer. [5]

Appendix D of the CS (Section D.1.8 and Figure 1) indicates that 58 unique RCT studies were included in the clinical effectiveness SLR, where 37 trials were included in the qualitative synthesis and eight trials which reported on guselkumab, risankizumab or vedolizumab were included in quantitative synthesis for the United Kingdom (UK).[5]

EAG comment:

- The company was asked to clarify the number of reviewers who performed title and abstract screening as well as the full-text screening, to which the company responded that two independent researchers conducted both title and abstract screening, as well as the full-text screening. The EAG is satisfied with the company's response.

- Because the non-English language publications without an English abstract were excluded from the SLR, the company was asked to provide the number of relevant studies omitted because of this and clarify the impact of this, to which the company responded that there were nine publications excluded due to being non-English including two records excluded in the first screening stage and seven records excluded in the second screening stage. The company further stated that the exclusion of non-English publications from our SLR is unlikely to impact the evidence networks pertaining to NMAs, as *"the population of interest includes UK patients, and we expect that publications written in languages other than English would primarily report data for patients with CD from single countries other than UK or North America"*.[4] The EAG notes that while the company asserts that excluding non-English publications is unlikely to impact the evidence networks, no sensitivity analysis was conducted to assess the potential bias introduced by this exclusion. Furthermore, the assumption that non-English studies primarily report data from populations outside the UK or North America may not fully account for relevant studies that could contribute to the broader evidence base.

3.2 Identified randomised controlled trials

Information on the included RCTs was gleaned from Document B,[2] and Appendices D to H[5] of the CS and the company's clarification response documents.[4]

3.2.1 Methods

The company identified two pivotal Phase III RCTs (GALAXI-2/-3 and GRAVITI) that evaluated guselkumab in adults with moderately to severely active CD. Both trials shared a similar treat-through design with 24-week follow-up periods. Both trials studied patients who had failed conventional or biologic therapy (including both BIO-failure and BIO-naïve subgroups), while GRAVITI focusses specifically on SC induction dosing.[2]

GALAXI-2/-3, considered the pivotal studies, were designed as superiority trials with co-primary efficacy endpoints of clinical remission and endoscopic response at Week 12. In contrast, GRAVITI served as a supportive study evaluating the SC induction regimen, though it also used the same co-primary efficacy endpoints. The fundamental difference between the trials was that GALAXI-2/-3 evaluated IV induction followed by SC maintenance, while GRAVITI assessed SC induction and maintenance throughout. [2]

For the primary outcomes, GALAXI-2/-3 were powered at >99% to detect a minimum 20% difference in clinical remission rates between guselkumab and placebo at Week 12, using a two-sided alpha of 0.05 with 2:2:2:1 randomisation to guselkumab regimens, ustekinumab, or placebo. The assumed response rates were 12-15% for placebo versus ≥32-35% for guselkumab. GRAVITI targeted >90% power to demonstrate superiority of guselkumab over placebo (50% versus 15% for clinical remission; 30% versus 13% for endoscopic response) with 1:1:1 randomisation.[2]

There was also a Phase II dose-ranging study (GALAXI-1) that informed the Phase III dosing regimens, where its evidence was presented in Appendix H as supportive data.[2]

EAG comment: No comments.

3.2.2 Results

The clinical efficacy of guselkumab in the treatment of moderately-to-severely active CD was assessed primarily through the GALAXI-2/-3 and GRAVITI trials. Both trials demonstrated that guselkumab was statistically significantly more effective than placebo across a range of clinically relevant endpoints, including clinical remission, endoscopic response, and patient-reported outcomes. In GALAXI-2/-3, guselkumab (200 mg IV induction) achieved clinical remission at Week 12 in [redacted] of patients

compared to [redacted] for placebo in the primary analysis set (Table 3.1), and [redacted] versus [redacted] in the BIO-failure subgroup. Similarly, endoscopic response was achieved in [redacted] compared to [redacted] (Table 3.2), with consistent results in the BIO-failure group. Improvements were also seen in patient-reported outcome (PRO)-2 remission (Table 3.3), fatigue response (Table 3.4), and endoscopic remission (Table 3.5).

Table 3.1: Clinical remission at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference,* % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 15 of the CS[2]
BIO-failure = biologic experienced; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CS = company submission; GUS = guselkumab; IV = intravenous
Notes: Clinical remission at Week 12 defined as CDAI score <150.
* Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference
† Nominal p-value
Source: Johnson & Johnson (Data on file, 2025).[6]

Table 3.2: Endoscopic response at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference,* % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 16 of the CS[2]
BIO-failure = biologic experienced; CI = confidence interval; CS = company submission; GUS = guselkumab; IV = intravenous; SES-CD = Simple Endoscopic Score for Crohn's Disease
Notes: Endoscopic response at Week 12 defined as ≥50% improvement from baseline in SES-CD score or SES-CD Score ≤2.
* Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference.
† Nominal p-value.
Source: Johnson & Johnson. Data on file (2025).[6]

Table 3.3: PRO-2 remission at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference,* % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 17 of the CS[2]
AP = abdominal pain; BIO-failure = biologic experience; CI = confidence interval; CS = company submission; GUS = guselkumab; IV = intravenous; PRO = patient-reported outcome; SF = stool frequency
Notes: PRO-2 remission at Week 12 was defined as AP mean daily score ≤1 AND SF mean daily score ≤3, and no worsening of AP or SF from baseline.
* Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference.
† Nominal p-value.
Source: Johnson & Johnson. Data on file (2025).[6]

Table 3.4: Fatigue response at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference,* % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 18 of the CS[2]
BIO-failure = biologic experienced; CI = confidence interval; CS = company submission; GUS = guselkumab; IV = intravenous; PROMIS-Fatigue SF = Patient-Reported Outcomes Measurement Information System-Fatigue Short Form
Notes: Fatigue Response at Week 12 was defined as an improvement of ≥ 7 points in the PROMIS-Fatigue SF 7a.
* Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference.
† Nominal p-value.
Source: Johnson & Johnson. Data on file (2025).[6]

Table 3.5: Endoscopic remission at Week 12 in pooled GALAXI-2/-3

Number of patients, n/N (%)	Placebo	Combined GUS 200 mg IV	Difference,* % (95% CI)	P-value
Primary Analysis Set	[redacted]	[redacted]	[redacted]	[redacted]
BIO-failure	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 19 of the CS[2]
BIO-failure = biologic experienced; CI = confidence interval; CS = company submission; GUS = guselkumab; IV = intravenous; SES-CD = Simple Endoscopic Score for Crohn's Disease
Notes: Endoscopic remission at Week 12 defined as SES-CD Score ≤2.
* Primary Analysis Set is adjusted treatment difference and BIO-failure is relative difference.
† Nominal p-value.
Source: Johnson & Johnson. Data on file (2025).[6]

Long-term data from GALAXI-2/-3 at Week 48 further supported the efficacy of guselkumab, showing statistically significant improvements in corticosteroid-free clinical remission ([redacted] compared to [redacted] with placebo; Table 20 of the CS[2]) and endoscopic response ([redacted] compared to [redacted]; Table 21 of the CS[2]). These benefits were consistent across both 100 mg SC Q8W and 200 mg SC Q4W maintenance doses, including within the BIO-failure population.

GRAVITI confirmed these findings using a 400 mg SC induction regimen. At Week 12, guselkumab demonstrated significant clinical remission (56.1% compared to 21.4%; Table 22 of the CS[2]), endoscopic response (41.3% compared to 21.4%; Table 23 of the CS[2]), clinical response (73.5% compared to 33.3%; Table 24 of the CS[2]), and PRO-2 remission (49.1% compared to 17.1%; Table 25 of the CS[2]). Maintenance efficacy at Week 24 was sustained with both 100 mg and 200 mg SC dosing regimens, showing 60.9% and 58.3% clinical remission, respectively, compared to 21.4% with placebo (Table 26 of the CS[2]). Across all these outcomes, the BIO-failure subgroup showed similar magnitudes of benefit.

EAG comment: The EAG considers the results to be positive, nevertheless, there are a couple of issues which merit caution. Firstly, subgroup analyses in the BIO-failure population were not part of the hierarchical testing and were not corrected for multiplicity, which means statistical significance should be interpreted as nominal. Secondly, while both IV and SC induction routes appeared similarly effective, as there were no direct comparison between these regimens, this limits certainty around the relative effectiveness of different formulations.

3.2.2.2 Safety

The safety profile of guselkumab in CD was evaluated using data from the Phase II/III GALAXI and GRAVITI trials. The CS[2] highlights how this comprised of a total of 1,054 patients, of whom 661 had at least 1 year of exposure. During the 12-Week induction periods, guselkumab (200 mg IV or 400 mg SC) demonstrated a safety profile broadly comparable to placebo. Adverse events (AEs), serious adverse events (SAEs), infections, and discontinuations occurred at similar or lower frequencies in the guselkumab groups compared to placebo. For instance, in the GALAXI trials, [redacted] of patients on guselkumab IV experienced AEs compared to [redacted] in the placebo group; similar trends were observed in GRAVITI (Table 3.6). The incidence of SAEs was numerically lower in guselkumab-treated patients across both studies.

Table 3.6: Overall summary of treatment-emergent AEs to Week 12 from GALAXI and GRAVITI

	GALAXI-1/-2/-3		GRAVITI	
	Placebo	**Guselkumab 200 mg IV Q4W**	**Placebo**	**Guselkumab 400 mg SC Q4W**
Safety Analysis Set, n	[redacted]	[redacted]	[redacted]	[redacted]
Average duration of follow-up, Weeks	[redacted]	[redacted]	[redacted]	[redacted]
Average exposure, n of administrations	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with one or more, n (%)				
AEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs by maximum intensity*				
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Infections^	[redacted]	[redacted]	[redacted]	[redacted]
Serious infections^	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 28 of the CS[2]

AE = adverse event; CS = company submission; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; Q4W = every 4 weeks; SAE = serious adverse event; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease

Notes:

***** The maximum severity event experienced by the patient is used.

^ Infections were defined as any AEs which were coded to the MedDRA system organ class 'Infections and infestations'. Includes only patients with a screening SES-CD score ≥6 (or ≥4 for patients with isolated ileal disease).

Source: Johnson & Johnson, Summary of Clinical Safety - Treatment of Adult Patients with Moderately to Severely Active Crohn's Disease - CNTO 1959 (guselkumab), 2024.[7]

Extended safety data through Week 48 in GALAXI and Week 24 in GRAVITI further supported the favourable profile of guselkumab. The rate of AEs per 100 patient-years remained lower in guselkumab arms (for example: [redacted]– [redacted] in active groups compared to. [redacted] in placebo. See Table 3.7. Rates of SAEs and serious infections were also generally lower or similar in guselkumab-treated patients. Notably, there was a single death in the GRAVITI study in a patient receiving 400 mg SC guselkumab, but no pattern of increased mortality emerged. Discontinuations due to AEs were relatively infrequent and less common in the guselkumab arms. Rates of infections and serious infections were comparable between active and placebo groups, suggesting no heightened infectious risk associated with guselkumab use.

Table 3.7: Overall summary of treatment-emergent AEs through to Week 48 in GALAXI and Week 24 GRAVITI

	GALAXI-1/-2/-3 to Week 48			**GRAVITI to Week 24**		
	Placebo	**Guselkumab 200 mg IV Q4W**		**Placebo**	**Guselkumab 400 mg SC Q4W**	
		100 mg SC Q8W	**200 mg SC Q4W**		**100 mg SC Q8W**	**200 mg SC Q4W**
Safety Analysis Set, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average duration of follow-up, Weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average exposure, n of administrations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patient-years of follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Events per 100 patient-years [number of events] (95% CI)						
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections^	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious infections^	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	GALAXI-1/-2/-3 to Week 48			GRAVITI to Week 24		
	Placebo	Guselkumab 200 mg IV Q4W		Placebo	Guselkumab 400 mg SC Q4W	
		100 mg SC Q8W	200 mg SC Q4W		100 mg SC Q8W	200 mg SC Q4W
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 29 of the CS[2]

AE = adverse event; CI = confidence interval; CS = company submission; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease

Notes:

***** The maximum severity event experienced by the patient is used.

^ Infections were defined as any AEs which were coded to the MedDRA system organ class 'Infections and infestations'. Includes only patients with a screening SES-CD score ≥ 6 (or ≥ 4 for patients with isolated ileal disease).

Source: Johnson & Johnson, Summary of Clinical Safety - Treatment of Adult Patients with Moderately to Severely Active Crohn's Disease - CNTO 1959 (guselkumab), 2024.[7]

EAG comment: Importantly, the safety findings in CD are consistent with guselkumab's known safety profile in other indications such as plaque psoriasis and psoriatic arthritis.[2, 7] Furthermore, pooled analyses across inflammatory bowel disease populations (CD and ulcerative colitis) and psoriatic disease demonstrated a consistent AE and SAE profile, with no evidence of disease-specific safety signals. This cross-indication consistency supports the overall tolerability of guselkumab. However, while safety findings are reassuring, exposure beyond 1 year remains limited. The data presented does not reveal cumulative long-term risks or uncommon events that may arise with prolonged immunomodulation. Therefore, it is worth mentioning that long-term extension data will be important to confirm safety durability.

3.3 Summary and critique of network meta-analysis

3.3.1 Methods

The EAG noticed that, given differences in trial design (e.g., treat-through versus re-randomised maintenance), the company stated in D.1.8.3 and D.1.9.2.2 of Appendix D (also referred to in Section B.3.8.5 of document B) that they performed a process referred to as 'normalisation', referring to NICE Technology Appraisal (TA) 633.[2] However, there was a lack of clarity in the details of the methodology, calculations, and data sources presented in the SLR report and appendices (referred to in the CS as Johnson & Johnson. [Data on file] Efficacy of guselkumab versus available biologic therapies for the maintenance treatment of moderate to severe Crohn's disease: A systematic review and meta-analysis. RF-XX2025).[8] This is partly because the calculations are only shown in the data tables in Appendix L with references to other tables or trial names with no references.[9] Also, only one comparator trial is included in both the induction and maintenance phase networks i.e. GEMINI 2. GEMINI 3, ADVANCE and MOTIVATE are only in the induction NMA, and FORTIFY is only in the maintenance NMA.

Therefore, in the clarification letter the company were asked:[3]

a) to clarify that re-randomisation only affects the validity of outcomes at maintenance, and not those for induction up to the point of re-randomisation.

The company did this:[4]

b) clarified that, although the company refers to ADVANCE and MOTIVATE as re-randomisation trials, given that they only report outcomes for the induction phase, they are not actually re-randomisation trials and that the only trials that are re-randomisation trials are GEMINI 2 and FORTIFY.

The company apologised and confirmed that ADVANCE and MOTIVATE are induction-only trials.[4]

c) conduct the induction NMA using only outcome data from the follow-up period immediately prior to re-randomisation.

The company confirmed that this was unnecessary because this had already been done.[4]

d) provide a full exposition of the process of normalisation with calculations, which is presented outside of the data tables and includes references to all data sources.

e) provide all data sources used for normalisation.

f) provide an estimate of the risk and size of any residual bias following normalisation, making specific reference to the possibility of equivalence between guselkumab, and risankizumab and vedolizumab.

For d) and e) the company provide a full exposition and all data sources.[4] For f) the company stated that the risk and size of residual bias was low. They pointed out that maintenance response/remission among induction non-responders in the placebo arm was imputed from GEMINI 2 for every trial in the network, so that they would not expect this choice to influence relative treatment effects between active comparators. Also, the results from the 1-year NMA without delayed responders, (a different normalisation process), lead to the same conclusion of comparable efficacy between treatments, which indicates that the conclusions of the NMAs are insensitive to the choice of normalisation process. The EAG note that the placebo effect might actually vary between trials and so the use of the same trial to estimate the placebo arm outcomes does not necessarily reduce the bias. The EAG would also point out that excluding delayed responders does not validate the treatment effect on those delayed responders. Nevertheless, the EAG cannot suggest a better alternative.

3.3.2 Results of network meta-analysis for efficacy outcomes

As stated in Section 1, the EAG noticed that the trial evidence is subdivided by induction therapy with GALAXI-2/-3 using the 200 mg IV dose and GRAVITI using the 400 mg SC dose, but that only the former trials were included in the NMA. Therefore, in the clarification letter the company were asked to update the NMA to include GRAVITI. The company presented the results of the NMA by including guselkumab 400 mg SC from the GRAVITI trial for the BIO-failure population at the clarification response to the EAG's request.[4] The company presented the results for both random-effects and fixed-effect models of NMAs for the induction phase.[4]

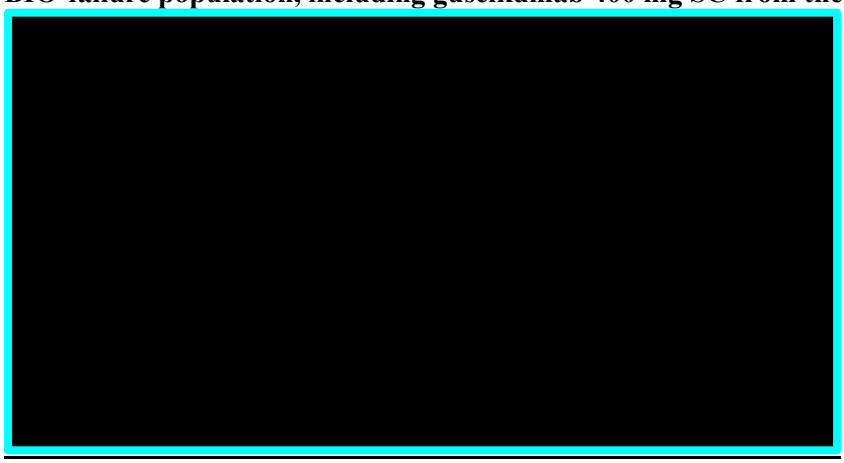
Induction phase: random-effects model

Figure 3.1 presents the forest plot for random-effects NMA of clinical response in the induction phase in the BIO-failure population by including guselkumab 400 mg SC from the GRAVITI trial. The results showed that guselkumab 400 mg SC was associated with a statistically significant increase in the clinical response rate ([redacted]) compared with vedolizumab. There was no statistically significant difference in the clinical response rate between guselkumab 400 mg SC and risankizumab.

Figure 3.2 presents the forest plot for random-effects NMA of clinical remission in the induction phase in the BIO-failure population by including guselkumab 400 mg SC from the GRAVITI trial. The results showed that guselkumab 400 mg SC was associated with a statistically significant increase in the clinical remission rate ([redacted]) compared with vedolizumab. There was no statistically significant difference in the clinical remission rate between guselkumab 400 mg SC and risankizumab.

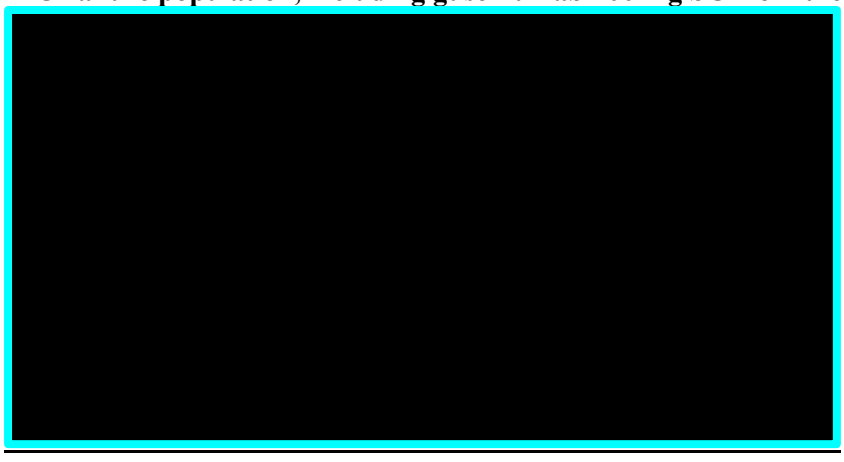
Figure 3.3 presents the forest plot for random-effects NMA of endoscopic response in the induction phase in the BIO-failure population by including guselkumab 400 mg SC from the GRAVITI trial. There was no statistically significant difference in the endoscopic response rate between guselkumab 400 mg SC and risankizumab.

Figure 3.1: Forest plot for random-effects NMA of clinical response in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial



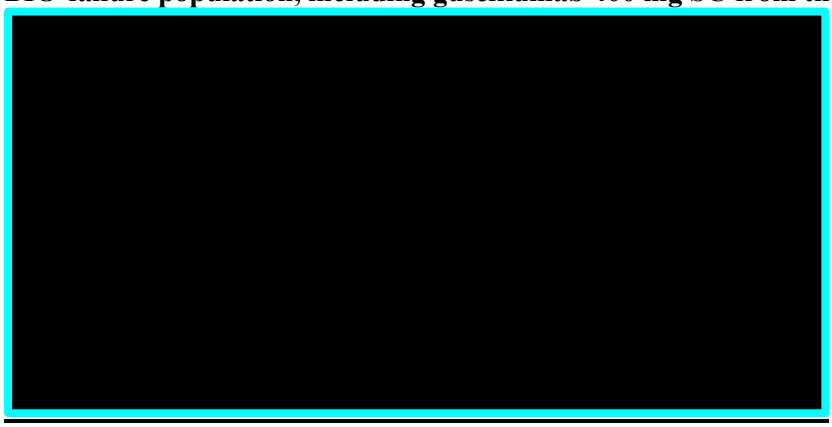
Based on Figure 3 of company clarification response.[4]
BIO-failure = biologic experienced; CrI = credible interval; GUS = guselkumab; NMA = network meta-analysis; OR = odds ratio; RIS = risankizumab; SC = subcutaneous; VEDO = vedolizumab

Figure 3.2: Forest plot for random-effects NMA of clinical remission in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial



Based on Figure 4 of company clarification response.[4]
BIO-failure = biologic experienced; CrI = credible interval; GUS = guselkumab; NMA = network meta-analysis; OR = odds ratio; RIS = risankizumab; SC = subcutaneous; VEDO = vedolizumab

Figure 3.3: Forest plot for random-effects NMA of endoscopic response in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial

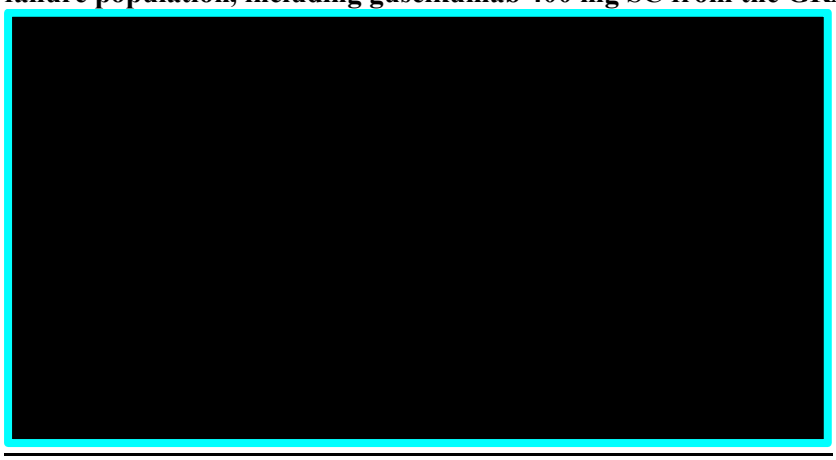


Based on Figure 5 of company clarification response.[4]
BIO-failure = biologic experienced; CrI = credible interval; GUS = guselkumab; NMA = network meta-analysis; OR = odds ratio; RIS = risankizumab; SC = subcutaneous

Induction phase: fixed-effects model

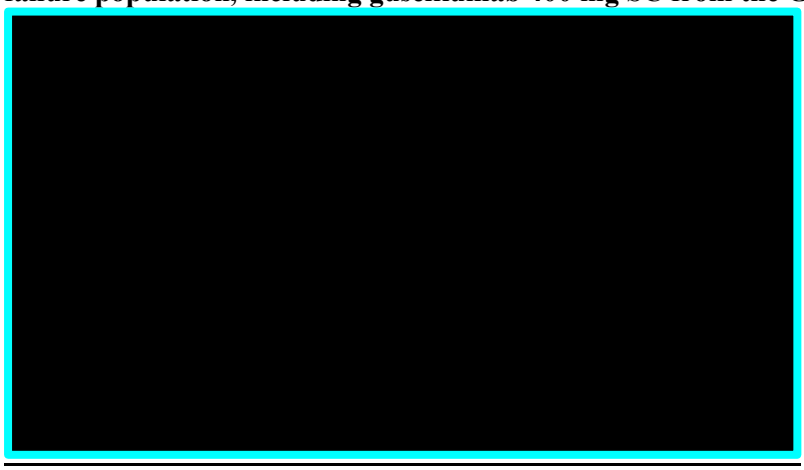
The company also conducted the fixed-effects models of NMA in the induction phase for BIO-failure population by including guselkumab 400 mg SC from the GRAVITI trial. Figure 3.4 presents the forest plot for fixed-effects NMA of clinical response in the induction phase in the BIO-failure population by including guselkumab 400 mg SC from the GRAVITI trial. Figure 3.5 presents the forest plot for fixed-effects NMA of clinical remission in the induction phase in the BIO-failure population by including guselkumab 400 mg SC from the GRAVITI trial. Figure 3.6 presents the forest plot for fixed-effects NMA of endoscopic response in the induction phase in the BIO-failure population by including guselkumab 400 mg SC from the GRAVITI trial. Based on these figures, the results of fixed-effect NMAs were consistent with those results of random-effects NMAs in the outcomes of clinical response, clinical remission and endoscopic response.

Figure 3.4: Forest plot for fixed-effects NMA of clinical response in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial



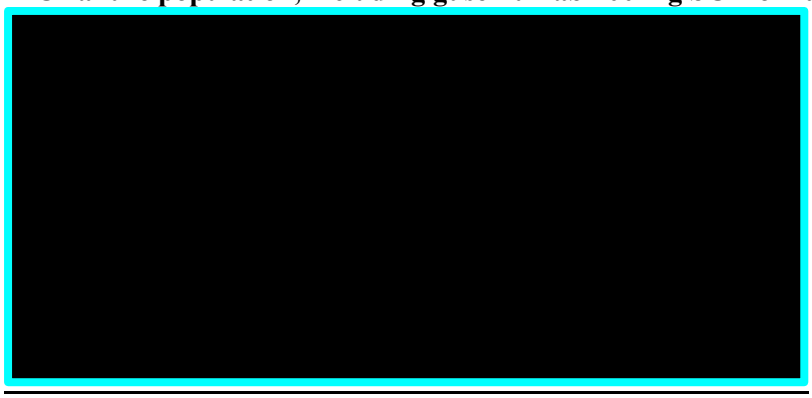
Based on Figure 1 of company factual accuracy check (FAC){National Institute for Health and Care Excellence, 2025 #218}
BIO-failure = biologic experienced; CrI = credible interval; GUS = guselkumab; NMA = network meta-analysis; OR = odds ratio; RIS = risankizumab; SC = subcutaneous; VEDO = vedolizumab

Figure 3.5: Forest plot for fixed-effects NMA of clinical remission in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial



Based on Figure 2 of company FAC{National Institute for Health and Care Excellence, 2025 #218}.
BIO-failure = biologic experienced; CrI = credible interval; GUS = guselkumab; NMA = network meta-analysis; OR = odds ratio; RIS = risankizumab; SC = subcutaneous; VEDO = vedolizumab

Figure 3.6: Forest plot for fixed-effects NMA of endoscopic response in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial



Based on Figure 8 of company clarification response.[4]
BIO-failure = biologic experienced; CrI = credible interval; GUS = guselkumab; NMA = network meta-analysis; OR = odds ratio; RIS = risankizumab; SC = subcutaneous

EAG comment: The company presented the results of the NMA by including guselkumab 400 mg SC from the GRAVITI trial for the BIO-failure population at the clarification response stage in responding to the EAG's request. The company presented the results for both random-effects and fixed-effect models of NMAs for the induction phase. The EAG considers that the results from the NMAs showed that guselkumab 200 mg IV and 400 mg SC demonstrated comparable efficacy to the comparators of vedolizumab and risankizumab for the outcomes of clinical response, clinical remission and endoscopic response rates. It should be noted that the results of fixed-effect NMAs were consistent with those results of random-effects NMAs in the outcomes of clinical response, clinical remission and endoscopic response rates.

3.3.3 Network meta-analysis results for adverse events

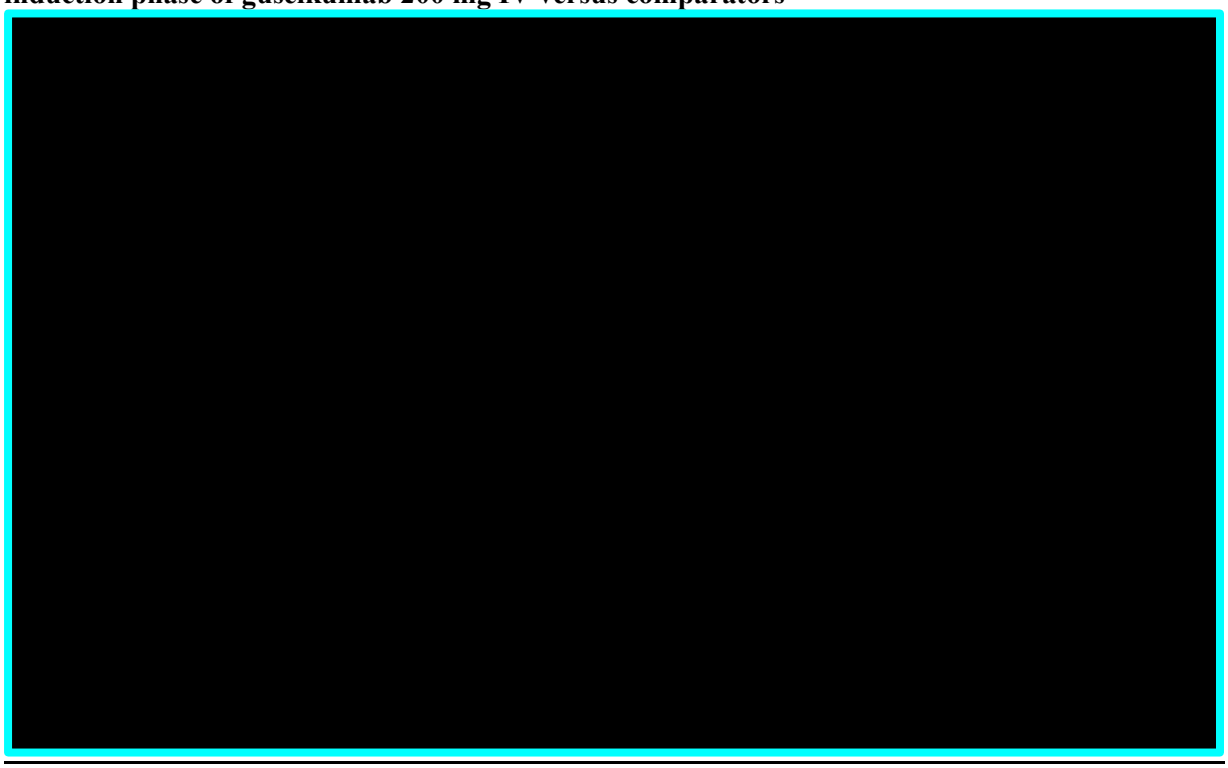
There was no NMA of any AE to demonstrate that the safety of guselkumab were broadly similar to the relevant comparators in the CS. Therefore, in the clarification letter the EAG asked the company to conduct NMAs for SAEs and discontinuation due to AEs to test whether outcomes are similar between guselkumab and relevant comparators. The company presented the results of NMA for SAEs and AEs

leading to discontinuation for the induction phase at the clarification response stage in responding to the EAG's request. The company presented the results for both random-effects and fixed-effect models of NMAs for these AE data for the induction phase.[4]

Induction phase: adverse events leading to discontinuation

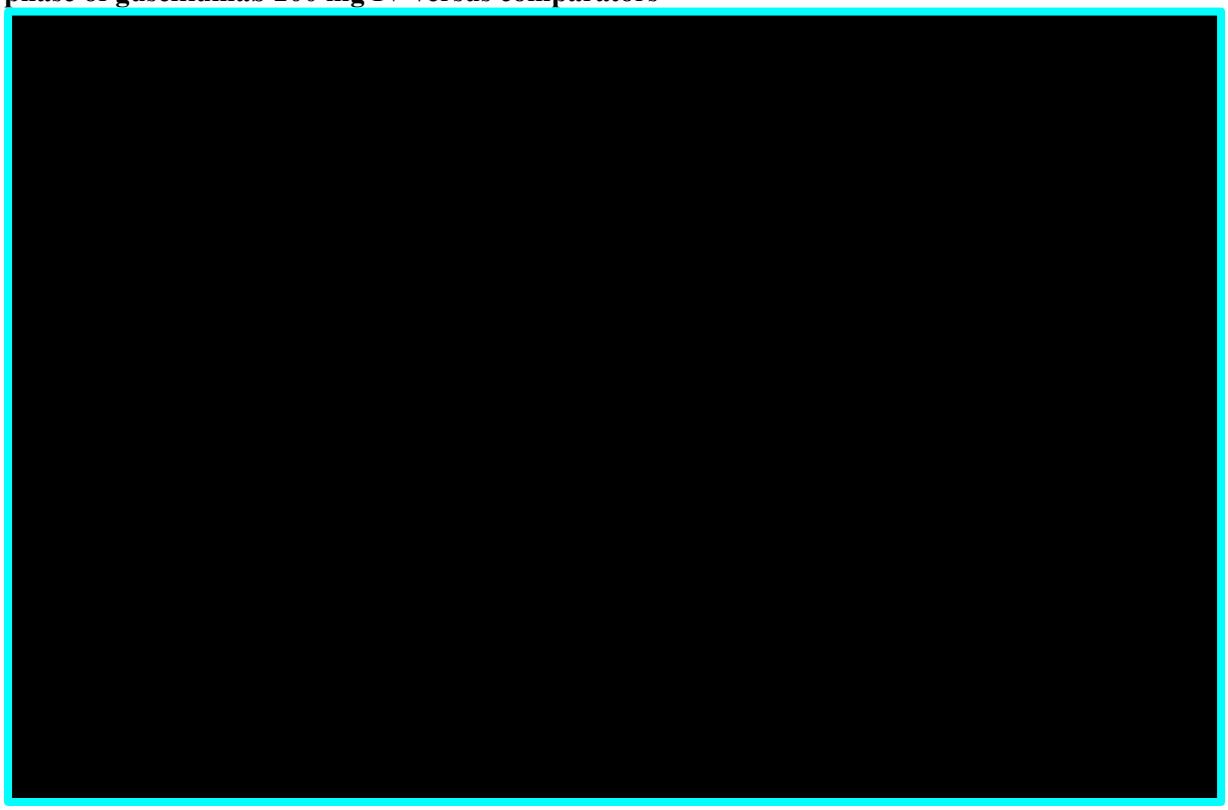
Figure 3.7 presents the forest plot for random-effects NMA of AEs leading to discontinuation in the induction phase of guselkumab 200 mg IV versus comparators. Figure 3.8 presents the forest plot for fixed-effect NMA of AEs leading to discontinuation in the induction phase of guselkumab 200 mg IV versus comparators. The results showed that there was no statistically significant difference in the AEs leading to discontinuation in the induction phase between guselkumab 200 mg IV and the comparators of guselkumab 400 mg SC, vedolizumab and risankizumab. Both the fixed- effect model and the random-effects model showed similar results.[4]

Figure 3.7: Forest plot for random-effects NMA of AEs leading to discontinuation in the induction phase of guselkumab 200 mg IV versus comparators



Based on Figure 12 of company clarification response.[4]
AEs = adverse events; CrI = credible interval; GUS = guselkumab; IV = intravenous; NMA = network meta-analysis; OR = odds ratio; RISA = risankizumab; SUCRA = surface under the cumulative ranking curve; VDZ = vedolizumab

Figure 3.8: Forest plot for fixed-effect NMA of AEs leading to discontinuation in the induction phase of guselkumab 200 mg IV versus comparators



Based on Figure 13 of company clarification response.[4]
AEs = adverse events; CrI = credible interval; GUS = guselkumab; IV = intravenous; NMA = network meta-analysis; OR = odds ratio; RISA = risankizumab; SUCRA = surface under the cumulative ranking curve; VDZ = vedolizumab

Induction phase: serious adverse events

Figure 3.9 presents the forest plot for random-effects NMA of SAEs in the induction phase of guselkumab 200 mg IV versus comparators. Figure 3.10 presents the forest plot for fixed-effect NMA of SAEs in the induction phase of guselkumab 200 mg IV versus comparators. The results showed that there was no statistically significant difference in SAEs in the induction phase between guselkumab 200 mg IV and the comparators of guselkumab 400 mg SC, vedolizumab and risankizumab. Both the fixed-effect model and the random-effects model showed similar results.

Figure 3.9: Forest plot for random-effects NMA of SAEs in the induction phase of guselkumab 200 mg IV versus comparators

Based on Figure 14 of company clarification response.[4]
CrI = credible interval; GUS = guselkumab; IV = intravenous; NMA = network meta-analysis; OR = odds ratio; RISA = risankizumab; SAEs = serious adverse events; SUCRA = surface under the cumulative ranking curve; VDZ = vedolizumab

Figure 3.10: Forest plot for fixed-effect NMA of SAEs in the induction phase of guselkumab 200 mg IV versus comparators

Based on Figure 15 of company clarification response.[4]
CrI = credible interval; GUS = guselkumab; IV = intravenous; NMA = network meta-analysis; OR = odds ratio; RISA = risankizumab; SAEs = serious adverse events; SUCRA = surface under the cumulative ranking curve; VDZ = vedolizumab

EAG comment: The company presented the results of NMA for SAEs and AEs leading to discontinuation for the induction phase at the clarification response stage in responding to the EAG's request. The company presented the results for both random-effects and fixed-effect models of NMAs for these AE data for the induction phase. The EAG considers that the results from the NMAs showed that guselkumab 200 mg IV and 400 mg SC demonstrated comparable safety profile to the comparators of vedolizumab and risankizumab for the outcomes of SAEs and AEs leading to discontinuation. It should be noted that the results of fixed-effect NMAs were consistent with those results of random-effects NMAs in the outcomes of SAEs and AEs leading to discontinuation.

4. EAG critique of cost comparison evidence submitted

4.1 Decision problem for cost comparison

The NICE Final Scope includes adult patients with moderately-to-severely active CD who have had an inadequate response, lost response or were intolerant to a biologic treatment (hereafter referred to as 'BIO-failure'). The population considered in this cost comparison that it is narrower than the anticipated MA for guselkumab and in line with the population evaluated in the GALAXI-3 study,[10] from which baseline characteristics including mean age at model start, mean patient weight, and proportions of male/female were derived.

The company's analysis compares guselkumab with risankizumab and vedolizumab. Patients received guselkumab according to the anticipated MA and corresponding to the GALAXI-2/-3 and GRAVITI trials, i.e. as induction therapy via two alternative administration routes (200 mg IV or 400 mg SC), and as maintenance therapy via two alternative injectable dosing regimens (100 mg Q8W SC or 200 mg Q4W SC). Patients receive risankizumab and vedolizumab as per their summary of product characteristics (SmPCs).

EAG comment: In response to clarification question B1, the company reiterated that the modelled population was indeed in line with UK clinical practice, given that the GALAXI studies included two UK centres. In addition, the high proportion of patients who had failed on a biologic therapy in the GALAXI and GRAVITI studies was in line with the anticipated patient population and the relevant trials for risankizumab and vedolizumab. Of note, the company also include patients for whom anti-tumour necrosis factors (TNFs) are not deemed suitable in the DP; the evidence from the NMA is not in line with that.

4.2 Cost-effectiveness searches

A SLR was conducted to identify economic studies investigating cost-effectiveness, cost-utility, and cost-per-event of therapy in moderately-to-severely active CD. The searches combined facets for CD with sensitive study design filters.

The CS, Appendix F and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[2, 4, 5] Searches were conducted on 18 October 2023 and covered a broad range of resources including MEDLINE (inc. In-Process & Other Non-Indexed Citations, Epub Ahead of Print and MEDLINE® Daily), Embase, the Database of Abstracts of Reviews of Effects (DARE), the HTA database, the National Health Service (NHS) Economic Evaluation Database (EED), CENTRAL and CDSR, all via the OvidSP interface. Searches were limited to data published from 2013 onwards, and no language limit was applied. Sensitive study design filters were applied to identify cost and economic studies. Grey literature searches were carried out for 10 conference proceedings held between 2019-2024 and on ClinicalTrials.gov. These searches were conducted in September 2024. In response to clarification, additional searches were conducted on 20 March 2025 on PubMed and Embase for recent economic evidence. For full details please see the CS, Appendix F and response to clarification.[2, 4, 5]

EAG comment:

- Searches were transparent and reproducible, and comprehensive strategies were used over a broad range of resources. Overall, the EAG has no major concerns regarding the literature searches.
- The company's economic SLR was conducted to inform the model structure for this appraisal and details are presented below and not to inform healthcare resource use and cost (details are reported in Appendix F). A total of 23 economic evaluations were included, including three that were

conducted in the UK setting and were cost utility analyses. The company used these studies to inform their model structure.

4.3 Company cost comparison model

The de novo Microsoft® Excel® model that was developed for the cost comparison has a time horizon of 10 years, and distinguishes between the following four health states: induction phase, maintenance phase, no treatment, and death. 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.

It is important to note that patients that discontinue their treatment for any reason are assumed to not receive further treatment. This was justified with the assumption of similar efficacy between guselkumab and its comparators, implying that downstream costs related to monitoring, subsequent treatments and surgery would be equal across all treatments. The company noted that this was consistent with cost comparisons in TA888 (risankizumab) and TA905 (upadacitinib).[11, 12] Further details regarding the model can be found in CS sections B 4.2.1 and B 4.2.2.{Johnson & Johnson, 2025 #7}

In the induction phase of the model, patients transit through a decision tree that includes the SmPC mandated timepoint for response assessment, which varies per treatment (CS, Figure 17)[2]. Patients can achieve adequate response and continue to maintenance phase. Patients with inadequate response continue to receive additional doses until a delayed/secondary response assessment. Here, patients with adequate response continue to maintenance phase while patients with inadequate response will discontinue treatment and do not incur any further treatment cost. It was assumed that all alive patients complete treatment induction (i.e. treat until secondary response assessment).

The maintenance phase had a Markov model structure consisting of three states: maintenance treatment, no treatment and death (CS, Figure 18). Patients cannot move backwards, i.e., they cannot move from no treatment back to maintenance treatment.

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

EAG comment: The model structure for the current cost-comparison can be regarded as reasonable, and is in line with the models used for e.g. TA888 and TA905.[11, 12] The assumption that patients who discontinue their treatment do not receive further treatment leads to an underestimation of the total costs per treatment arm, and the impact on the incremental costs between guselkumab and its comparators is unclear. In particular, the starting treatment may determine the order of downstream treatments, and this may result in differences in incremental costs irrespective of treatment effectiveness. In addition, a shorter than life-time time horizon may also result in an under-estimation of total costs, but for the purposes of this cost comparison, the shorter time horizon was likely sufficient to capture differences in costs between treatments.

4.4 Model parameters

4.1.1 Treatment effect

In the model, the clinical response outcome (rather than clinical remission) determines whether patients achieve adequate response and move onto maintenance therapy. This was justified in the CS with expert opinion, given that the primary and secondary response assessment points are generally too short to determine remission status. Clinical response in the model was defined as a reduction in the Crohn's

Disease Activity Index (CDAI) by ≥100 points or achievement of a CDAI score of <150, indicating decreased disease activity (as per the GALAXI-2/-3 and GRAVITI trials). This was consistent with the NMA. Response rates were modelled to be the same for all treatments (see CS, Table 31).

For the secondary response assessment, the probability of response was based on overall response data from TA456 on ustekinumab (at 41.45%) rather than the NMA, because the available data were considered to be insufficient given the variations in trial design and the fact that the delayed response assessment period was not placebo-controlled in any trial.[13] This response rate was also modelled to be the same for all treatments.

EAG comment: Based on the NMA, it is reasonable to assume that all three treatments are equivalent. The EAG asked the company in clarification question B2 whether secondary/delayed response assessments for all treatments were in line with evidence and (anticipated) clinical practice. In response, the company explained that secondary/delayed response assessments were indeed in line with SmPCs for all treatments. The company's clinical experts provided more nuanced opinions, for example stating that in practice not all non-responders would be likely to continue to 24 Weeks if no benefits were observed. The company provided a scenario disabling secondary/delayed response assessments, which showed that incremental costs versus vedolizumab and risankizumab decreased. The company explained this by stating that *"This reduction is attributable to the discontinuation of treatment by all non-responders following the primary response assessment."* In addition, the EAG reasons that the decrease is likely caused by guselkumab being [redacted]. In summary, there is uncertainty about the time point at which secondary/delayed response assessments would be performed (there is likely variation in clinical practice), the proportion of non-responders that would continue treatment after the primary assessment. The EAG explores the impact of only a primary assessment in a scenario but notes that this does not affect the numbers of patients who experience dose escalation in the vedolizumab arm.

4.1.2 Mortality

The company included mortality in the model by using general population all-cause mortality rates, adjusted for the age and sex of the cohort in each cycle.

4.1.3 Costs and resource use

Acquisition costs

The acquisition costs and administration schedules of guselkumab, risankizumab and vedolizumab are reported in CS, Table 33. Whereas list prices were used for risankizumab and vedolizumab, for guselkumab a Patient Access Scheme (PAS) discount of [redacted] applied.

Treatment schedule

The treatment frequency varied depending on the drug in question, treatment stage and mode of administration.

Guselkumab is administered as 200 mg IV or 400 mg SC during induction. Referencing UK clinical expert opinion, the company assumed that 20% would receive IV and 80% SC treatment. After primary assessment at Week 12, responders enter maintenance treatment and receive 100 mg SC from Week 16 onwards, Q8W. Non-responders receive 200 mg SC at Week 12 and Q4W until secondary assessment at Week 24. If responsive, they keep this schedule for maintenance.

Risankizumab is administered as 600 mg IV during induction with a primary assessment at Week 12. Primary responders enter maintenance treatment and receive 360 mg SC from Week 12 onwards, Q8W. Non-responders receive the same treatment, and responsiveness is assessed again at Week 24.

Vedolizumab is administered as 300 mg IV three times during induction. Primary response assessment occurs at Week 6. Identified non-responders receive an additional IV dose at Week 10. Identified responders start maintenance treatment at Week 14, receiving either the same IV dose Q8W or a SC 108 mg dose once every 2 weeks (Q2W). Referencing UK clinical expert opinion and NICE TA888,[11] the company assumed that the share of IV and SC treatment would be 50% respectively. Secondary response assessment occurs at Week 14.

Dose escalation

In NHS clinical practice, patients that lose response to IV-administered 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. No adjustments are proposed for SC patients. The company base-case assumes that 30% of patients on vedolizumab administered via IV require dose escalation in form of a shorter 4-Week interval. The estimate was stated to be based on published literature and in line with TA888.[11, 14, 15] Patients were assumed to receive the escalated dosing schedule from the first Week of maintenance. No dose escalation was assumed for guselkumab and risankizumab as per the respective SmPCs (draft for guselkumab).

Treatment discontinuation

In the induction phase of the model, treatment discontinuation is not possible, i.e., all patients are assumed to complete the induction phase until secondary response assessment. In the maintenance phase, the proportion of responders were assumed to discontinue treatment at a constant rate which was informed by the all-cause treatment discontinuation observed in the GALAXI-3 trial (CS, Table 32). The same discontinuation rate was applied to all treatments. The observed probability of discontinuation at Week 48 was converted to a 2-weekly probability via geometric conversion, resulting in a 2-weekly probability of discontinuation of [redacted].

Treatment administration costs

Administration costs were assigned for every IV visit and the first SC dose (CS, Table 37). IV visits were assumed to occur in an outpatient setting, and derived as a weighted average of consultant- and non-consultant led follow-up appointments from the 2022/2023 NHS reference costs.

Adverse event and miscellaneous costs

The CS excluded disease management and AE costs, and did not identify further miscellaneous cost items.

Addressing disease management, the company stated that due to equal efficacy of guselkumab and the comparators, monitoring and testing during induction and health state occupancy during maintenance would be similar. The company further stated that a similar approach was pursued in TA888 and TA925.[11, 16]

AEs were not included since firstly, clinical trial evidence did not *"suggest a clinical meaningful difference between the safety profiles of guselkumab 200 mg SC Q4W and 100 mg SC Q8W"* (CS, B.4.2.4.). Secondly, safety profiles of intervention and comparators were considered *"broadly similar"* (CS, B.4.2.4.), and finally, the company referred to other TAs having the same approach.[11, 12, 16] The CS further noted that SAEs would be indirectly captured in all-cause discontinuation.

EAG comments: The main concerns of the EAG relate to a) 20%/80% share of IV/SC for guselkumab induction and 50%/50% share of IV/SC for vedolizumab maintenance, b) dosing of guselkumab (100 mg Q8W/200 mg SC Q4W), c) start of SC vedolizumab maintenance, d) dose escalation of vedolizumab, and e) treatment discontinuation.

a) Referencing UK clinical expert opinion, the company assumed that 20% would receive IV and 80% SC guselkumab treatment. Upon request, the company provided an extreme scenario where all patients received guselkumab induction via IV, causing an increase in the incremental costs by [redacted] compared to the base-case. Another scenario explored an equal share of guselkumab IV and SC administration respectively during induction which was suggested by one clinical expert consulted by the company, resulting in an incremental cost increase of [redacted].

   The equal share of IV and SC administration in patients receiving vedolizumab during maintenance, taken from TA888, could not be backed up by further literature or evidence by the company. One clinical expert consulted by the company suggested an alternative estimate of 1/3 of patients getting IV administration, based on experience in their Trust. Another provided experience-based values of 40% IV and 60% SC administration. The Welsh clinical expert consulted by the company, who mentioned long infusion wait times as a limiting factor, suggested a substantially lower share of 5% IV and 95% SC administration. The company did not provide a rationale for why the IV/SC split differed between guselkumab and vedolizumab. Therefore, the EAG uses for both, a 50%/50% split in their analyses.

b) All four clinical experts consulted by the company stated that the share of patients receiving 200 mg guselkumab compared to those receiving 100 mg guselkumab might be higher in UK clinical practice. Two of them found the 200 mg Q4W dosage to be more applicable for partial responders, which implies a further differentiation between partial and non-responders not mirrored in the health economic model. One clinical expert consulted by the company suggested that the current dose split may be too simplified, with patients potentially transitioning from higher to lower dosage in case of disease improvement. Assuming equal efficacy between guselkumab, risankizumab and vedolizumab, [redacted].

c) The company initiated vedolizumab maintenance after three induction IV doses. The SmPCs state that at least two IVs should be administered during induction (allowing for two IV induction doses), and that the last IV dose could be replaced by a first SC dose. The company did not explore this in the model. The company's model thus potentially over-estimates vedolizumab costs.

d) The EAG wishes to highlight that the 30% dose escalation estimate was originally sourced from a critical review of dose escalation of adalimumab and infliximab,[17] does not pertain to vedolizumab and is thus uncertain. Two clinical experts consulted by the company agreed that 30% would be appropriate, one estimated 20%, and one 20-30%. Upon EAG clarification question B4c, the company presented evidence from the GEMINI-2 clinical trial for patients with TNF-alpha failure, with a vedolizumab dose escalation share of 27%. The company's simplistic approach to modelling vedolizumab dose escalation from the first Week of maintenance onwards (CS, B 4.2.1.3.) inflates the affected amount of patients and thus vedolizumab costs compared to a per cycle-assignment because patients can have dose escalation at any point while on maintenance treatment and patients discontinue treatment over time. Patients might need at least one cycle in maintenance before loss of response (which may lead to dose escalation) occurs. As this is not captured in the health economic model, vedolizumab costs are inflated. Additionally, if the share of patients receiving vedolizumab as IV is uncertain or potentially over-estimated as detailed in a), the number of patients with dose escalation is even further inflated. Moreover, the company did not consider later vedolizumab de-escalation (as it is not included in the vedolizumab SmPC). Given that there is no clear evidence on dose escalation with vedolizumab and the company's approach likely over-

estimates the number of patients having dose escalation, the EAG considers the 30% as uncertain and uses 20% in the base-case.

e) Treatment discontinuation in the induction phase is possible and not reflected in the model. The company explained that treatment discontinuation in the induction phase was uncommon in clinical trials as it will take time to see response from the initiation of drug therapy, and the most severe patients who would be more likely to need emergency surgery were excluded from the trials. The company did not elaborate on differences in safety-related treatment discontinuation in the induction phase. A scenario (in response to EAG clarification question B3) exploring equal treatment discontinuation in the induction phase of [redacted] as an assumption taken from the GALAXI-3 trial had a minimal impact on the cost comparability. It should be noted that a scenario with differences between treatments was not explored, but might be of interest since treatment discontinuation was linked to the secondary response assessment, which differs in timepoint for guselkumab and vedolizumab. One clinical expert consulted by the company stated that at Week 12, *"not all […] [primary non-responders] would be offered/likely to benefit from the higher dose, and some patients may discontinue guselkumab/ switch to a different treatment"*. [18] This notion of potential earlier discontinuation (instead of at Week 24) was backed up by another clinical expert consulted by the company. Contrary, one clinical expert consulted by the company noted that later line or highly refractory patients would continue guselkumab treatment beyond Week 24 to achieve remission. Nevertheless, assuming equal effectiveness and safety, the assumption of no treatment discontinuation in the induction phase is likely appropriate, as is the assumption of no differences per treatment in treatment discontinuation in the maintenance phase, and the assumption of constant treatment discontinuation.

4.5 Validation and External Assessment Group model check

The company stated that four UK clinicians were consulted individually to validate posology and health economic assumptions described in the dossier. The company also performed technical validation with an independent health economist and technical and stress tests. The EAG deemed the validation efforts appropriate.

The EAG conducted a range of checks on the company's cost-comparison model. This included a verification that the dosing scheme of the treatments in Microsoft® Excel® matched the described scheme in the CS and verification that the costs are in line with the costs described in the CS. The EAG also performed an inspection of the main formulae used in Microsoft® Excel®.

4.6 Company's model results

The CS base-case results contrast the total treatment costs for guselkumab, risankizumab, and vedolizumab (Table 4.1). For guselkumab, the PAS price was utilised, for risankizumab and vedolizumab the respective list prices (CS, Table 33). Given the use of the PAS price for guselkumab it was [redacted].

Parameter uncertainty was explored with one-way sensitivity analyses (OWSA) of guselkumab versus risankizumab and vedolizumab. For missing standard errors (SEs), a 20% SE was assumed. Parameters used jointly for intervention and comparators were not fixed for the comparators in the OWSA. The most impactful input parameters on incremental costs were the discontinuation rate, the NMA guselkumab OR of response after induction, and the NMA placebo absolute probability of response after induction (CS, Table 41, 42). For the input parameters included in the OWSA, guselkumab

consistently [redacted] when compared to risankizumab and vedolizumab. No further probabilistic analyses were performed.

Scenario analyses addressed a shorter time horizon of 5 years, and an introduction of 3.5% discounting on costs. In both scenarios, guselkumab [redacted] (CS, Table 44, 45).

Table 4.1: Company base-case (10-year time horizon, not discounted)

Cost category	Costs guselkumab (PAS price)		Costs risankizumab (list price)		Costs vedolizumab (list price)	
	Induction	Maintenance	Induction	Maintenance	Induction	Maintenance
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total treatment costs	[redacted]		[redacted]		[redacted]	
Incremental cost versus guselkumab	[redacted]		[redacted]		[redacted]	

Values may not add up due to rounding.
Source: CS, Table 40 and health economic model.
CS = company submission; N/A = not applicable; PAS = Patient Access Scheme

EAG comment: The company justified the implementation of a 10-year time horizon as the base-case with the percentage of patients still on treatment, i.e., [redacted]. For the 5-year time horizon explored in a scenario, it was [redacted] of patients. To capture all differences in costs, an even longer time horizon than 10 years may be necessary. In EAG clarification response B12, the company visualised the development of incremental costs of guselkumab versus risankizumab and vedolizumab, showing that incremental cost differences increase gradually but more slowly over time. The EAG concludes that most of the cost differences occur in the early months and years of treatment and given that subsequent treatment lines are not modelled, the 10-year time horizon is likely appropriate.

4.7 External Assessment Group exploratory analysis

The EAG undertook two additional exploratory analyses using the company's Microsoft® Excel® model as submitted in response to the clarification letter. The analyses presented in this Section reflects the PAS discount price for guselkumab whilst list prices were used for vedolizumab and risankizumab. Results using discounted prices for vedolizumab and risankizumab are shown in a confidential appendix to this report.

The EAG base-case includes:

- A 20% rate of dose escalation for vedolizumab
- A 50%/50% IV/SC split in the guselkumab induction phase

EAG exploratory analyses include:

- No secondary/delayed assessment

Results of the EAG base-case and scenarios are shown in Tables 4.2 and 4.3 respectively.

Table 4.2: EAG base-case analysis results

Technologies	Disaggregated results		Total treatment costs (£)	Incremental costs of guselkumab relative to comparator (£)
	Total induction costs (£)	Total maintenance costs (£)		
CS base-case				
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
EAG_1: A 20% rate of dose escalation for vedolizumab				
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
EAG_2: A 50%/50% IV/SC split in the guselkumab induction phase				
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case: EAG_1 + EAG_2				
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]

CS = company submission; EAG = External Assessment Group; IV = intravenous; SC = subcutaneous. Results are deterministic unless indicated.

Table 4.3: EAG scenario analysis results

Technologies	Disaggregated results		Total treatment costs (£)	Incremental costs of guselkumab relative to comparator (£)
	Total induction costs (£)	Total maintenance costs (£)		
EAG base-case				
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]
S1. No secondary/delayed assessment				
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]

EAG = External Assessment Group
Results are deterministic unless indicated.

5. External Assessment Group commentary on the robustness of evidence submitted by the company

The company's evidence appears to be robust enough to confirm comparability of efficacy and safety between the two induction dosing regimens of guselkumab and both risankizumab and vedolizumab in the BIO-failure population.[2, 4] However, no evidence was presented for the biologic naïve/conventional only experienced population.

The model structure for the current cost-comparison can be regarded as reasonable. The assumption that patients who discontinue their treatment do not receive further treatment leads to an underestimation of the total costs per treatment arm and the impact on the incremental costs between guselkumab and its comparators is unclear, particularly given that the starting treatment may determine the order of downstream treatments, and this may result in differences in incremental costs between treatment arms irrespective of treatment effectiveness.

The model assumes equal clinical efficacy for all three drugs. For the induction phase, this is supported by the NMA, but after that, there is limited evidence. There is particular uncertainty about the time point at which secondary/delayed response assessments would be performed (there is likely variation in clinical practice), the proportion of non-responders that would continue treatment after the primary assessment and the proportion of non-responders that respond at the secondary/delayed assessment. The company and EAG scenario that does not allow for secondary/delayed response assessments explores this uncertainty, although it is likely optimistic as it still includes vedolizumab dose escalation. Overall, the EAG considers that the company's model is likely over-estimating vedolizumab costs because all patients receive three IV doses and the proportion of patients with dose escalation is likely over-estimated.

With the PAS price for guselkumab and list prices for risankizumab and vedolizumab, guselkumab is estimated to be [redacted] compared to the two comparators. This applies for the company's revised base-case analysis and for all company and EAG scenario analyses.

6. References

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[6] Johnson and Johnson. *GALAXI-2/-3 and GRAVITI data [Data on file]* Johnson and Johnson, 2025

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[8] Eversana. *Efficacy of guselkumab versus risankizumab and vedolizumab for the treatment of moderate to severe Crohn's disease: a systematic review and network meta-analysis. Draft 2 Technical report for United Kingdom [PDF provided by Company]*: Eversana, 2025. 107p.

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[11] National Institute for Health and Care Excellence. *Risankizumab for previously treated moderately to severely active Crohn's disease [TA888]*. London: NICE, 2023 Available from: https://www.nice.org.uk/guidance/ta888

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Single Technology Appraisal

Guselkumab for previously treated moderately to severely active Crohn's disease [ID6238]

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 Thursday 15th May** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 2 Identified Factual Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1, page 7, states: The company also demonstrated similarity in safety in the form of serious adverse events (SAEs) and discontinuation due to adverse events (AEs), also in response to clarification request, although only for the induction phase in the BIO-failure population, which the company explained was due to time constraints	Please amend as follows: The company also demonstrated similarity in safety in the form of serious adverse events (SAEs) and discontinuation due to adverse events (AEs), also in response to clarification request, although only for the induction phase in the **primary analysis population**, which the company explained was due to time constraints	The safety NMAs conducted as part of the response to the clarification questions considered the full primary analysis population given that safety data for the bio-failure populations are not available in the relevant comparator publications.	Amended.
Section 1, page 7, states: The main limitation of the evidence provided is that it is confined to the BIO-failure population, whereas the company have extended the decision problem (DP) population to include the	Please amend as necessary as per the rationale provided.	As discussed in the company submission and clarification questions, is it anticipated that guselkumab would primarily be used in the bio-failure population of patients with moderately to severely active Crohn's disease however, it is anticipated that guselkumab	Not a factual inaccuracy.

biologic naïve/ conventional only experienced population.		may be used in a small proportion of patients where patients are unsuitable to TNF-inhibitors. This is also in line with the marketing authorisation and NICE recommendations for vedolizumab and risankizumab. Although NMAs were not conducted in the bio-naïve population for this submission, the publication by Disher et al, 2025 presents a wider NMA network (using the same methodology) where guselkumab is compared to several treatments including vedolizumab and risankizumab. The point estimates were favourable towards guselkumab in the bio-naïve population (referred to as non-BIO-IR in the publication), in the clinical response, clinical remission and endoscopic response endpoints versus risankizumab and significantly better than vedolizumab in the	

		clinical response and clinical remission endpoints.	
Section 3.2.1, page 11, states: The company identified two pivotal Phase III RCTs (GALAXI-2/-3 and GRAVITI) that evaluated guselkumab in adults with moderately to severely active CD	Please amend as follows: The company identified **a** Phase III RCT (GALAXI-2/-3 that evaluated guselkumab in adults with moderately to severely active CD.	GRAVITI data was not published within the time frame of the SLR searches.	Not a factual inaccuracy. GRAVITI was identified even if not published.
Section 3.2.1, page 11, states: GALAXI-2/-3 studied patients who had failed conventional or biologic therapy (including both BIO-failure and BIO-naïve subgroups), while GRAVITI focused specifically on SC induction dosing.	Please amend as follows: GALAXI-2/-3 **and GRAVITI** studied patients who had failed conventional or biologic therapy (including both BIO-failure and BIO-naïve subgroups), while GRAVITI **focusses** specifically on SC induction dosing.	As per the GALAXI and GRAVITI trial protocols/design.	Amended.
Section 3.2.2, page 13, states: Secondly, while both IV and SC induction routes appeared similarly effective, as there were no direct comparison between these	Please amend as follows: Secondly, while both IV and SC induction routes appeared similarly effective, as there were no direct comparison between these regimens, this limits certainty around the relative effectiveness of different formulations.	To clarify that no direct comparisons were made between the two guselkumab induction routes as the GALAXI and GRAVITI trials were not designed or powered to allow for this comparison.	Not a factual inaccuracy.

regimens, this limits certainty around the relative effectiveness of different formulations	**However, it should be noted that the GALAXI and GRAVITI trials were not designed nor powered to directly compare the 200mg IV induction regimen to the 400mg SC induction regimen.**		
Section 3.3.2, page 19 and 20: Figures 3.4 and 3.5	Please see appendix 1	Upon reviewing the EAG report, Johnson & Johnson identified an error in the fixed effect NMA outcomes presented as part of the response to question A6 of clarification questions. Please see appendix 1 for the updated outcomes that should replace figures 3.4 and 3.5 of the EAG report.	Amended.
Section 4.1, page 25, states: Of note, the company also include patients for whom anti-tumour necrosis factors (TNFs) are not deemed suitable in the DP; the evidence from the NMA is not in line with that.	Please amend as necessary as per the rationale provided.	As discussed in the company submission and clarification questions, is it anticipated that guselkumab would primarily be used in the bio-failure population of patients with moderately to severely active Crohn's disease however, it is anticipated that guselkumab may be used in a small proportion of patients where	Not a factual inaccuracy.

		patients are unsuitable to TNF-inhibitors. This is also in line with the marketing authorisation and NICE recommendations for vedolizumab and risankizumab. Although NMAs were not conducted in the bio-naïve population for this submission, the publication by Disher et al, 2025 presents a wider NMA network (using the same methodology) where guselkumab is compared to several treatments including vedolizumab and risankizumab. The point estimates were favourable towards guselkumab in the bio-naïve population (referred to as non-BIO-IR in the publication), in the clinical response, clinical remission and endoscopic response endpoints versus risankizumab and significantly better than vedolizumab in the clinical response and clinical remission endpoints.	

Section 4.3, page 26, states: In the induction phase of the model, patients transit through a decision tree that includes the SmPC mandated timepoint for response assessment, which varies per treatment (CS, Figure 17)[2]	Please amend as follows: In the induction phase of the model, patients transit through a decision tree that includes the SmPC mandated timepoint**s** for **primary and secondary** response assessment**s**, which varies per treatment (CS, Figure 17)[2]	To clarify that there are two response assessments included in the model as per each treatment SmPC (draft for guselkumab).	
Section 4.1.1, page 27, states: The EAG is concerned that the probability of response at the secondary assessment quoted by the company could not be attributed to TA456, resulting in uncertainty about this estimate.	Please amend as necessary based on the rationale provided.	The probability of response at the secondary assessment was informed by Table 40, page 178 in the company submission for TA456. The committee papers do not seem to be visible on the NICE website, however, Johnson & Johnson have provided the committee papers for TA456 as part of this response.	Amended.
Section 4.1.3, page 28, states: No dose escalation was assumed for guselkumab and risankizumab	Please amend as follows: No dose escalation was assumed for guselkumab and risankizumab **as per the respective SmPCs (draft for guselkumab).**	To clarify that dose escalation was not included for guselkumab and risankizumab based on the dosing recommendations provided in	Amended.

		the respective treatment SmPCs.	
Section 4.1.3, page 29, states: The EAG wishes to highlight that the 30% dose escalation estimate was originally sourced from a critical review of dose escalation of adalimumab and infliximab,[17] does not pertain to vedolizumab and is thus uncertain	Please amend as necessary based on the rationale provided.	To clarify that in response to the CQs, data pertaining to vedolizumab dose escalation was provided, where Johnson & Johnson presented an extract from the vedolizumab SmPC which states that in the GEMIINI-2 trial, 27% of patients received dose escalation from vedo 300mg Q8W to vedo 300mg Q4W.	Amended.
Section 4.1.3, page 29 states: Additionally, if the share of patients receiving vedolizumab as IV is uncertain or potentially over-estimated as detailed in a), the number of patients with dose escalation is even further inflated. Moreover, the company did not consider	Please amend as follows: Additionally, if the share of patients receiving vedolizumab as IV is uncertain or potentially over-estimated as detailed in a), the number of patients with dose escalation is even further inflated. ~~Moreover, the company did not consider later vedolizumab de-escalation.~~	Johnson & Johnson do not agree with de-escalation being included in the model as this is not recommended in the vedolizumab SmPC and would be considered off label.	Amended.

later vedolizumab de-escalation.			
Section 4.1.3, page 30, states: a) The EAG considers the CS' brief mentioning of the concept of re-induction following vedolizumab dose escalation without further elaboration on its relevance and effect on costs an additional minor uncertainty.	Please amend as necessary based on the rationale provided.	Johnson & Johnson apologise for the reference to re-induction for vedolizumab, this was in error as re-induction does not apply to vedolizumab as per it's SmPC.	Amended.
Section 4.1.3, page 30, states: A scenario (in response to EAG clarification question B3) exploring equal treatment discontinuation in the induction phase of [redacted] as an assumption taken from the GALAXI-3 trial had a	Please amend as follows: A scenario (in response to EAG clarification question B3) exploring equal treatment discontinuation in the induction phase of [redacted] as an assumption taken from the GALAXI-3 trial had a minimal impact on the **cost comparability.**	As a cost comparison model was provided, only cost comparability can be assessed.	Amended.

minimal impact on the incremental cost-effectiveness ratio (ICER)			
Section 5, page 33, states: However, no evidence was presented for the biologic naïve/conventional only experienced population.	Please amend as necessary as per the rationale provided.	As discussed in the company submission and clarification questions, is it anticipated that guselkumab would primarily be used in the bio-failure population of patients with moderately to severely active Crohn's disease however, it is anticipated that guselkumab may be used in a small proportion of patients where patients are unsuitable to TNF-inhibitors. This is also in line with the marketing authorisation and NICE recommendations for vedolizumab and risankizumab. Although NMAs were not conducted in the bio-naïve population for this submission, the publication by Disher et al, 2025 presents a wider NMA network (using the same methodology) where guselkumab is compared to several treatments including	Not a factual inaccuracy.

		vedolizumab and risankizumab. The point estimates were favourable towards guselkumab in the bio-naïve population (referred to as non-BIO-IR in the publication), in the clinical response, clinical remission and endoscopic response endpoints versus risankizumab and significantly better than vedolizumab in the clinical response and clinical remission endpoints.	

Issue 3 Data and Reporting Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2, page 13, states: Long-term data from GALAXI-2/-3 at Week 48 further supported the efficacy of guselkumab, showing statistically significant improvements in corticosteroid-free clinical	Please amend as follows: Long-term data from GALAXI-2/-3 at Week 48 further supported the efficacy of guselkumab, showing statistically significant improvements in corticosteroid-free clinical remission of patients receiving **guselkumab 100mg Q8W and 200mg Q4W ([redacted] and [redacted] respectively**, compared to	Week 48 data from the GALAXI trials include both guselkumab maintenance doses.	Not a factual inaccuracy. The 100 mg dose is not part of the M, and therefore is excluded from the decision problem.

remission ([redacted] compared to [redacted] with placebo; Table 20 of the CS[2]) and endoscopic response ([redacted] compared to [redacted]; Table 21 of the CS[2]).	[redacted] with placebo; Table 20 of the CS[2]) and endoscopic response ([redacted] **and [redacted] respectively,** compared to [redacted]; Table 21 of the CS[2]).		
Section 3.2.2.2, page 14, Table 3.6, column "guselkumab 400mg SC Q4W" states: [redacted]	Please amend as follows: [redacted]	This is incorrect as per the company submission, section B.3.9.2.	Not a factual inaccuracy – this came from Table 28 of the CS.

Issue 4 Minor Typographical and Grammatical Errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 3.3.1, page 17 states: The company apologised and confirmed that ADVANCE and MOTICATE are induction-only trials.[4]	Please amend as follows: The company apologised and confirmed that ADVANCE and **MOTIVATE** are induction-only trials.[4]	Minor typographical error.	Amended.

Section 4.3, page 26, states: Further details regarding the model can be found in CS sections B 4.2.1 and B 4.2.2.s	Please add reference 2 as this relates to the company submission	Minor formatting error.	Amended.
Section 4.1.3, page 27, states: After primary assessment at Week 12, responders enter maintenance treatment and receive 100 mg SC from Week 16 onwards, Q8Q	Please amend as follows: After primary assessment at Week 12, responders enter maintenance treatment and receive 100 mg SC from Week 16 onwards, **Q8W.**	Minor typographical error.	Amended.
Section 4.6, page 31, states: The company justified the implementation of a 10-year time horizon as the base-case with the number of patients still on treatment, i.e., 12%. For the 5-year time horizon explored in a scenario, it was 24% of patients	Please amend as follows: The company justified the implementation of a 10-year time horizon as the base-case with the **proportion** of patients still on treatment, i.e., 12%. For the 5-year time horizon explored in a scenario, it was 24% of patients	Minor grammatical error.	Amended.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3.2.2, page 13, states: GRAVITI confirmed these findings using a 400 mg SC induction regimen. At Week 12, guselkumab demonstrated significant clinical remission ([redacted] compared to [redacted] Table 22 of the CS[2]), endoscopic response ([redacted] compared to [redacted]; Table 23 of the CS[2]), clinical response ([redacted] compared to [redacted]; Table 24 of the CS[2]), and PRO-2 remission ([redacted] compared to [redacted]; Table 25 of the CS[2]). Maintenance efficacy at Week 24 was sustained with both 100 mg and 200 mg SC dosing regimens, showing [redacted] and [redacted] clinical	As per the company submission provided to NICE on 7th March 2025, this data can be unmarked.	GRAVITI confirmed these findings using a 400 mg SC induction regimen. At Week 12, guselkumab demonstrated significant clinical remission (56.1% compared to 21.4%; Table 22 of the CS[2]), endoscopic response (41.3% compared to 21.4%; Table 23 of the CS[2]), clinical response (73.5% compared to 33.3%; Table 24 of the CS[2]), and PRO-2 remission (49.1% compared to 17.1%; Table 25 of the CS[2]). Maintenance efficacy at Week 24 was sustained with both 100 mg and 200 mg SC dosing regimens, showing 60.9% and 58.3% clinical remission, respectively, compared to 21.4% with placebo (Table 26 of the CS[2]). Across all these outcomes, the BIO-failure	Amended.

remission, respectively, compared to [redacted] with placebo (Table 26 of the CS[2]). Across all these outcomes, the BIO-failure subgroup showed similar magnitudes of benefit.		subgroup showed similar magnitudes of benefit.	
Section 4.1.3, page 29, states: Assuming equal efficacy between guselkumab, risankizumab and vedolizumab, [redacted]	Pricing strategy for guselkumab is confidential.	Assuming equal efficacy between guselkumab, risankizumab and vedolizumab, [redacted]	Amended.

Appendix 1

Upon reviewing the EAG report, Johnson & Johnson identified and apologise for an error in the fixed effect NMAs presented as part of the response to question A6 of the clarification questions. The outcomes corresponding to the random effect NMAs were accidentally presented for the fixed effect NMAs for the clinical response and clinical remission endpoints. Johnson & Johnson can confirm that Figure 1 and Figure 2 below should replace Figure 3.4 and Figure 3.5 of the EAG report. It should be noted that the EAG conclusions of the fixed effect NMAs being consistent with the results of the random effect NMAs for all endpoints presented remains.

Figure 1: Forest plot for fixed-effects NMA of clinical response in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial

Figure 2: Forest plot for fixed-effects NMA of clinical remission in the induction phase, BIO-failure population, including guselkumab 400 mg SC from the GRAVITI trial